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Editors

Acupuncture Therapy for Neurological Diseases

A Neurobiological View

TSINGHUA UNIVERSITY PRESS

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With 87 figures

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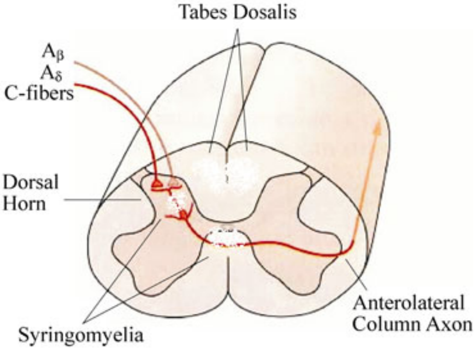

Figure 3.2 Diagram showing the damaged areas in spinal cord of the patient with Tabes dorsalis and Syringomyelia.

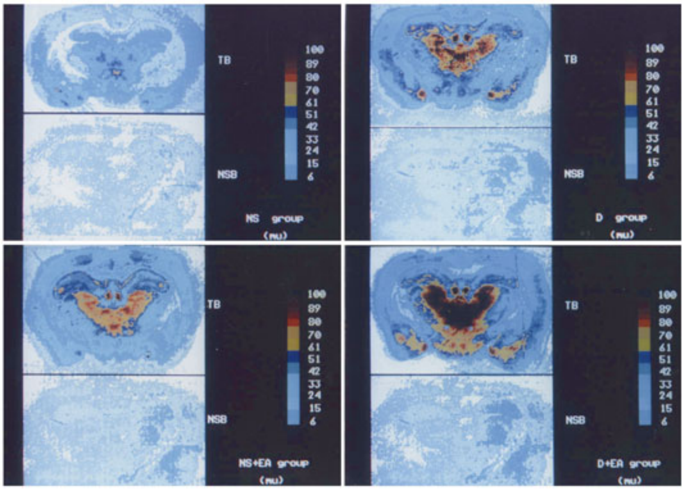

Figure 6.5 Droperidol (Dro) further enhances the EA-induced increase in μ-opioid receptor density. The μ opioid receptor was labeled with 3H ohmefentany (OMF), and the rats were divided into four groups. For Dro + EA group, 10 min after the injection of Dro (1.25 mg/kg, i.p.), EA stimulation was given at Zusanli (ST 36) and Kunlun (BL 60) acupoints lasting for 20 min. For the NS + EA group, normal saline (NS) administration was followed by EA treatment. The rats in the Dro or NS group received i.p. injection of Dro or NS, respectively, as the control. In the autoradiographic images, the red color indicates higher density of the opioid receptors, while the blue indicates lower density. Note that when EA was applied alone (NS + EA), μ like binding sites were significantly increased in the telencephalon (caudate nucleus, accumbens, septum, preoptic area), diencephalon (medial nuclei of thalamus and hypothalamus, reticular nucleus of thalamus, amygdala), and midbrain [periaqueductal gray (PAG), etc.], when compared with the NS group. When Dro was combined with EA (Dro + EA), the increase in μ like binding sites in the abovementioned nuclei was higher than that observed in the EA + NS group. Upper left: NS group; Upper right: Dro group; Lower left: NS + EA group; Lower right: Dro + EA group.

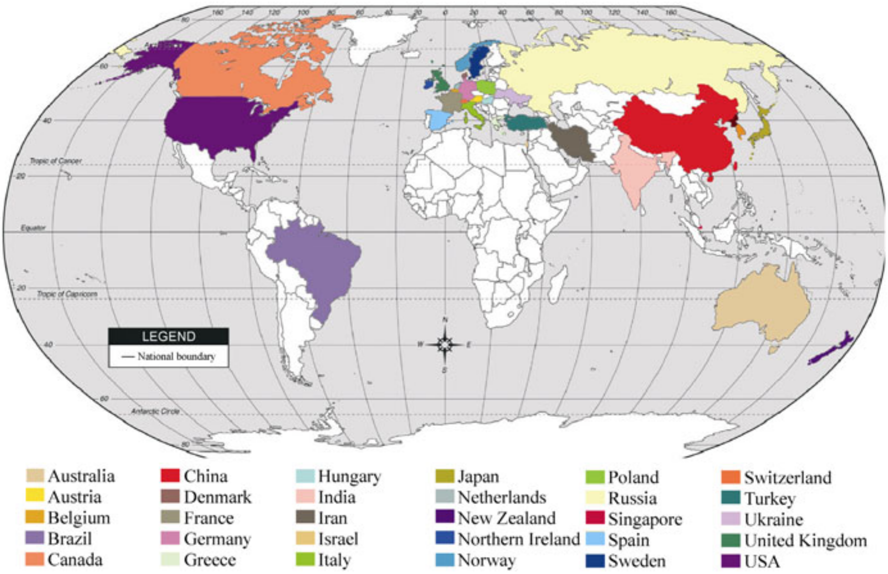

Figure 7.1 Countries where clinical acupuncture is practiced for pain relief. Note that acupuncture analgesia is used in most of the major countries and regions all over the world.

Figure 8.2 Peripheral inflammatory pain model induced by injecting CFA into the hand paw of rats.

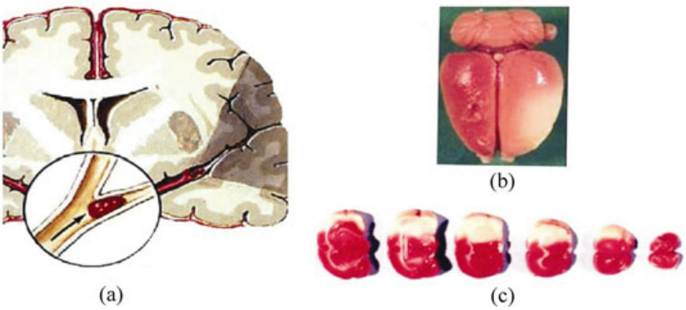

Figure 9.2 Infarction after MCAO. (a), A clot blocks the blood flow of MCA and induces infarction, which is represented by grey color. (b) and (c), Triphenyltetrazolium chloride (TTC) staining after transient MCAO and reperfusion. Infarction is represented by pale white color. (b) shows the whole brain tissue. (c) shows the coronal brain section.

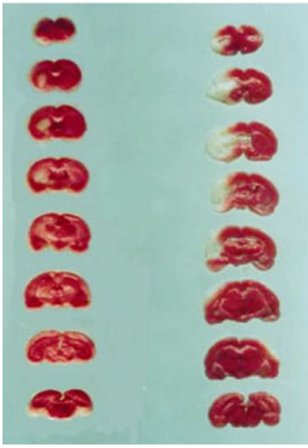

Figure 9.4 The decrease in the ischemic infarction volume after EA treatment. The rat brains were cut into a series of 2 mm thick slices and stained using TTC. Left column, EA plus ischemia (MCAO). Right column, ischemia alone.

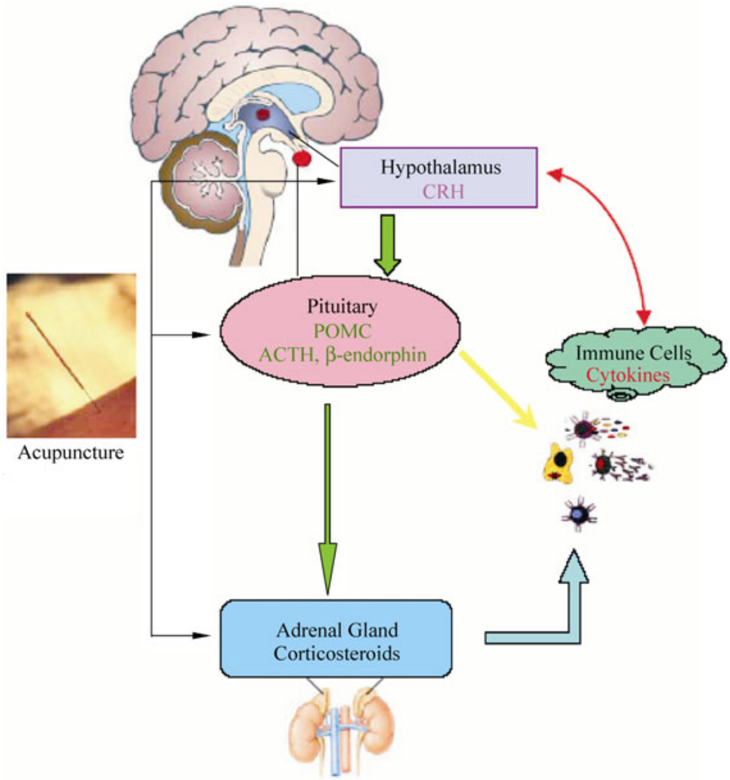

Figure 13.3 Schematic pathways involved in the acupuncture-induced effect on immune system.

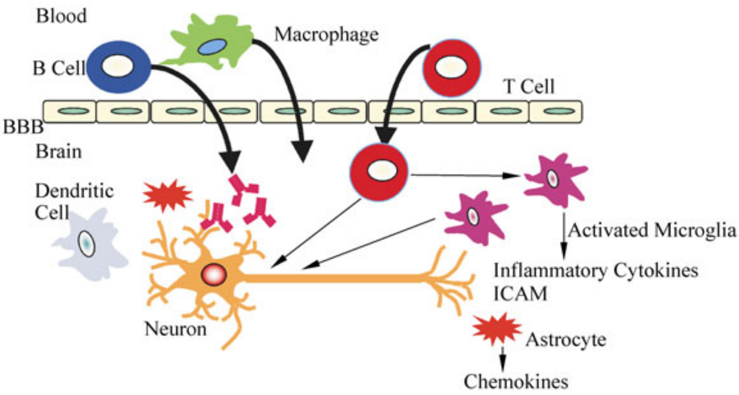

Figure 13.4 Schematic representation of the initiation pathway of immune response within brain. Stimulators like virus, bacteria, dead cells or debris, and toxic central nervous system proteins, could be recognized by the immune competent cells, and subsequently, immune responses are initiated. In this process, proinflammatory cytokines, chemokines, and neurotransmitters are found to be involved.

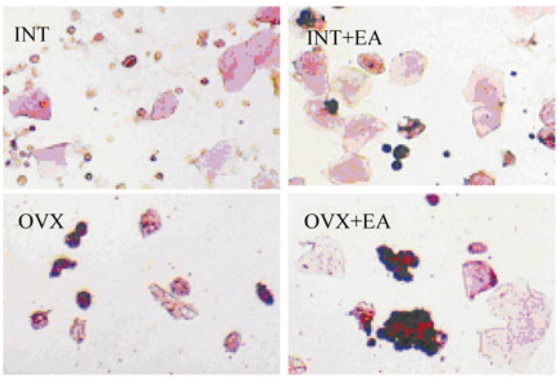

Figure 14.2 Effects of EA on maturation and exfoliation of rat vaginal epithelium × 200. This picture shows the maturation and exfoliation of rat vaginal epithelium with HE staining under optical microscope. Some matured exfoliative epithelium and white blood cells were detected in the vaginal smears of INT rats during preestrus, but no change in the vaginal exfoliative epithelium of INT rats following EA treatment was observed. Some epithelium debris were detected in the vaginal smears of OVX rats 4 weeks after ovariectomy, but the matured, exfoliative epidermic keratinocytes reappeared in the vaginal smears of OVX + EA rats after three successive EA treatments.

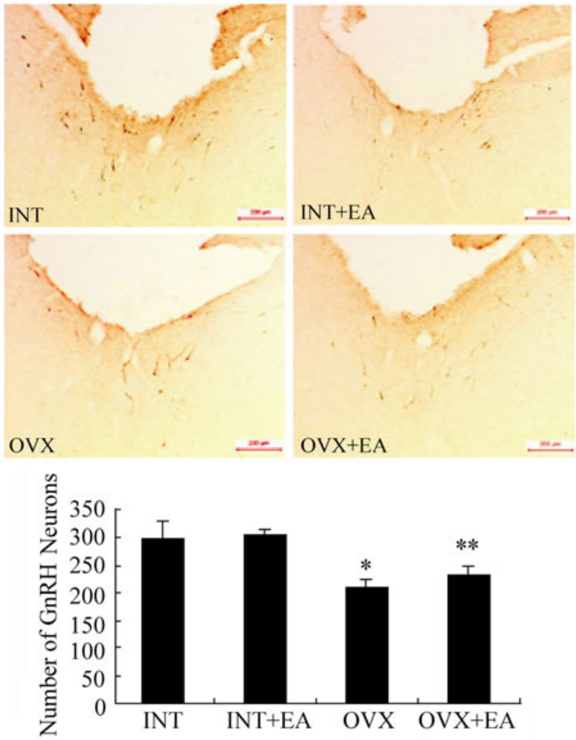

Figure 15.2 The GnRH neurons around organum vasculosum of the lamina terminalis (OVLT) of the INT, INT + EA, OVX, and OVX + EA rats. Female Sprague Dawley rats (180 – 200 g), with regular 4 day estrus cycles were divided into four groups: intact (INT), intact with EA (INT + EA), ovariectomized (OVX), and ovariectomized with EA (OVX + EA). The acupoints employed were Guanyuan (RN 4), Zhongji (RN 3), Zigongxue (EXTRA 22), and Sanyinjiao (SP 6). The stimulation was generated by an EA apparatus and lasted for 30 min (8:00 – 10:00 AM), once a day, total for 3 days. The stimulation parameters were 2 mA of density and a low burst frequency of 3 Hz. The upper picture shows the light micro graphs of the GnRH immunoreactive neurons around OVLT by immunohistochemical method (ABC). The GnRH immunoreactive neurons were detected by the polyclonal antibody. The numbers of GnRH neurons in the all continuous slices was expressed as mean ± SEM ($n = 6$ per group) in each column, indicated in the lower panel. *$p<0.05$ vs. INT and INT + EA; **$p<0.05$ vs. OVX.

Note that EA may modulate the synthesis and release of central GnRH at the molecular level, and also enhance the pituitary GnRH R mRNA level, which may be the central mechanism by which acupuncture regulates the dysfunction of hypothalamic pituitary adrenal axis (HPAA).

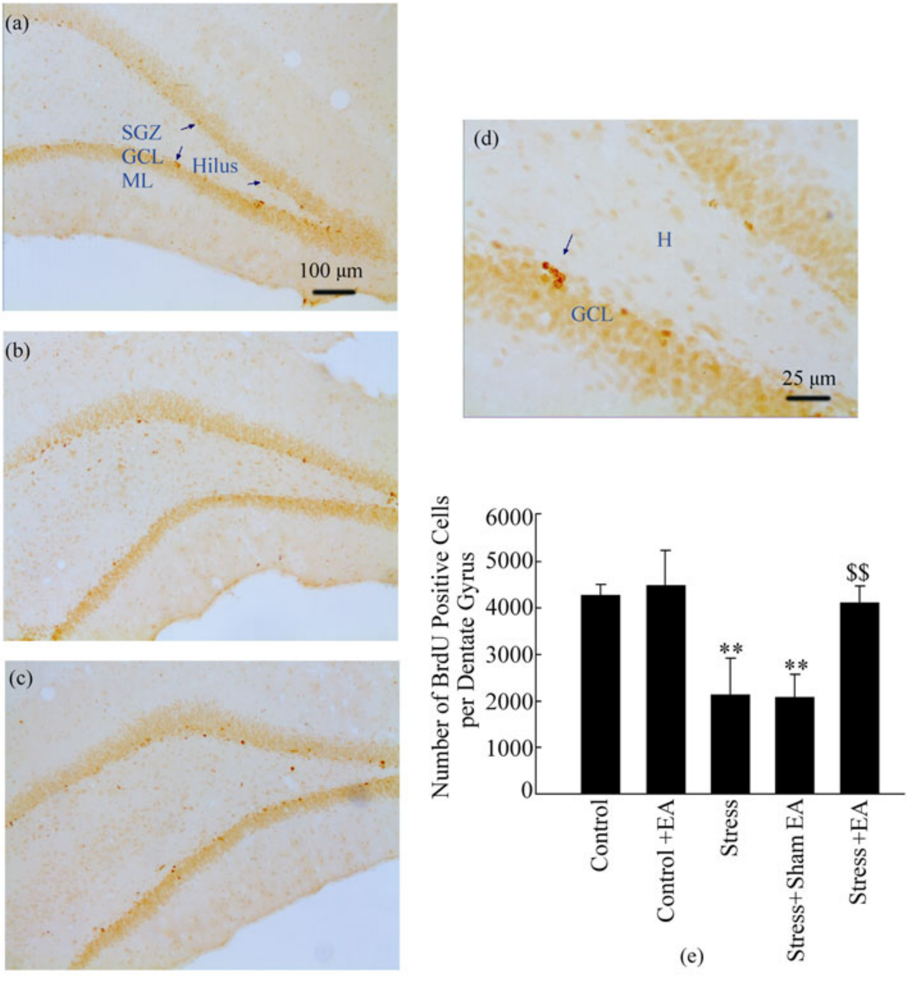

Figure 17.1 EA attenuates the decrease in the hippocampal progenitor cell proliferation in the adult rats exposed to CUS. Panels (a) (b), and (c) are representative photographs showing the distribution of BrdU labeled cells in the hippocampus from the groups of Control (a), Stress (b), and Stress + EA (c). The BrdU labeled cells, as indicated by arrows, appear in pairs or clusters in the subgranular zone (SGZ) of the DG. Under a 40× with a 100× zoom magnification, individual cells in the clusters are clearly visualized (d). The BrdU labeled cells in the SGZ were counted under high magnification. Panel (e) shows the number of BrdU labeled cells in the SGZ of rats. The results are expressed as the estimated mean total number (± SEM). ***p*<0.01 for the stress group vs. the control group; $$*p*<0.01 for the Stress + EA group vs. the Stress + sham EA group.

1 History of Modern Acupuncture Research in China

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Summary This chapter will review the history of modern acupuncture research in China. The concept of "channels" and "collaterals" has been used for a long time in the traditional Chinese medicine (TCM). Clinical acupuncture yields therapeutic effects on many diseases, according to the general principles of "channels" and "collaterals". In the past 5 decades, acupuncture research has been very popular in many major Chinese medical institutions, among which Shanghai Medical College of Fudan University (formerly Shanghai First Medical College, and then, Shanghai Medical University) has made substantial contribution to this field. Comprehensive scientific data obtained from normal subjects, patients, and animals have shown that needling of acupuncture points activates the afferent fibers of the peripheral nerves to elicit the *De-Qi* sensation, and subsequently, the nerve-mediated signals ascend to various levels of the central nervous system (CNS), producing analgesic effect. The pain relief is the most effective outcome of acupuncture treatment. As acupuncture enhances the analgesics' effect of pain relief, the combination of acupuncture with small doses of analgesic drugs is now being adopted in the management of various types of pain and surgical anesthesia. In addition, clinical and bench studies on acupuncture therapy of other neurological diseases, such as epilepsy, cerebral ischemia, neuroimmune disorders, and woman's reproductive disorders have also been successfully carried out in the recent years. This chapter will briefly summarize the research progress and present an overall picture of acupuncture research in China.

Keywords *acupuncture research, traditional Chinese medicine, history, mechanism, progress*

1.1 Acupuncture and Traditional Chinese Medicine

Acupuncture, which originated in China more than 2500 years ago, is an important part of the traditional Chinese medicine (TCM) and is a component of the Chinese health care system. It was brought to the Far East (Korea, Japan, etc.) and Southeast Asia in the sixth century, and subsequently, to Europe and the United States in the seventeenth and the nineteenth centuries.

According to the ancient Chinese literature (the *Suwen* of *Neijing*), early in the primitive society, the primitive stone needle (*bian*) was employed to treat diseases. With the development of productive forces, bone and bamboo needles appeared. However, after the invention of metal-casting techniques and metal tools, people began to use metal medical needles made of bronze, iron, gold, and silver. At present, stainless steel needles are widely adopted for the treatment (Qian 1986).

By the time of the Spring and Autumn Period and the Warring States (770 – 221 BC), the theory of *Jingluo* (channels and collaterals) was established. The ancient classic *Huangdi Neijing* (Yellow Emperor's Classics of Internal Medicine) provides a systematic illustration of the points of the channels and collaterals, as well as the theory and methods of acupuncture and moxibustion. The book *Zhen-jiu Jiayijing* (A – B Classic of Acupuncture and Moxibustion), a classic on acupuncture and moxibustion, was compiled between AD 256 and 260. This book consists of 12 volumes with 128 chapters, depicting 349 acupoints. It describes the locations, indications and manipulations of these points, manipulating techniques and the precautions of acupuncture and moxibustion, and the treatment of common diseases by acupuncture and moxibustion. It is the earliest and the most complete book on acupuncture and moxibustion, and also one of the most influential works in the history of acupuncture and moxibustion.

From the third century to the end of the nineteenth century, new developments took place in the Chinese acupuncture and moxibustion. On one hand, the number of acupuncture points used for treating various diseases greatly increased, and in classification, the "points of the 14 channels" appeared. On the other hand, from the past practice, many vital points were determined, such as *Wushu, Shumu, Sizong,* and the 12 points used by Mandayang. In particular, the variation of the modes of needling was obvious. Furthermore, the use of filiform needles was a significant development. The theory of acupuncture and moxibustion was continuously enriched and raised to a higher level. In the fourth century, *Yancetu,* the chart showing the locations of the acupuncture points, was developed, while the ninth century ushered in the blockprinted edition of books on acupuncture and moxibustion. Subsequently, the printed wall-chart illustrating the acupuncture points made its appearance in the seventeenth century.

In 1882, acupuncture and moxibustion faculties in the Imperial Medical College were disbanded by the Qing Dynasty that disdained these medical arts. Further, in 1840, with the invasion of China by the United Kingdom in the wake of the Opium War, western medicine was introduced in China, shoving the TCM to the background. In addition, under the reign of the *Kuomintang* government, orders were issued to forbid the practice of TCM, and consequently, the development of TCM was inhibited. However, being simple, effective, and rooted in the masses, the practice of acupuncture and moxibustion still prevailed among the people.

Since the establishment of the People's Republic of China, the science of acupuncture and moxibustion has developed vigorously because of the implementation of the policies for TCM. Therapy using acupuncture and moxibustion has been extensively popularized in China. On the basis of the several hundred points already in use, many new ones have been discovered in practice, and new methods of acupuncture and moxibustion have been developed. The methods of acupuncture mainly include needling with filiform needles, electro-needling, auricular needling, scalp needling, heat needling, warming needling, skin needling, point injection of a small amount of drugs, needle retention, point ligation, point ultraviolet light radiation, point iontophoresis, point laser stimulation, point ultra-sound stimulation, point magnetotherapy, etc. The advent of these new points and new techniques has played a very important role in widening the scope of the application of acupuncture and moxibustion, as well as in improving the results of the therapy.

Since the 1950s, the science of acupuncture and moxibustion has become popular in the international communities. Many countries have sent their doctors to China to learn acupuncture and moxibustion. Particularly, after 1971, when China proclaimed the achievements of acupuncture anesthesia, it evoked strong repercussions in the medical field of foreign countries, and a great upsurge in the study and research on acupuncture, moxibustion, and acupuncture anesthesia was witnessed. Since 1975, at the request of the World Health Organization (WHO), the International Acupuncture Training Courses have been offered in Beijing, Shanghai, and Nanjing, which train acupuncturists from various countries (Lu et al. 1990).

1.1.1 The Channels and Collaterals

The theory of channels and collaterals deals with the courses and distributions, physiological functions, pathological changes of the channels and collaterals of the human body, and their relations to the *zang-fu* organs. It is one of the important components of TCM (Lu et al. 1990). The channels and collaterals are comprehensively termed "*Jingluo*" in TCM. The channels, meaning paths, are the main trunks that run longitudinally and interiorly-exteriorly within the body; while the collaterals, meaning networks, that are thinner and smaller than channels, are the crisscross branches that run over the body.

Based on the theory of TCM, the channels and collaterals pertain to the *zang-fu* organs interiorly, and extend to the extremities and joints exteriorly, integrating the *zang-fu*, tissues, and organs into an organic whole, by which diseases are cured mainly by means of adjusting the relationship between *Yin* and *Yang*, promoting the communication between the channels and collaterals, regulating the vital energy (*Qi*) and blood, reinforcing positive factors, and eliminating negative ones. From the viewpoint of western medicine, the principle action of acupuncture and moxibustion is to regulate the function of the human body and increase its resistance against diseases (e.g., enhancing immunity and the antiphlogistic, analgesic, antispastic, antishock, and antiparalytic ability of the body) (Qian 1986). In practice, the channel tropism by signs symposiums differentiation, the corresponding channel-point selection, reinforcement and reduction, etc., are all based on the theory of channels and collaterals (Lu et al. 1990).

1.1.2 Acupoints

Acupoints are the sites through which the *Qi* and *zang-fu* organs and channels are transported to the body surface. Acupoints fall roughly into 3 categories: acupoints of the 14 channels, extraordinary points, and Ashi points, which are described as follows (Lu et al. 1990).

Acupoints of the 14 channels, also known as the "regular points," are distributed along the 12 regular channels and the *Du* (Governor Vessel) and the *Ren* (Conception Vessel) Channels, which are the major part of the acupoints. Extraordinary points are those with regular names and regular locations, but are not among the above-mentioned 14 channels. *Ashi* points are also called tendor spots. *Ashi* points have no specific names and definite locations, and the tender spots and other sensitive spots are the places for needling and moxibustion.

The clinical practice has gained solid evidence to prove the therapeutic properties of the acupoints. Interestingly, needling certain points may bring forth biphasic beneficial regulation on a variety of functional abnormalities of the body. For instance, puncturing Tianshu (ST-25) is considered to provide relief from both diarrhea and constipation (Lu et al. 1990).

1.1.3 General Principles of Acupuncture Treatment

Clinical observations on acupuncture and moxibustion have shown that the two methods are fairly effective in the treatment of many diseases. In fact, ancient medical classics suggest that doctors should treat diseases according to the principles of acupuncture treatment.

1. Regulating the *Yin* and *Yang*

Regulation of *Yin* and *Yang* is a fundamental principle in clinical acupuncture. According to the theories of TCM, diseases result mainly from relative imbalance of *Yin* and *Yang*, i.e., *Yang* in excess (or deficiency) or *Yin* in excess (or deficiency). The mechanism of acupuncture treatment lies in regulating the *Yin* and *Yang*, which brings the body back to the physiological state of "*Yin* and *Yang* in equilibrium" and cures the patient.

2. Strengthening the body resistance and eliminating the pathogenic factors

According to the theories of TCM, *Xu* (the insufficiency or asthenia) indicates the insufficiency of genuine *Qi* (including the body resistance), while *Shi* (the excess) indicates the exuberance of pathogenic *Qi* (or pathogen). "In acupuncture therapy, the insufficiency should be made up and strengthened while the excess should be relieved", which clearly points out the principle of "strengthening the body resistance and eliminating the pathogenic factors" in clinical treatment (the first chapter of *Miraculous Pivot*). By employing different manipulations of acupuncture or moxibustion and the autoregulation mechanism, strengthening of the body resistance and elimination of the pathogenic factors can be achieved in clinical treatment.

Therefore, for a patient with excessive-heat syndrome, superficial puncture to cause bleeding is often used for eliminating excessive heat, while for a patient with asthenic-cold syndrome, the reinforcing method, such as retaining the needle for a long period or applying moxibustion for restoring *Qi* and dispelling cold, is often employed. However, for a patient with intermingled insufficiency and excess syndrome, reinforcing and reducing methods are used simultaneously.

3. Distinguishing the primary from the secondary

The conceptions of the primary fundamental and secondary incidental are relative to each other, involving different meanings. For instance, the genuine *Qi* is the primary, and the pathogenic factor is the secondary; the etiology is the primary, and the manifestation is the secondary; and the original disease is the primary, while the consequent disease is the secondary. This concept represents the two opposite aspects of one entity during the course of a disease. The incidental is generally the phenomenon and the secondary aspect of a disease, while the fundamental cause is normally the nature and the primary aspect of a disease. Under general circumstances, the principle is to treat the incidental first when it is acute or emergent, and subsequently treat the fundamental later, when the course becomes insidious or gradual. However, if the incidental and the fundamental are both emergent, then they must be treated at the same time. In acupuncture treatment, a disease should be assessed according to different conditions, such as the primary, secondary, root cause, symptoms, acute, and chronic, so as to determine the principle of the treatment (Lu et al. 1990).

1.2 Modern Developments in Acupuncture Treatment

Though acupuncture has been used to treat many diseases, the pain relief is the most effective in the history of acupuncture. The ability of acupuncture to inhibit pain is referred to as "acupuncture analgesia"(AA). Based on AA, acupuncture anesthesia on thyroidectomy was developed in 1958 at the First People's Hospital in Shanghai. Apart from Shanghai, doctors in other cities of China, such as Xi'an, Wuhan, and Nanjing, carried out operations such as tooth extraction, detachment of retina, thyroidectomy, and appendectomy using acupuncture anesthesia in the same or the subsequent year. In 1960, the First Tuberculosis Central Hospital in

Shanghai succeeded in applying acupuncture anesthesia to pneumonectomy. Subsequently, many other major and difficult operations (such as surgery on the anterior cranial fossa, total laryngectomy, cardiac surgery, cholecystectomy, subtotal gastrectomy, pan-hysterectomy, cesarean section) were also carried out using acupuncture anesthesia between 1960s and 1970s, which showed satisfactory results (Zhang 1989).

However, during that period, acupuncture failed to produce sufficient analgesia during operation, although it had prominent analgesic effect and could be used in many surgical operations. It was found that the shortcoming of acupuncture anesthesia could be overcome by combining acupuncture with certain drugs (Xu et al. 1989). Acupuncture combined with selected drugs to fulfill the requirement of anesthesia is termed as acupuncture-balanced anesthesia, which is a type of balanced anesthesia (Cao 1997).

Scientific advances in AA research have promoted the use and development of acupuncture worldwide. Although the Chinese medicine, as a part of the Chinese culture, came to the United States in 1836, acupuncture was not officially recognized until 1972, when President Richard M. Nixon brought acupuncture back to the United States from China. In June 1971, James Reston, the Director of the Washington Bureau of *The New York Times*, who was a gifted reporter and writer, was sent by the *Times* to China, prior to the official visit by Nixon. During his visit in Beijing, he suffered an acute attack of appendicitis. His appendectomy was performed under conventional chemical anesthetics, while his post-surgical complications were treated by acupuncture. Twenty minutes after acupuncture treatment, he felt a noticeable relaxation of the pressure and distension within an hour, and no recurrence thereafter. On July 26, 1971, Reston published his famous essay titled, *Now, About My Operation in Peking,* in the *Times*, in which he reported his personal experience about acupuncture in China (Reston 1971). Most Americans deeply trusted what he wrote. In addition, Schwartz reported, "Acupuncture: The Needle Pain-Killer comes to America" and "Nothing in the American discovery of China has excited the popular imagination more than acupuncture anesthesia" (Schwartz 1972; Li and Singer 2006). Liao et al (1994) pointed out that "Since the late 1960s and early 1970s, well-designed laboratory studies, initiated in China, confirmed the effectiveness of AA. The discovery of a relationship between acupuncture analgesia and neurochemicals, particularly endorphins, was exciting indeed, and began to provide a scientific basis for understanding its mechanism".

For achieving the goal, "health for all by the year 2000", the WHO, in 1979, listed 43 kinds of indications that may benefit from the use of acupuncture and/or moxibustion.

The Consensus Development Conference (CDC) on Acupuncture held by the National Institutes of Health (NIH) in 1997 evaluated the scientific and medical data on the uses, risks, and benefits of acupuncture procedures for a variety of conditions. The statement of CDC on acupuncture suggested that acupuncture is effective for some diseases, such as adult post-operative and chemotherapy nausea and vomiting, some painful diseases, addiction, stroke rehabilitation, and asthma. One of the advantages of acupuncture is that the occurrence of adverse side effects is extremely low. Findings from basic research have begun to elucidate the mechanisms of action of acupuncture (National Institutes of Health 1997). Both the NIH and WHO have issued statements confirming the usefulness of acupuncture in the treatment of a wide variety of conditions, and the establishment of the World Federation of Acupuncture and Moxibustion. Currently, the practice of acupuncture is spread over 160 countries and regions. In brief, acupuncture research is one of the rare fields that has influenced the western science and technology.

1.3 Acupuncture Research at Shanghai Medical University

Acupuncture research with modern scientific techniques commenced in China in the 1950s. As a top Chinese medical institution in China, Shanghai First Medical College (later Shanghai Medical University; now Shanghai Medical College of Fudan University) made significant contributions to the mechanistic exploration of acupuncture. Using neurophysiological, neuropharmacological, neurobiochemical, and neuromorphological methods, scientists in the institution initiated several important studies on AA effects and the underlying mechanisms in normal subjects, patients, as well as animal models, since 1958. As all the research papers before 1972, were published in Chinese internal publications, a brief introduction to the major contributions made by our institution is presented in the following section.

1.3.1 Relationship Between the Meridian-Points and Peripheral Nerves

Immediately after the application of acupuncture anesthesia to thyroidectomy in 1958 in Shanghai, the teachers from the Departments of Anatomy and Histology dissected 324 points of the 12 meridians and Conception Vessel meridian from 8 adult cadavers, where 49 detached the upper extremities and 24 detached the lower extremities, from 1958 to 1960, to explore the relationship between channels or acupoints and nerves. They found most of the points, except the *Qugu* (CV-2) point (323 out of 324) that could be located by the naked eyes on the nervous structure, either on the branches of the cranial or the spinal. Under the microscope, CV-2 was also found to be related to the nerve endings. This was the first direct evidence that all the meridians where the points were lying could be traced to certain peripheral nerves. They also found that (1) the nerve supply of acupoints and the related viscera could be traced to the same spinal segment or around that segment; and (2) each pairs of “*Yin*” and “*Yang*” or “Outer” and “Inner” meridians could be located at the same spinal segment, communicating with different side branches, overlapping or anastomosing (Zhou et al. 1979).

Please refer to Chapter 2 and Appendix for more information on the relationships between meridian-acupoints and peripheral nerves.

1.3.2 Acupuncture Analgesia and Acupuncture Anesthesia

The achievements of acupuncture anesthesia on patients attracted great attention from many medical doctors and researchers, and therefore, the early studies mostly focused on the mechanisms of acupuncture-induced analgesia and acupuncture anesthesia.

1.3.2.1 Effect of acupuncture on pain perception on normal subjects

1. Effect of acupuncture on normal volunteers

In 1965, Professor Fengyan Xu of our institution (Shanghai First Medial College) initiated the investigation of the mechanism underlying AA, and personally experienced the sensation of needle acupuncture on himself. A large-scale study was carried out with our medical students and teachers (totally 624 people/times) at the beginning of 1965. The changes in the pain threshold and pain-tolerance threshold were measured from 41 classical points of the body surface before and during acupuncture. About 29 unilateral and 10 pairs of classical needling points were studied, each from 16 subjects (Department of Physiology, SMU et al. 1973a). The results showed that the manual twisting of the needling point separately could elevate the pain and pain-tolerance threshold in most of the subjects. Among the 17 points of *Yang* channels tested, Hegu (LI-4) point was the most effective, while among the 12 points of *Yin* channels tested, Gongsun (SP-4) point was the most effective. Simultaneous stimulation of the bilateral points was observed to induce better effect than that of unilateral needling. The effectiveness of AA was significantly different among different subjects, i.e., individual variation in AA existed. The study of the time course showed that 20 min, instead of 60 min, is sufficient for the induction. After the cessation of acupuncture, the acupuncture effect characterized by the increase in the pain threshold, gradually disappeared, suggesting the involvement of neurohumoral mechanism in AA.

2. Effect of sham acupuncture on normal subjects

In 1976, the Institute of Physiology, Shanghai Academy of Sciences, collaborated with us and performed another set of experiments on young volunteers (aged 20 – 26 years; medical students and teachers). Each of these subjects participated in 3 kinds of studies randomly ordered: (1) complete rest; (2) acupuncture with needle inserted into Hegu (LI-4) point and twisted manually at the beginning, and then operated by a mechanical manipulator instead of manual maneuver; and (3) sham acupuncture. In the sham acupuncture, the conditions were similar to those of true acupuncture, except that after the subject had the needling-feeling, the needle was drawn out swiftly without the subject being aware of the needle being pulled out, while the mechanical manipulator was kept running with its rhythmic noise within the subject's hearing range and its rhythmic wave displayed on the screen (Jiang et al. 1978). The data were analyzed using sensory decision theory. The results showed that the sensory discrimination between faint pain and pain or between touch and faint pain was significantly decreased when subjected to acupuncture (Study 2). At the same time, the verbal report criteria of both faint pain and pain were also markedly elevated. In contrast, these changes were not found in the same subjects during rest (Study 1) or when exposed to sham acupuncture (Study 3). These data indicate that the analgesic effect of acupuncture does have its physiological basis, but not necessarily the psychological basis.

1.3.2.2 Clinical features of acupuncture anesthesia on patients

The clinical observations on patients during pneumonectomy under acupuncture anesthesia from 1964 to 1966 at the First Tuberculosis Central Hospital in Shanghai, as well as on patients during brain surgery from 1972 to 1974 at Hua Shan Hospital of Shanghai First Medical College, showed no abnormal changes in the EEG and ECG readings, and no significant changes in knee jerk, tender jerk, touch sensation, and taste sensation. Furthermore, the changes in blood pressure, pulse rate, and respiratory movements were to lesser extent than those under general anesthesia. However, there were marked changes in the pain threshold, pain-tolerance threshold, galvanic skin reflex (GSR) (Fig. 1.1, Table 1.1), finger plethysmogram, and skin temperature (Fig. 1.2) measured at the palm and fingers. Further studies indicated that acupuncture could elevate the pain threshold, warmth threshold, and pain-tolerance threshold; however, only the pain-tolerance threshold correlated well

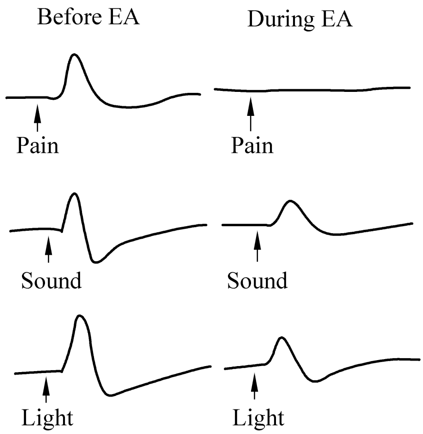

Figure 1.1 Inhibitory effect of acupuncture on galvanic skin reflex (GSR). Note that GSR could be elicited by a ring, flash, or pinch on the skin of the arm and can be greatly depressed by EA.

Table 1.1 Inhibitory Effect of Acupuncture on GSR

Stimuli	No. of Cases	Amplitude of GSR	
		Changes in amplitude (mV)	***T* Test**
Pain	22	−2.00 ±0.31	p<0.001
Sound	21	−2.06 ±0.32	p<0.001
Light	22	−1.74 ±0.27	p<0.001
Control	18	+0.16 ±0.38	p>0.05

Note that GSR elicited by pain, sound, or light stimuli was reduced by EA, but no significant changes were observed in the control group without EA.

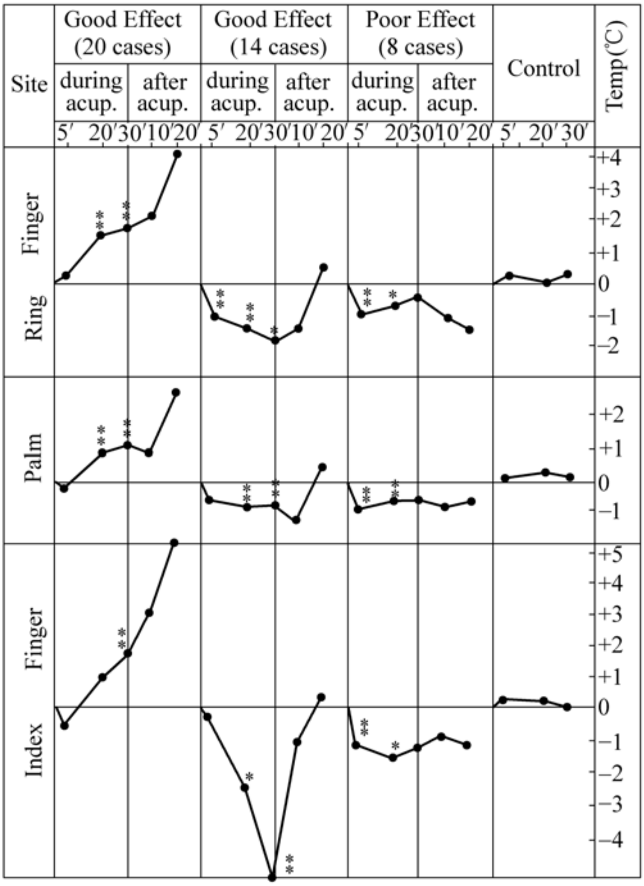

Figure 1.2 Effect of acupuncture on the skin temperature of index finger, palm, and ring finger. The study was performed on 47 patients for brain surgery and 9 normal subjects. Ordinate: Changes in temperature; Abscissa: Time (min); *p<0.05; **p<0.01.

with the efficacy of AA, suggesting that the limbic system might play an important role in AA. Furthermore, we also noticed individual variation in AA: patients with high pain-tolerance threshold, increased skin temperature, and inhibition of pain responses in finger plethysmogram and GSR during acupuncture might experience a good analgesic effect (Department of Physiology, SMU et al. 1973b). These observations suggest that acupuncture is able to inhibit the functional activity of the sympathetic nervous system (Cao et al. 1983).

The patients were divided into 3 groups according to their responses to acupuncture. In Group A (far left), the skin temperature showed a constant rise during acupuncture stimulations in 20 cases, and all these patients responded very well to acupuncture during operations. In Group B (to the right of Group A), the skin temperature dropped at the early period of acupuncture, then went up after 20 min of acupuncture in 13 cases, and these patients also experienced a good acupuncture-analgesic effect. Group A + Group B comprised 70.21% of the total patients. In Group C (to the right of Group B), the skin temperature constantly decreased after acupuncture in 14 patients (29.79%), who demonstrated poor acupuncture-analgesic effect. The Control Group (far right) comprised the data of 9 normal subjects without EA.

1.3.2.3 Neurohumoral mechanism of acupuncture analgesia

After studying the clinical features of acupuncture anesthesia on patients, many experiments have been performed in the institution to address the underlying mechanism.

1. Peripheral neuropathway of acupuncture feeling

Studies on animals. As acupoints are closely linked to the nerves, it is necessary to determine the kinds of nerve fibers that are activated by acupuncture. It was found that needling of acupuncture point could activate A-β (type Ⅱ) and A-δ (type Ⅲ) afferent fibers of the peripheral nerves, to elicit *De-Qi* sensation and produce AA (Chiang et al. 1975; Lu 1983). In consistence with this notion, Pomeranz and Paley (1979) also found that type Ⅱ afferent fibers were sufficient to produce AA. However, our researches found that an excessive, high-intensity electro-acupuncture (EA) stimulation may cause stress analgesia, which is different from AA (Zhang et al. 1979).

Studies of acupuncture feeling (*De-Qi*) on patients. When needling an acupuncture point, a feeling of soreness, numbness, heaviness, and distension may be immediately elicited, which is termed as "*De-Qi*" in TCM.

The needling sensation (*De-Qi*) was reported by patients in our affiliated hospital (Hua Shan Hospital), and at the same time, the myoelectric potentials (EMG) led from the points also represented the needling sensation. The needling sensation of 168 affected points was compared with that of 131 normal points in 76 patients with various neurological diseases (Department of Physiology, SMU et al. 1973c; Chen et al. 1986). It was found that in patients with complete brachial plexus and spinal transectional lesions, the needling sensation was absent at all points in the affected regions (Fig. 1.3); in patients with infantile paralysis sequelae involving spinal motor neuron, the acupuncture feeling was normal (Fig. 1.4); in patients with Syringomyelia involving anterior commissure or posterior horn in the spinal cord, the needling sensation was markedly weakened or completely absent in such points with pain and thermal deficits (Fig. 1.5); whereas in patients with deep sensory deficits such as Tabes dorsalis involving posterior column of the spinal cord, the needling sensation was felt at all the affected points, but the after effect of the needling sensation disappeared quickly (Fig. 1.6). These results indicate that the

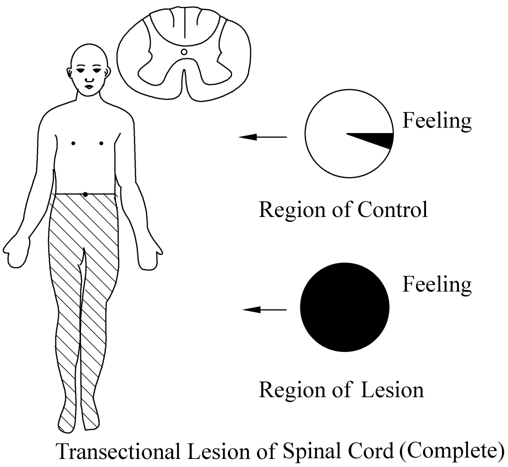

Figure 1.3 Patient with transectional lesion of spinal cord (complete).

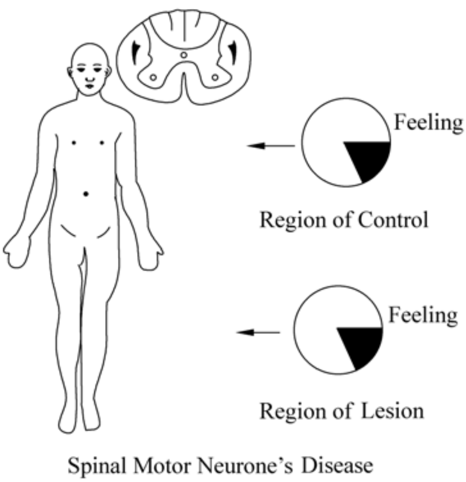

Figure 1.4 Patient with spinal motor-neuron disease such as infantile paralysis sequelae.

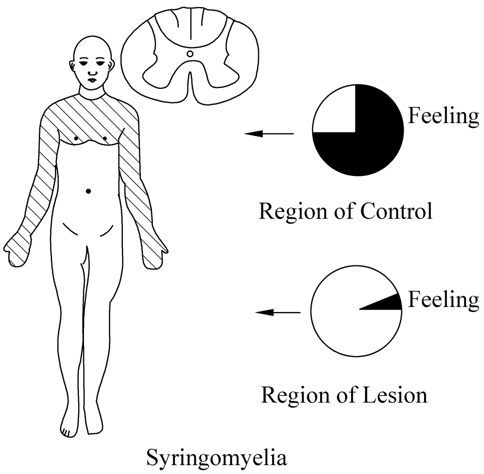

Figure 1.5 Patient with Syringomyelia involving anterior commissure or posterior horn in the spinal cord.

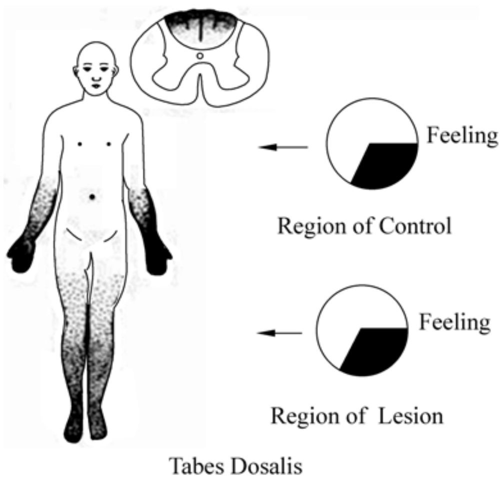

Figure 1.6 Patient with deep sensory deficits such as Tabes dorsalis involving posterior column of the spinal cord.

needling sensation and acupuncture effect are closely related to the functional integrity of the pathway conducting pain and temperature sensation. The impulses of needling sensation were observed to ascend mainly through the ventro-lateral funiculi, which conduct pain and temperature sensation upward to the brain.

2. Central neuromodulatory mechanism of acupuncture analgesia

Based on the experimental studies, Chang (1973) indicated that the analgesic effect is essentially the result of interaction between the afferent impulses from the region of pain and those from the point of acupuncture. By stimulating and/or destroying some brain nuclei, using microinjection of some agonists or antagonists of the neurotransmitters or opioid peptides individually, and employing electrophysiological methods to record the unit discharges of neurons, these interactions were observed to take place at different levels in the central nervous system (CNS).

Our experimental studies of the role of caudate nucleus (CN) in AA showed that the pain threshold of rabbits markedly increased when the dorsal part of the head of the CN was stimulated, when the caudate stimulation accompanying EA brought about a more prominent elevation of the pain threshold. Under caudate lesion, the analgesic effect of the acupuncture was weakened. This indicates that there are similarities between the caudate and EA stimulation (Dept. of Physiology 1973d; He and Xu 1981). In addition, it was also found that the Ach content in the perfusate of the lateral ventricles increased simultaneously with the elevation of pain threshold when the rabbits were needled, exhibiting a significant association between them. The microinjection of the cholinergic blocker, scopolamine, into the CN of the animals reduced the pain threshold, raising the effect of needling and demonstrating a block of various degrees. Thus, a cholinergic mechanism may possibly take an active part in AA.

In clinical observations, it was found that the caudate stimulation through chronic implanted electrodes resulted in alleviation of intractable pain in patients, caused by late malignancies. Furthermore, the clinical observations also showed that EA or caudate stimulation could relieve intractable pain. The Ach content in the cerebrospinal fluid (CSF) of the lateral ventricles of the patients was observed to increase with the onset of analgesia (Acupuncture Anesthesia Coordinating Group, Hua Shan Hospital of Shanghai First Medical College 1977; Chen et al. 1982).

Thus, the abovementioned clinical and animal experiments demonstrated that the afferent impulses arising from the acupuncture point, traveling along the ventrolateral funiculi of the spinal cord, reaching the CNS, activated the antinociceptive system including certain brain nuclei (CN, periaqueductal gray, N. raphe, etc.), modulators (opioid peptides), transmitters (5-HT, Ach, etc.), through the descending inhibitory pathway resulting in analgesia (He 1987).

1.3.2.4 Endogenous opioid peptides and acupuncture analgesia

1. Release of endogenous opioid peptides by acupuncture

Since 1975, we have been studying the interrelation between the endogenous opioid peptides (EOP) and AA. The measurement of the EOP levels in the CSF is a potential approach to evaluate their release from the brain to CSF.

Our group was the first to observe that in the patients with brain tumor at Hua Shan Hospital, Shanghai First Medical College, EA at the bilateral Hegu (LI-4) point increased the content of β-endorphin-like immunoreactive substances in the ventricular CSF (Fig. 1.7) (Acupuncture Anesthesia Research Coordinating Group, Shanghai First Medical College 1978; Pan et al. 1979; Zhang et al. 1980; Chen and Pan 1984). There was a linear correlation between the percentage increase of β-endorphin-like immunoreactive substances and the pain threshold or pain-tolerance threshold of the patients.

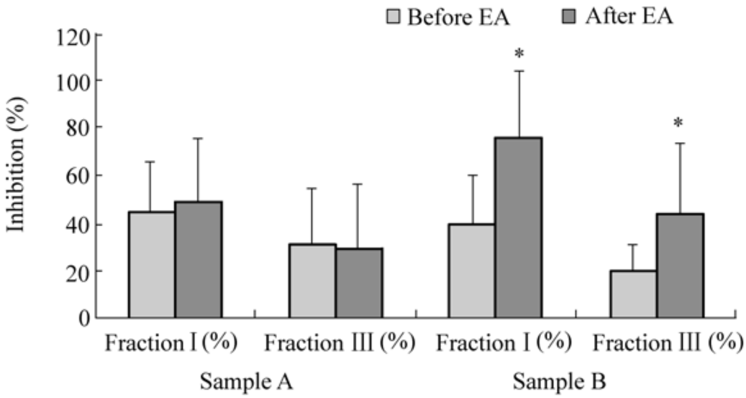

Figure 1.7 The levels of morphine-like substances in human CSF before and after EA. Sample A: The CSF was collected immediately after draining the patient. Sample B: The CSF was collected one day after draining the patient. Ordinate: percent change in competitive binding inhibition. *$p<0.05$ vs. before EA. Note that the content of morphine like substances increased in human CSF after EA at LI 4 point. This work was done in 1975.

Xi and Li (1983) and Li et al (1984) found that the serum levels of morphine-like substances in patients with chronic pain were lower than those in healthy pain-free subjects. The EA was observed to raise the serum morphine-like substances to normal level in patients demonstrating good acupuncture effects, but not in those showing poor effects.

In laboratory, using push-pull perfusion techniques and radioreceptor binding assay, a marked increase of endorphin was observed in fraction I in the perfusate of the periaqueductal gray after EA of Hegu (LI-4) and Waiguan (TE-5) points, and the release of endorphin was observed to be related to the analgesic effect of the acupuncture (Zhang et al. 1980).

2. Antagonism of acupuncture analgesia by naloxone

Reversal by narcotic antagonists is a necessary condition for characterizing an analgesic manipulation as narcotic.

Zhang et al (1979) observed that i.v. administration of 0.4 mg/kg of naloxone markedly antagonized the analgesic effect of the moderate-strength EA, but failed to antagonize the superstrength EA, on the rabbit model. This observation suggests that the analgesic effect of moderate-strength EA stimulation results, at least partially, from the activity of opiate receptors, and its mechanism differs, at least in some aspects, from the superstrength EA producing "stress analgesia", which may not be suitable for conscious patients.

3. Effect of orphanin FQ on acupuncture analgesia

Our research was the first to demonstrate that orphanin FQ (OFQ) (a newly discovered 17-amino acid neuropeptides) has an obvious dose-dependent effect in antagonizing AA, which is different from other EOP members, such as enkephalins, endorphins, and dynorphins. The OFQ might play its antagonistic role via activating OFQ receptors, as the blockade of OFQ receptor synthesis with antisense oligonucleotide (ASO) completely abolished the OFQ-induced anti-AA effect (Zhu et al. 1996).

The abovementioned clinical and laboratory results indicate that the EOP participate in AA from the presynaptic level to the receptor sites. Furthermore, the studies on EOP release and antagonist injections show that the EOP are closely related to AA.

1.3.2.5 Combination of acupuncture with therapeutic drugs

Substantial evidences have been accumulated which demonstrate that acupuncture has prominent analgesic effect. Acupuncture anesthesia has a scientific foundation and presents certain advantages in surgical operations. However, although acupuncture plays its analgesic role via activating the endogenous pain-modulating system, it fails to induce sufficient analgesia during operation. This limitation has hindered the widespread use of acupuncture anesthesia in clinical surgery, and is a primary shortcoming of this technique. From numerous studies, researchers have found that the this limitation can be overcome by combining acupuncture with certain drugs, i.e., the combination of acupuncture with small doses of analgesics (epidural or local ones) or non-analgesics (such as metoclopramide) may achieve a better result (Xu et al. 1989). We also found that metoclopramide not only produces antiemetic effect, but also analgesic effect (Xu et al. 1983).

1. Selection of drugs affecting acupuncture analgesia

Using animal models, the commonly used clinical drugs were screened and classified into three main categories according to their effect on AA (Xu et al. 1989).

(1) Drugs potentiating AA effect. These include agonists of opioid receptors (fentanyl, pethidine); antagonists of dopamine (DA) receptors (droperidol, haloperidol, perphenazine); and 5-HT releaser (fenfluramine).

These drugs also include those targeting the central neurotransmitters, such as anticholinesterase and antidopamine drugs (metoclopramide), which are clinically used as antiemetic drugs. For example, both laboratory and clinical results show that metoclopramide enhances AA. Tetrahydrocannabinol, which can bind to the μ-opioid receptor and inhibit the synthesis of DA and norepinephrine (NE), is also observed to potentiate AA. In addition, paired drugs (e.g., fentanyl + droperidol, fentanyl + metoclopramide, fentanyl + fenfluramine) are observed to induce better effect than individual treatment in terms of enhancing AA (Xu et al. 1989).

(2) Drugs reducing AA effect. These include ketamine（a sigma opioid receptor agonist），diazepam, and chlorpromazine (Xu et al. 1989).

(3) Drugs having no effect on AA. These include sulpiride and phenobarbital (Xu et al. 1989).

Thus, these translational studies may provide useful guidelines for clinical practice in acupuncture.

2. Development of acupuncture-balanced anesthesia

Acupuncture anesthesia was established on the basis of AA. Currently, acupuncture anesthesia is being developed to acupuncture-balanced anesthesia (ABA). The term ABA was recommended by Dr. Jue Wu, a renowned professor of Anesthesiology in China and Dr. Hsiang-Tung Chang, a well-known Chinese neuroscientist. At present, ABA has been successfully used in anesthesia for surgical operations, such as craniocerebral operation, thyroidectomy, neolarynx reconstruction, pneumonectomy, cardiac surgery, subtotal gastrectomy, and renal transplantation (Cao 1997). In surgical operations under ABA, the doses of anesthetics could be reduced by 30% – 45% (Qu et al. 1996; Qin et al. 1996).

In addition, for post-operative analgesia, the combination of acupuncture with drugs was used in patients and animals (Dai et al. 1993). In the clinics, in patients who received cholecystectomy, when EA was combined with epidural injection of morphine (1 mg) after operation, the adverse reactions, such as nausea, vomiting, urinary retention, immunosuppression (Zhang et al. 1996), inhibition of intestinal peristalsis and respiration, produced by morphine were reduced (Du et al. 1994a; 1994b; 1997).

The ABA has demonstrated many advantages in surgical operation as well as postoperative analgesia, through substantial clinical application: it is safer with fewer complications; the blood pressure and pulse rates are more stable when ABA is employed; the effect of surgery can be checked on time to avoid damage to the vital function; and the patients under ABA show a better and faster postoperative recovery, which shortens the period of postoperative hospitalization (Cao 2002).

3. Mechanism of acupuncture analgesia and drugs synergism

Using multidisciplinary techniques, the mechanism of the combination of acupuncture with drugs has been systematically investigated in the past (Zhu et al. 1997b).

Presynaptic mechanisms. The EOP are known to increase after AA. When opioid drugs, such as fentanyl or pethidine are combined with acupuncture, they might enhance each other producing synergistic analgesia. Earlier researches on the EOP release following the combination of acupuncture with droperidol, the DA blocker, demonstrated that the contents of enkephalin and ß-endorphin in perfusate from periaqueductal gray, CN, and preoptic area, were increased significantly after EA for 30 min, which were further enhanced by droperidol (Fig. 1.8) (Zhu et al. 1995a). This result indicates that the EA-induced EOP release can be further promoted by the analgesic drugs.

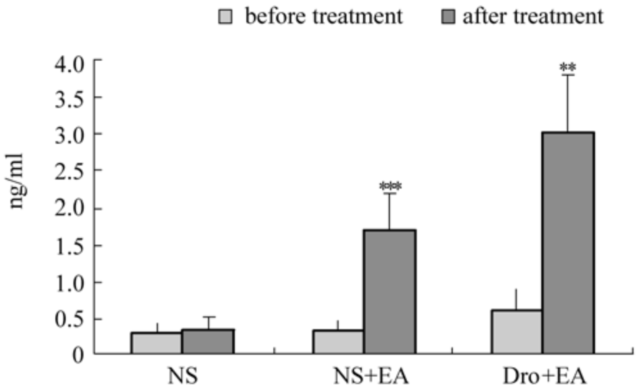

Figure 1.8 Release of EOP in periaqueductal gray during EA and EA plus droperidol (Dro) ** $p<0.01$, *** $p<0.001$ vs. before treatment.

The EOP are derived from prohormones (proenkephalin, proopiomelanocortin, and prodynophin). The studies using in situ hybridization showed that after EA with droperidol, the gene expression of endogenous opioid peptidergic precursors markedly increased. The EA could induce the expression of preproenkephalin (PPE) mRNA and preproopiomelanocortin (POMC) mRNA in many pain-modulation-related nuclei (e.g., CN, amygdala, hypothalamus, and periaqueductal gray in the brain). Furthermore, when EA was combined with droperidol, the expression of PPE mRNA and POMC mRNA was further enhanced (Zhu et al. 1995c). In the spinal dorsal horn, EA enhanced the preprodynorphin (PPD) mRNA expression, and the combination of EA with droperidol further promoted the expression (Zhu et al. 1997a). The abovementioned results suggest that the release of EOP is related to the gene expression of prohormones in the presynaptic processes, which accounts for, at least partially, the mechanism of potentiating the effect of droperidol on AA at the molecular level.

Postsynaptic mechanisms. By using receptor-binding autoradiography and computer-assisted image analysis system, the binding sites of the μ-receptors were observed to increase in most pain-modulation-related nuclei after EA, while EA combined with droperidol was found to further elevate the binding density in these brain regions. These observations indicate that droperidol partly potentiates AA by increasing the density of the opioid receptor (Zhu et al. 1995b).

The abovementioned studies suggest that droperidol further up-regulates the opioid peptidergic system at both presynaptic (EOP release and prohormone gene expression) and postsynaptic (opioid receptors) levels.

Both the laboratory and clinical studies have indicated that some drugs could potentiate acupuncture-induced analgesia with reduced side effect of the drugs. Drugs and acupuncture can help each other to produce a better therapeutic effect, and the combination of acupuncture with drugs represents the integration of Chinese medicine with the western medicine. Joseph Jacobs, a formal director of the NIH Office of Alternative Medicine in USA, and a Yale-trained physician, also appreciated how traditional medicine can effectively be combined with modern methods (Langone 1996). Hence, combination of acupuncture with drugs which represents one of the excellent methods for surgical anesthesia as well as in the management of various pains, with a solid scientific basis, should be widely adopted (Cao 2002).

The details of ABA are presented in Chapter 6 of this book.

1.3.3 Therapeutic Effects and Mechanisms of Acupuncture on Neurological Disorders

Acupuncture therapy has been an effective method for treating some neurological diseases in China for thousands of years.

Our laboratory is one of the first laboratories in China to study the effects of acupuncture on neurological diseases, such as stroke and epilepsy. Since the late 1980s, we have carried out a series of researches on animals about the relationship between the efficacy of EA and some neuroactive factors or neurological events. Our research has provided several lines of new scientific evidence on the new applications of acupuncture in clinic.

1. Acupuncture and epilepsy

Our results indicate that the protective efficacy of EA on epilepsy is dependent on the stimulation parameters and points selected. Using EEG and power spectrum analysis technique, we compared the efficacies of EA among several conditions: (1) same stimulated parameters (frequency and amplitude) with different acupoints (Governor Vessel GV-16 and GV-8 or non-Governor Vessel LI-4 and TE-5); and (2) same acupoints (GV-16 and GV-8) with different frequencies or amplitudes. Our research indicate that acupuncture at Governor Vessel points (GV-16 + GV-8) with high frequency and intensive current could produce better anticonvulsive effect in penicillin-induced epileptic seizure (He et al. 1985).

Our results also suggest that EA might prevent the occurrence of penicillin-induced convulsions if it was performed prior to penicillin injection, which was observed when we performed EA prior to the injection of penicillin on rats. Using power spectrum analysis technique, we investigated the effect of EA on electroconvulsive shock (ECS) and penicillin-induced convulsions on rats. We found that EA suppressed animal convulsions significantly (He et al. 1986a; 1986b; He et al. 1990a).

Apart from the anticonvulsive effect of EA, we experimentally observed that several neuroactive molecules were also affected during and after EA performance against epilepsy. Our results indicate that acupuncture modulation might be related to the excitatory/inhibitory amino acids system, neuropeptidergic system, nitric oxide system, etc.

The EA could inhibit experimental epilepsy by increasing the release of γ-amino butyric acid (GABA), taurine, and glycine, and decreasing the release of glutamate in hippocampus (Wang and Cheng 1994a; Liu and Cheng 1995; Yan et al. 1999). We also found that their receptors including N-methyl-D-aspartic acid (NMDA) (Wang and Cheng 1994a), non-NMDA, and $GABA_A$ (Liu and Cheng 1997) might be involved in the epileptic activity and the antiepileptic effect of EA.

Neuropeptides are a group of neuromodulators. Our research studies showed that neuropeptides, including cholecystokinin (CCK) (Yang et al. 1996), somatostatin (Liu et al. 1998), enkephalin, dynorphin, and various opioid receptors (He et al. 1989; He and Cao 1989; He et al. 1990b; Wang and Cheng 1994b; 1995; Gao and Cheng 1998) were all related to the antiepileptic effect of EA.

Both nitric oxide (NO) and nitric oxide synthase (NOS) were observed to be involved in the epileptic seizures and acupuncture treatment (Wang and Cheng 1997a; 1997b). We found that NO concentration in rat hippocampus increased after penicillin-induced epilepsy (Huang et al. 1999). However, application of acupuncture decreased the NO concentration, with the inhibition of EEG. Furthermore, acupuncture decreased the neuronal and inducible NOS, whereas had no effect on the epithelial NOS (Yang et al. 2000). Further details on this topic are presented in Chapter 12 of this book.

2. Acupuncture and cerebral ischemia

Cerebral ischemia is one of the major causes of stroke. Our results strongly supported the bedside application of EA in the treatment of stroke, especially ischemic stroke.

We have defined the optimal condition of EA parameters for maximal protection effects in the experimental model of cerebral ischemia (Zhou et al. 2007a; 2007b; 2007c). Our results indicate that EA effects are critically dependent on the stimulation parameters, such as acupoint, stimulating intensity and frequency, and the duration time of EA. The data from the experimental studies provide important hints for determining the optimal conditions at the bedside. Based on our results, acupuncture delivered on head acupoints at Governor Vessel (i.e., GV-20 and GV-26) showed better recovery efficacy than other points. Furthermore, the EA initiated at the acute stage of cerebral ischemia was observed to produce significant neuroprotective efficacy (Si et al. 1998; Zhao and Cheng 1997; Jin and Cheng 1998a; Jin et al. 1999; Gao et al. 2002).

In our results, EA stimulation, especially when head acupoints were acupunctured, had rapid but short-term influence on the regional cerebral blood flow (rCBF) (Ying and Cheng 1994a; Gao et al. 2002). The rCBF of ischemic rats rose during EA performance and fell back to pre-EA level when the stimulation stopped.

Furthermore, it was also demonstrated that EA had long-term effects on some neurotransmitters and other neuroactive molecules. Our studies on multiple ischemic models have shown that EA treatment could significantly decrease the ischemia-induced increasing levels of extracellular excitatory amino acids (glutamate and aspartate) (Ying and Cheng 1994b; Zhao and Cheng 1997; Guo and Cheng 2000) and NO production (Jin and Cheng 1998b; Zhao et al. 2000). On the contrary, the levels of extracellular inhibitory amino acid, taurine (Zhao et al. 2000), and some neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), glial-derived nerve growth factor (GDNF) (Wei et al. 2000), and basic fibroblast growth factor (bFGF) (Ou et al. 2001) were all increased to a greater extent than those without EA treatment. Based on our results, it can be concluded that EA also induces intracellular regulation of the expression of some inflammatory factors, apoptotic-related factors, and immediate early genes (Ying and Cheng 1994c; Dong and Chen 2001; Chen et al. 2003; Xu et al. 2002; Li et al. 2003; Guo et al. 2004). Further details on this topic are provided in Chapter 9 of this book.

3. Acupuncture and cardiovascular diseases

In the history of Chinese medicine, acupuncture has been used for a long time to relieve cardiovascular symptoms, such as palpitations, vertigo, choking sensation in chest, and precordial pain observed with cardiovascular diseases. In the past 30 years, several studies performed in our institution have provided strong evidence on the efficacy of acupuncture on cardiovascular diseases, such as cardiac arrhythmia, hypertension, and hypotension. The underlying mechanisms have also been well-addressed by experimental research. The massive information obtained demonstrate that the efficacy of acupuncture on cardiovascular diseases is dependent on the diseases treated, acupoints selected, needling manipulation, stimulus intensity, applying windows, and the time of treatment. The mechanistic research has developed the idea that acupuncture signals initiated at the acupoints are transferred to the brain through the nervous pathway, which modulate multiple neurotransmitter systems, thus, affecting the nerve output and regulating the cardiovascular system. In addition, acupuncture has been observed to affect the endocrine secretion as well as humoral and dielectric regulation. Moreover, these mechanisms are observed to be involved in the alterations of gene expression and intracellular modulation of signal transduction. Thus, acupuncture is observed to induce an integrated and complex effect on the cardiovascular system, which is dependent on multiple factors.

The details of acupuncture effects on cardiovascular disorders are presented in Chapters 10 and 11 of this book.

4. Acupuncture and neuroimmune disorders

The immune system of humans can recognize and eliminate foreign substances. This is an important defense mechanism to confront foreign invasion. Our studies have shown that acupuncture could modulate the immune function of the body through nervous system.

We established a traumatic rat model to explore the underlying mechanism of the effect of acupuncture on neuroimmune disorders. We observed that trauma could induce quantitative and qualitative changes in the immune functions. For example, the activities of tyrosine protein kinase (TPK) in membranous and cytosolic fractions of the activated T lymphocytes (Cheng et al. 1998), ConA-induced spleen lymphocyte proliferation (Sun et al. 2000), natural killer (NK) cell activity (Du et al. 1998), the induction of IL-2 production of the spleen lymphocytes (Cheng et al. 1997) were all inhibited, while the activity of peritoneal macrophage as well as the apoptotic cell death in splenic lymphocytes were increased (Zhao et al. 2002a; 2002b; Wang et al. 2005). The EA was observed to almost completely restore the effect of trauma, which is in agreement with the clinical observation.

In parallel with the changes in the immune response, the CNS was observed to be the main target of trauma and EA. Furthermore, the endogenous opioid peptidergic system (Sun et al. 2000, Zhao et al. 2002c), hypothalamic CRF, one component of hypothalamus-pituitary-adrenal (HPA) axis (Zhang et al. 2000), and POMC-derived peptides (Huang et al. 2002) were all observed to be involved in EA on Zusanli (ST-36), which functioned on the improvement of traumatic stress-induced immune depression. In addition, the activation of sympathetic nervous system by EA and the subsequent relief of the body from traumatic stress formed another important modulation pathway (Cao et al. 1983; Wang et al. 2007). In particular, the interaction between OFQ and IL-1β (Zhao et al. 2002c), and the maintenance of blood brain barrier (BBB) integrity (Wu et al. 2001) may also be a part of the mechanism of the curative effect of EA in this profile.

Our data suggest that the modulation of EA on traumatic stress was mediated by a complex network of bidirectional signals between the nervous, endocrine, and immune systems, although the exact cellular mechanism as well as the EA function on the immune regulation as a whole still requires further elucidation. Further details on this topic are presented in Chapter 13 of this book.

5. Acupuncture and woman's reproductive disorders

Since 1985, we have performed clinical studies to explore the effects of EA on woman patients with reproductive disorders. The clinical observations showed that EA with effective acupoints [Guanyuan (CV-4), Zhongji (CV-3), Sanyinjiao (SP-6) and bilateral Zigong (EXCA-1)] could cure some woman's reproductive disorders, such as woman infertility, polycystic ovarian syndrome (PCOS), and perimenopausal syndrome, at a highly effective rate.

On exploring the underlying mechanism, we observed that EA normalized the dysfunction of hypothalamic pituitary-ovarian axis (HPOA). In the rat model with perimenopausal syndrome induced by ovariectomy, EA is presumed to normalize the dysfunction of HPOA through several ways. The EA could ameliorate the body's sympathetic nervous function by increasing the body's β-endorphin level and decreasing the blood luteinizing hormone (LH) level, resulting in the normalization of HPOA abnormal function and ovulation induction in the infertility patients (Yu et al. 1989; Chen and Yu 1991).

In 1990, we adopted the ovariectomized rats as the animal perimenopausal model to perform a series of animal experiments, and obtained numerous remarkable results that might not only validate the therapeutic effects (Chen 1997; Chen and He 1992), but also change the status of the transnormal hypothalamic gonadotropin-releasing hormone (GnRH) release, pituitary LH hypersecretion, and increase in the blood estradiol (E_2) level (Chen 1997; Chen and He 1992; Chen et al. 1994).

Further studies on ovariectomized rats showed that EA might enhance the extragonadal aromatization and promote the interaction of HPOA and HPA axis (Chen et al. 1994; Cheng and Chen 2001; Zhao et al. 2004a), which might increase the blood E_2, suggesting that EA might promote the body compensative mechanisms, and consequently normalize the levels of hormones, such as GnRH, LH, estrogen.

We observed that the GnRH immunoreactive substance (GnRH-ir) appears in the hypothalamic periventricular nucleus (PVN) and is co-localized with the corticotropin-releasing hormone (CRH) in the same neuron following EA treatment in the ovariectomized rat. This observation is very interesting because GnRH-ir is usually not found in the PVN of rats (Zhao et al. 2004b). This phenomenon may have a great impact on physiological function and pathological significance.

Recently, we found that brain prolactin-releasing peptide (PrRP) and hypothalamic OFQ participate in the normalization effect of EA on HPOA dysfunction in ovariectomized rats (An et al. 2005; Feng et al. 2006), suggesting that EA might regulate the dysfunction of HPOA in several ways resulting in the normalization of HPOA dysfunctions. Further details on this topic are provided in Chapters 14 and 15 of this book.

1.4 Concluding Remarks

The TCM represents the accumulation of medical experience of the Chinese people in their long-standing struggle against diseases. Acupuncture, which originated in China more than 2500 years ago, is an important part of the TCM. The concept of channels and collaterals forms the theoretical basis of acupuncture-moxibustion treatment, which guides the acupuncture treatment in the right track to regulate the *Yin* and *Yang*, strengthen the body resistance, eliminate the pathogenic factors, and distinguish the primary from the second pathological cause.

Our clinical and laboratory results indicate that: (1) Needling of acupuncture point could activate the afferent fibers of the peripheral nerves to elicit *De-Qi* sensation, then ascend mainly through the ventro-lateral funiculi that conduct pain and temperature sensation upward to the brain, and activate the antinociceptive system including certain brain nuclei, modulators (opioid peptides), neurotransmitters, through the descending inhibitory pathway, resulting in analgesia; (2) The studies on EOP release and antagonist injections showed that EOP participate in AA and drugs synergism from the presynaptic levels to the receptor sites, which provide a scientific basis to understand their underlying mechanism; (3) Some drugs can potentiate acupuncture-induced analgesia with reduced side effect of the drugs. Drugs and acupuncture can help each other to produce a better therapeutic effect, and the combination of acupuncture with drugs has been used in anesthesia for surgical operation, in postoperative analgesia, and in the management of various painful symptoms or diseases; and (4) Acupuncture therapy has been an effective method in treating some neurological diseases, such as epilepsy and cerebral ischemia, and their mechanism might be related to the excitatory/inhibitory amino acids system, neuropeptidergic system, NO system, etc. In the history of the TCM, acupuncture has been used to relieve cardiovascular symptoms and treat cardiovascular diseases such as cardiac arrhythmia, hypertension, and hypotension. Furthermore, clinical observations and experimental researches have shown that acupuncture could modulate the immune function of the body and cure some of the woman's reproductive disorders, such as woman infertility, PCOS, and perimenopausal syndrome through neuro-endocrine-immune system.

This chapter has laid special emphasis on certain important events: the influence of acupuncture anesthesia and the attention from the WHO and CDC on Acupuncture held by the NIH, USA, in 1997. The CDC on Acupuncture indicated that acupuncture was efficacious for some diseases and its adverse reactions were very low. Scientific advances in acupuncture research have promoted the usage and development of acupuncture treatment worldwide. Currently, acupuncture has spread to over 160 countries and regions.

As the mechanism of AA and acupuncture treatment involves many factors, we should study it from different angles. In other words, we should learn the basic sciences of medicine, not only of the western medicine, but also the theory of TCM. According to a general notion: (1) When using neurobiological method to analyze the clinical materials and experimental results, the researchers should always study the theory of channels and collaterals, the acupoints of the 14 channels, and the general principles of acupuncture treatment, and keep them in mind; and (2) The researchers should study western medicine with respect to the theory of TCM to carry out research works on acupuncture. In brief, everyone should study the mechanism of AA and acupuncture treatment by integrating TCM and western medicine, under the guidance of the theories of TCM.

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2 Neuroanatomic Basis of Acupuncture Points

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Summary Acupoints, the sites on the body for acupuncture therapy, have relatively special structure that receives the acupuncture signals. Anatomically, acupoints have abundant nerves, muscles, vessels, and tendon. Histologically, there are various kinds of free nerve endings, receptors, Ruffini corpuscles, Meissner corpuscles, Krause corpuscles, lamellated corpuscles, and muscle spindle around the acupoints. The complexity of these tissues are presumed to be responsible for the acupuncture sensation at acupoints. Type Ⅱ and Ⅲ fibers of the afferent nerves may mediate the afferent transmission of the acupuncture signals. In the central nervous system (CNS), the spinal cord, brainstem, hypothalamus, thalamus, and cerebral cortex integrate the afferent signals of the acupuncture and form regulatory outputs via afferent pathways. In addition, there exists a strong relationship between the meridian-points and viscera in terms of nerve connection. The mechanism underlying the interaction between the meridian-points and viscera is related to the segmental innervations and convergence of the somatic and autonomic nerves at the same spinal segments. Although there have been numerous theories concerning meridians and points, we believe that the peripheral nervous system forms the main basis of acupoints as well as afferent and efferent pathways of the acupuncture signals.

Keywords *acupuncture signal, acupoint, meridian and collateral, anatomic structure, nerve*

2.1 Introduction

Acupuncture therapy is a unique therapeutic approach that treats diseases by puncturing certain points of the human body (called "acupoints") with various

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types of needles and manipulation. For thousands of years, the Chinese doctors have been using tiny acupuncture needles for the treatment of numerous diseases. The theory of meridians and collaterals has been formed and developed accumulatively based on ancient doctors' long-term practice, and has guided the diagnosis and treatment in the traditional Chinese medicine (TCM), especially for acupuncture, moxibustion, and Tuina (massage). Acupuncture therapy and the theory of meridians and collaterals are the greatest inventions in the ancient Chinese medical history.

In the theories of TCM, meridians and acupoints are two important concepts. Although there have been hundreds of theories concerning meridians and acupoints, there is no theory with convincing evidence to demonstrate the physical structures of the meridians and acupoints. Based on the knowledge of current neuroscience, we believe that the function of the so-called "meridians and acupoints" are highly dependent on the activity of the nervous system.

2.2 Phenomena of Meridians and Acupoints

2.2.1 Theory of Meridians, Collaterals, and Acupoints

The meridians are comprehensively termed "*Jing and Luo*". According to the literatures of TCM (Cheng 1990; Zhang 1990; Qiu and Chen 1992; Zhu 1998; Zhao and Li 2002; Li 2003), meridians refer to the routes that transport vital energy (Qi) and blood, regulate yin and yang, connect the *Zang*-organs with the *Fu*-organs, and associate the external with the internal as well as the upper with the lower part of the human body. The meridians not only harmonize the activity of the human body, but also integrate the human body and the circumstance into a whole entity. Meridians include both meridians and collaterals. Meridians, meaning paths, are the main trunks that run longitudinally and interiorly-exteriorly within the body; while the collaterals, meaning networks, which are thinner and smaller than the meridians, are the branches which run crisscross on the body. It has been stated in Miraculous Pivot that "meridians locate inside and their transverse branches are collaterals; the further branches of collaterals are minute collaterals" (Cheng 1900; Zhang 1990; Qiu and Chen 1992). According to the theories of TCM, the system of meridians is mainly composed of the fourteen regular meridians, twelve meridian branches, fifteen collaterals, twelve meridian tendons, twelve skin areas, and eight extraordinary vessels, which form a network connecting all parts of the body, including the viscera, five sensory organs, nine orifices, four limbs, and the skeleton, into an whole organic entity (Cheng 1990; Zhang 1990; Qiu and Chen 1992; Zhu 1998; Zhao and Li 2002).

"Acupoint" is another crucial concept in the theories of TCM. Acupoints refer to the effective sites on the body for acupuncture therapies in the treatment of various diseases. They are usually located in the interstices in the thick muscles or between the tendons and bones. According to the theory of meridians and acupoints, the acupoints are the locations where *Qi* and blood from the meridians and their internal organs effuse and infuse in the body surface. During the ancient times, they were known as *Shuxue, Qixue, Kongxue, Xuedao,* etc. The word "Shu" means transportation, while "Xue" means hole. These names indicate the basic characteristics of acupoints: the locations where *Qi* and blood from the viscera and meridians effuse and infuse. The acupoints are usually located in the interstices in the thick muscles or between the tendons and bones. All the acupoints have close relations with the meridians. They are connected with both the internal organs and the meridians and collaterals, thus, forming a close relationship, known as points-meridians and collaterals-internal organs. According to the theory of meridian and acupoints, the acupoints can be used to treat diseases and keep good health by removing obstruction in the meridian, regulating *Qi* and blood, reinforcing the deficiency, and reducing the excess. In other words, acupoints are those special somatic positions that can accept a stimulation, reflect a syndrome, and treat diseases (Cheng 1990; Zhang 1990; Qiu and Chen 1992; Zhu 1998; Zhao and Li 2002).

Acupuncture, moxibustion, Tuina, and other modalities are performed based on the theory of meridians and acupoints. In the acupuncture literature (Cheng 1990; Zhang 1990; Qiu and Chen 1992; Zhu 1998; Zhao and Li 2002), more than 670 specific sites on the body are considered to be acupoints. The names of 409 acupoints in the fourteen meridians and the extra acupoints were standardized by the State Supervision Bureau of Technology of China and WHO. Each acupoint has its own size and depth at different locations. A large number of acupoints can be allocated to the point categories with reference to their semantic origin, functional significance, localization, and the links between the separate categories. Furthermore, based on the meridians, these acupoints can be classified into points of the fourteen meridians, extra points, and Ashi points (Qiu and Chen 1992; Zhao and Li 2002; Li 2003).

Currently, filiform needle puncture is the fundamental clinical technique. In addition, there are also other therapies developed based on the acupuncture practice. These include electroacupuncture, electrothermal acupuncture, laser acupoint radiation, microwave, acupoint infrared therapy, acupoint magnetic therapy, etc., and all these use the concept of " meridian" and "acupoint" on the human body (Li 2003).

Clearly, the study on the specificity of the acupoints and meridians helps to elucidate the mechanisms of the acupuncture therapy. In recent years, many researchers have been trying to elucidate various kinds of meridian phenomenon from different points of view, such as physics, chemistry, biology, TCM, etc. (Reviewed by Liu and Huang, 2007). The results have shown that there exist certain biophysical specificities of the meridians, including electricity, heat, sound, light, magnesium, the migration of the injected isotope along the running route of the meridian, and the close relationship with the activities of some chemical substances (ions, PO_2, neurotransmitters) within the tissues along the meridian (Wu et al. 1993; Hu et al. 1993; Lee et al. 2005; Zheng et al. 2005; Xu et al. 2005, Liu and Huang 2007). Unfortunately, the fundamental nature of the meridians is still unclear, and indeed, there are many controversial results in this field (Xie et al. 2007; Xie 2008). Till date, the questions regarding the specificity of the acupoints have been explored in several ways: comparing the effects of true points versus the sham points, studying the unique physiological features of the acupoints as well as the anatomical structure at the acupoints, and studying the nerves activated by acupuncture at the acupoints.

2.2.2 Relatively Specific Effects of Acupoints

Acupoints are the sites on the body for acupuncture therapy. They are the structural and functional basis for effective acupuncture treatment. Acupoints can transport the *Qi* of the *Zang-Fu* organs and meridians to the body surface. Thus, when an abnormal function of the meridians and organs occurs, it would lead to the sensation of pain or pressing pain at the relative acupoints (Qiu and Chen 1992; Li 2003). For example, the sensation of pressing pain often appears at the points of Zusanli (ST-36) and Shangjuxu (ST-37) in patients with appendicitis. This implies that there are some special relationships between the acupoints and viscera (Qiu and Chen 1992; Chen et al. 1995).

Several researchers have shown that needling at true points produces marked analgesia, while needling at sham points produces very weak effects (Stacher and Wancura 1975; Chapman et al. 1977; Takashige 1985). Needling at sham points was observed to be effective in 33% – 50% of the patients, which is similar to the effect of placebo analgesia, while needling at acupoints was found to be effective in 55% – 85% of the cases.

Using animal models (Pomeranz and Chiu 1976; Chan and Fung 1975; Fung and Chan 1975; Cheng and Pomeranz 1980; Takashige 1985; Toda and Ichioka 1978; Fung and Chan 1976; Liao et al. 1979), many researchers have shown that true acupoints work better than sham needling in acute pain studies. These results are consistent with the studies on human subjects. In other models, such as experimental stroke (Zhou et al. 2007) or pregnant rats (Chen et al. 2007, 2008), electroacupuncture-induced regulatory effects were observed to be relatively acupoints-specific. Lietz et al (2008) also confirmed the specificity of the acupuncture points, TH-3 and GB-43 (both considered to be specific for auditory system), other than the non-specific points of TH-7 and ST-44 with respect to the auditory system, by investigating the acupuncture of the specific points influencing the cortical auditory evoked potentials (CAEP). By using techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), recent studies have found more direct evidences on the specific brain areas that respond to the stimulation of different acupoints (Zaslawski et al. 2003;

Zhang et al. 2004; Compbell 2006; Zhang et al. 2007b, 2007c, 2007d; Wu et al. 2007; Huang et al. 2007; Lai and Huang 2007; Gao et al. 2008; Lietz et al. 2008; Li, et al. 2008). For example, Li et al (2008), using fMRI, observed the CNS activation by acupuncture of the acupoints LR-3 (Taichong) and LR-6 (Zhongdu), which belong to the Liver meridian of Foot-Jueyin; ST-36 (Zusanli) and ST-43 (Xiangu), which belong to the Stomach meridian of Foot-Yangming; and the two nearby sham acupoints. In contrast to the CNS activation by sham acupoints, all the four real acupoints under consideration produced a common effect of the activation of two specific areas of the brain: the bilateral primary somatosensory area and the ipsilateral cerebellum. Acupuncture stimulation of both the acupoints, LR-3 and LR-6, evoked activation at the ipsilateral superior parietal lobe (BA7). Furthermore, acupuncture stimulation of both the acupoints, ST-36 and ST-43, evoked activation at the ipsilateral middle frontal gyrus (BA10). These results suggest that different acupoints on the same meridian may activate similar areas of the brain. In addition, acupoints that are commonly used in clinical practice might affect a greater extent of the cortical areas than the uncommonly used acupoints.

2.2.3 Unique Physiological Features of Acupoints

The so-called "acupoints" may have some special physiological feature than the non-acupoints. There have been a number of reports stating that the skin resistance (impedance) over acupoints is lower than that of the surrounding skin (Zeng 1958; Becker and Reichmanis 1976; McCarroll and Rowley 1979; Chan 1984; Xu 1987; Lu 1987; Chen et al. 1995; Lee et al. 2005). Normally, dry skin has a DC resistance in the order of 200,000 ohms. However, in the studies claiming the unique properties of the acupoints, this value was found to be 50,000 ohms at the acupoints. It is further claimed that during the course of a disease of particular organs, the resistances at the acupoints become abnormally low (even lower than the usual low resistance at the acupoints) (Hu 1987; Gao 1987). Another finding at acupoints is the presence of a voltage source. Some reports showed a potential difference of 5 mV or more in the positive direction between the acupoints and the neighboring skin (Zeng 1958; Tseng and Chang 1958). In addition, Jaffe and Barker (1982) also showed that the human skin has a resting potential across its epidermal layer from 20 mV to 90 mV (outside negative, inside positive). From these studies, one can speculate that acupoints with low resistance tend to short-circuit this battery across the skin, and consequently, give rise to a source of current in a source-sink map of the skin. Some studies (Xu 1987) also demonstrated that the regeneration of the amputated amphibian limbs was enhanced by the application of the electric fields (and currents) in the direction of the negative pole. Furthermore, the DC fields and currents have also been implicated in bone healing, plant growth, embryology, and spinal cord regeneration.

The phenomenon of distinctive resistance and voltage of the skin (acupoints vs. non-acupoints) could also explain the scientific basis of the appearance of Ashi acupoints that are usually unfixable and painful to be directly acupunctured to relieve local pain or disease effectively (Qiu and Chen 1992).

However, some scientists and clinicians are quite skeptical about the entire skin resistance phenomenon and most of the voltage measurements (Summarized by Stux and Pomeranz in 1988), because the measurements were not made according to the established biophysical practice. In particular, the electrochemical potential artifacts produced at the electrode-to-skin interface are observed to be high when compared with the millivolts being generated by the body. Furthermore, neither the published reports nor the clinical anecdotal observations were based on properly conducted studies. Hence, it seems unclear whether the low resistance or high voltage could be of any physiological significance to acupoints. There is a possibitity that the presence of a large nerve, emerging from deep tissues to more superficial layers, induce changes in the skin resistance.

2.2.4 Relatively Specific Anatomical Structures of Acupoints

Since acupoints have relative specificity of therapeutic effects and potential physiological features, scientists have presumed that there might be special anatomical structures around the acupoints. Unfortunately, no unique structures have been found for the acupoints in most of the histological studies of the skin and subcutaneous structures. However, several authors have made the astute observation that the anatomical structures of acupoints have some special particularities.

Some investigators reported that the acupoints are motor points, at which the nerve enters the muscle and approximates, but are not identical to the end-plate zone of the motor nerve endings (Gunn and Milbrandt 1977, 1980; Dung 1984). For example, some acupoints are just proximal to the Achilles tendon or immediately proximal to the tendon insertion on a bony prominence, while some are located at the arterial arch of hand or foot, for example, Hegu (LI-4) on the back of the hand and Taichong (LR-3) on the back of the foot. Hence, needling at these acupoints is very effective in influencing the sympathetic activity.

Some researchers, through cross-sectional dissection, observed that 55% of the acupoints on the body were located just at the cluster of the muscles, and those muscles and fascias at the acupoints were considerably thick and centralized (Liu et al. 1975). The muscles are observed to be wrapped around by superficial and deep fascias, and must be penetrated by the needles permeating the fascias. Therefore, it was proposed that the acupoints were just trigger points of the muscles. For example, Melzack and Wall (1965) and Melzack (1975) found that 71% of the acupoints correspond to trigger points.

On the other hand, some studies suggest that connective tissues are the structural basis of the acupoints and meridians, as well as responsible for inducing the sensation of "*De-Qi*" of acupuncture. For example, Shi and Zhang (1996) reported that after acupuncture at Zusanli (ST-36) with one-direction twirling manipulation until an objective sensation was felt by the operator's hand, a puncturing pore and different transformation of the surrounding tissue were observed clearly. In the hypodermis, the connective tissue fibers circling the puncturing pore demonstrated a whirly form. Furthermore, in the muscle layer, the connective tissue fibers of the endomysium circled the pore, and the relative muscle fibers were twisted and dislocated. The adjacent vessels and nerves were dislocated and transformed. Hence, the authors regarded that the various needling-sensitive tissues and structures were simultaneously stimulated by the twirling needle force, with the connective tissue acting as a mediator, which might be the possible biological basis of needling sensation and its complexity. In addition, Langevin et al (2001, 2002) also hypothesized that needle grasp is owing to the mechanical coupling between the needle and the connective tissue, with winding of the tissue around the needle during the needle rotation, and that needle manipulation transmits a mechanical signal to the connective tissue cells via mechanotransduction. Furthermore, they (Langevin and Yandow 2002; Langevin et al. 2002) even speculated that the network of acupuncture points and meridians can be viewed as a representation of the network formed by the interstitial connective tissue by mapping the acupuncture points in serial gross anatomical sections through the human arm, and found an 80% correspondence between the sites of acupuncture points and the location of the intermuscular or intramuscular connective tissue planes in the postmortem tissue sections. However, further research is needed to validate their interesting hypothesis.

In addition, some studies suggest that the mast cells under the acupoints play a key role in the stimulation of local tissues and generation of acupuncture signal (Yang and Wang 1986; Zhu and Xu 1990; Deng et al. 1996a, 1996b; Popov et al. 2001; Sun et al. 2002; Zhang et al. 2007a, 2008). Particularly, the mast cells were found to be distributed extensively in the connective tissues of the whole body, and were especially clustered in the positions that receive more external irritants, such as subcutaneous tissue and submucous layers. Moreover, more mast cells were observed to be distributed at the acupoints than at non-acupoints, and were usually distributed among the small vessels and nerve tract along their meridian course. Some studies suggest that acupuncture might affect the amount and activity of mast cells at the acupoints. For example, Zhang et al (2007a, 2008) showed that the quantity of mast cells of deeper fascia at Zusanli (ST-36) significantly decreased after 20 min of acupuncture induction. It has been found that acupuncture or electric stimulation induces mast cells degranulation at the stimulated acupoints along the same meridian (Popov et al. 2001). All these reports indicate that mast cells at acupoints might play a role in accepting the stimulation and producing acupuncture response. However, the transmission of the mast cell-mediated chemical signal may still depend on the nerves at the acupoints.

Many studies have been carried out to determine the specificity of the acupoints with respect to the morphological structure (nerves, blood vessels, musculotendons, connective tissues, etc.), biophysical characteristics (electricity, sonics, photology, thermology, electromagnetism), pathological response, and effectiveness (Xu et al. 2005; Lee et al. 2005; Jin et al. 2008). However, these studies were basically restricted to phenomenon-observation stage, and provided no/few convincing results regarding some key factors influencing the acupoint specificity and the underlying mechanisms. Further studies should aim at those acupoints employed for the effective treatment of certain diseases (or symptoms) through acupuncture, using multiple modern scientific techniques. In addition, some key scientific issues about the biophysical characteristics, pathological responses, efficacy, and combination regularity of the acupoints should be solved by employing advanced approaches.

2.3 Neuroanatomic Structure of Acupoints

From the perspective of neuroscience, we may regard acupoints as both signal receptor and effector apparatus. However, there are many questions regarding its nature. Are there any special structures at the acupoints when compared with that at the non-acupoints? If yes, what are the tissues/cells that form the special structure of the acupoint? What is the component(s) that is stimulated by needling at the acupoints? What structure mediates the afferent and efferent signals of the acupuncture to induce the biological effects? All these questions are essential to clarify the theory of meridian in TCM. Although these issues are still unclear even today, we have comprehensive data suggesting that the structural basis of acupoints are closely related to the special distribution of the peripheral nerves around the vessel, muscle, tendon, and other structures, with the signals being transmitted to the brain for processing (see Chapter 3). Some of us started this work in 1958 and obtained successful results to illustrate the neuroanatomical basis of the acupoints. In this section, we will provide an introduction to our pioneer work as well as the related studies carried out by others.

In the pioneer studies, which were partially published in Chinese in 1959 and 1973 (Department of Anatomy, Shanghai First Medical College 1973), careful observations were made on 8 intact adult cadavers, 49 dissociated upper limbs, and 24 lower limbs using neuroanatomical approaches. To maintain the cadavers intact and under conditions similar to that of the living body for observing the relationship between the acupoints and the tissues under them, they were fixed by injecting the antiseptic fixation liquid, composed of formalin (10%), carbolic acid (5%), 95% alcohol (40%), glycerin (10%), and water. A well-renowned acupuncturist and TCM expert (Dr. Ding Li at former Shanghai TCM College) localized the acupoints with common acupuncture needles. All the acupoints were confirmed following the meridians based on the TCM literature, and the metal milli-needles were inserted into these acupoints and transverse dissections were subsequently performed. The distribution of the nerves around the needle of about 0.5 cm circumference was carefully examined.

The tissues underneath the most commonly used 21 acupoints were incised. The acupoints included Neiguan (PC-6), Yifeng (TE-17), Yamen (GV-15), Ermen (TE-21), Tinghui (GB-2), Yanggu (SI-5), Yangchi (TE-4), Yangxi (LI-5), Hegu (LI-4), Zusanli (ST-36), Lanwei (Ex/LE-7), Kongzui (LU-6), Yuji (LU-10), Zhongfu (LU-1), Chize (LU-5), Taiyuan (LU-9), Qihai (CV-6), Shenque (CV-8), Tiantu (CV-22), Sanyinjiao (SP-6), and Qugu (CV-2). The general tissue histology of these tissues was observed by HE staining, Mallory staining, elastic fiber staining, and reticular fiber staining. The ends of the nerves were observed by Cajal method and Bielschowsky-Gros method.

The results showed that meridians and acupoints are very closely related to the distribution of the peripheral nerves, although there are other structures at acupoints, such as skin, subcutaneous tissues, blood vessels, muscles, and connective tissues. For example, at Zhongfu (LU-1, Lung Meridian of Hand-Taiyin), located at the level of the first intercostal space, laterosuperior to the sternum, 1 *cun* below Yunmen (LU-2), and 6 *cun* lateral to the anterior midline, we could find the intermediate branch of supraclavicular nerves and lateral branch of the first intercoastal nerve in the superficial layer of the subcutaneous nerve, and anterior thoracic nerve in the deep-layer nerve. At another acupoint, Chize (LU-5), located on the cubital crease and in the depression of the radial side of the tendon of the biceps muscle of arm, we could observe the lateral antebrachial cutaneous nerve in the superficial layer and radial nerve in the deep layer. Furthermore, at the acupoint Kongzui (LU-6), located on the palmar aspect of the forearm and the line joining Taiyuan (LU-9) and Chize (LU-5), 7 *cun* above the transverse crease of the wrist, we could locate the same subcutaneous nerve of the lateral antebrachial cutaneous nerve, similar to Chize (LU-5), with another deep-layer nerve of the superficial branch of the radial nerve. Under another common acupoint, Neiguan (PC-6) that belongs to the Pericardium Meridian of Hand-Jueyin, located at 2 *cun* above the transverse crease of the wrist, between the tendons of the long palmar muscle and the flexor radials muscle, we could observe the medial antebrachial cutaneous nerve, lateral antebrachial cutaneous nerve, palmar cutaneous branch of the median nerve in the superficial layer, and the trunk and palmar interosseous nerve of the median nerve in the deep layer. The details of the relationship between the acupoints and nerve distribution are summarized in the subsequent section.

2.3.1 Gross Anatomical Observation of Meridians and Acupoints

In our study, initiated in 1958, we examined 324 acupoints of 12 main meridians and Conception Vessel meridian, which were partially published in Chinese in 1959, 1960, and 1973 (see Appendix) and are now listed in Tables 2.1 – 2.12. We found that 323 acupoints are associated with nerves, except for Qugu (CV-2). Thus, 99.69% (323/324) of the acupoints examined were observed to have a close relationship with the nerves. Among them, 304 acupoints were found to be related to the superficial layer of the cutaneous nerves, accounting for 93.83%, while 170 acupoints were observed to be related to the deep-layer nerves, accounting for 52.50%. Furthermore, we observed 149 acupoints being related to both superficial and deep-layer nerves, accounting for 45.99%. Although we did not observe nerve distribution under Qugu (CV-2) with the naked eyes, we did find dense nerve distribution under this acupoint, by observing it under a microscope.

Table 2.1 Acupoints of the Lung Meridian of Hand Taiyin (LU)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Zhongfu (LU 1)	Intermediate branch of supraclavicular nerve, lateral branch of the 1st intercostal nerve	Anterior thoracic nerve
Yunmen (LU 2)	Branch of the supraclavicular nerve	Anterior thoracic nerve
Tianfu (LU 3)	Lateral brachial cutaneous nerve	Musculocutaneous nerve
Xiabai (LU 4)	Same as LU 3	Same as LU 3
Chize (LU 5)	Lateral antebrachial cutaneous nerve	Radial nerve
Kongzui (LU 6)	Same as LU 5	Superficial branch of the radial nerve
Lieque (LU 7)	Same as LU 5	Same as LU 6
Jingqu (LU 8)	Same as LU 5	
Taiyuan (LU 9)	Same as LU 5	
Yuji (LU 10)	Same as LU 5	
Shaoshang (LU 11)		Median nerve (end part)

Table 2.2 Acupoints of the Pericardium Meridian of Hand Jueyin (PC)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Tianchi (PC 1)		The 5th intercostal nerve
Tianquan (PC 2)	Medial brachial cutaneous nerve	
Quze (PC 3)	Medial antebrachial cutaneous nerve, lateral antebrachial cutaneous nerve	Trunk of the median nerve
Ximen (PC 4)	Medial antebrachial cutaneous nerve	Trunk and palmar interosseous nerve of the median nerve
Jianshi (PC 5)	Medial antebrachial cutaneous nerve, lateral antebrachial cutaneous nerve, palmar cutaneous branch of median nerve	Same as PC 4
Neiguan (PC 6)	Same as PC 5	Same as PC 4

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Daling (PC 7)	Medial antebrachial cutaneous nerve, palmar cutaneous branch of median nerve	Trunk of the median nerve
Laogong (PC 8)	The 4th common palmar digital nerve of the median nerve	
Zhongchong (PC 9)	Terminal branch of the median nerve	

Table 2.3 Acupoints of the Heart Meridian of Hand Shaoyin (HT)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Jiquan (HT 1)	Medial brachial cutaneous nerve	Trunk of the ulnar nerve
Qingling (HT 2)	Medial brachial cutaneous nerve, medial antebrachial cutaneous nerve	Trunk of the ulnar nerve
Shaohai (HT 3)	Medial antebrachial cutaneous nerve	
Lingdao (HT 4)	Medial antebrachial cutaneous nerve	Trunk of the ulnar nerve
Tongli (HT 5)	Medial antebrachial cutaneous nerve	Trunk of the ulnar nerve
Yinxi (HT 6)	Medial antebrachial cutaneous nerve	Trunk of the ulnar nerve
Shenmen (HT 7)	Medial antebrachial cutaneous nerve	Trunk of the ulnar nerve
Shaofu (HT 8)	The 4th common palmar digital nerve of the ulnar nerve	
Shaochong (HT 9)	Terminal branch of the ulnar nerve	

Table 2.4 Acupoints of the Large Intestine Meridian of Hand Yangming (LI)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Shangyang (LI 1)	Terminal branch of the median nerve	
Erjian (LI 2)	Superficial branch of the radial nerve	
Sanjian (LI 3)	Superficial branch of the radial nerve	
Hegu (LI 4)	Superficial branch of the radial nerve	
Yangxi (LI 5)	Superficial branch of the radial nerve, lateral antebrachial cutaneous nerve	
Pianli (LI 6)	Lateral antebrachial cutaneous nerve, dorsal antebrachial cutaneous nerve	
Wenliu (LI 7)	Same as LI 6	
Xialian (LI 8)	Dorsal antebrachial cutaneous nerve	
Shanglian (LI 9)	Dorsal antebrachial cutaneous nerve	
Shousanli (LI 10)	Dorsal antebrachial cutaneous nerve	
Quchi (LI 11)	Dorsal antebrachial cutaneous nerve	Trunk of the radial nerve
Zhouliao (LI 12)	Dorsal antebrachial cutaneous nerve	Trunk of the radial nerve
Shouwuli (LI 13)	Dorsal antebrachial cutaneous nerve	Trunk of the radial nerve
Binao (LI 14)	Dorsal brachial cutaneous nerve	Trunk of the radial nerve
Jianyu (LI 15)	Supraclavicular nerve	
Jugu (LI 16)	Supraclavicualr nerve	

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Tianding (LI 17)	Cervical cutaneous nerve	Phrenic nerve
Futu (LI 18)	Cervical cutaneous nerve, great auricular nerve	
Heliao (LI 19)	Infraorbital nerve, branch of facial nerve	
Yingxiang (LI 20)	Infraorbital nerve, branch of facial nerve	

Table 2.5 Acupoints of the Sanjiao (Triple Energizer) Meridian of Hand Shaoyang (TE)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Guanchong (TE 1)	Terminal branch of the ulnar nerve	
Yemen (TE 2)	Dorsal branch of the ulnar nerve	
Zhongzhu (TE 3)	Dorsal branch of the ulnar nerve	
Yangchi (TE 4)	Dorsal branch of the ulnar nerve, dorsal antebrachial cutaneous nerve	
Waiguan (TE 5)	Dorsal antebrachial cutaneous nerve	Dorsal interosseous nerve of the radial nerve, palmar interosseous nerve of the median nerve
Zhigou (TE 6)	Dorsal antebrachial cutaneous nerve	Same as TE 5
Huizong (TE 7)	Dorsal antebrachial cutaneous nerve, medial antebrachial cutaneous nerve	Same as TE 5
Sanyangluo (TE 8)	Dorsal antebrachial cutaneous nerve	Same as TE 5
Sidu (TE 9)	Dorsal antebrachial cutaneous nerve, medial antebrachial cutaneous nerve	Same as TE 5
Tianjing (TE 10)	Dorsal brachial cutaneous nerve	
Qinglengyuan (TE 11)	Dorsal brachial cutaneous nerve	
Xiaoluo (TE 12)	Dorsal brachial cutaneous nerve	Radial nerve
Naohui (TE 13)	Dorsal brachial cutaneous nerve	Radial nerve
Jianliao (TE 14)		Branch of the axillary nerve
Tianliao (TE 15)		Accessory nerve, branch of the suprascupular nerve
Tianyou (TE 16)	Lesser occipital nerve	
Yifeng (TE 17)	Great auricular nerve	Trunk of the facial nerve
Chimai (TE 18)	Branch of great auricular nerve	
Luxi (TE 19)	Branch of great auricular nerve	
Jiaosun (TE 20)	Branch of auriculotemporal nerve	
Ermen (TE 21)	Branch of facial nerve, auriculotem poral nerve	
Heliao (TE 22)	Branch of facial nerve	
Sizhukong (TE 23)	Branch of facial nerve, supraorbital nerve	

Table 2.6 Acupoints of the Small Intestine Meridian of Hand Taiyang (SI)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Shaoze (SI 1)	Terminal branch of the ulnar nerve	
Qiangu (SI 2)	Dorsal branch of the ulnar nerve	
Houxi (SI 3)	Dorsal branch of the ulnar nerve	
Wangu (SI 4)	Dorsal branch of the ulnar nerve	
Yanggu (SI 5)	Dorsal branch of the ulnar nerve	
Yanglao (SI 6)	Dorsal branch of the ulnar nerve	
Zhizheng (SI 7)	Medial antebrachial cutaneous nerve	
Xiaohai (SI 8)	Medial antebrachial cutaneous nerve	Trunk of the ulnar nerve
Jianzhen (SI 9)	Intercostal brachial nerve	
Naoshu (SI 10)	Supraclavicular nerve	
Tianzong (SI 11)		Suprascapular nerve
Bingfeng (SI 12)	Supraclavicular nerve	Suprascapular nerve
Quyuan (SI 13)		Suprascapular nerve
Jianwaishu (SI 14)	Lateral branch of the posterior branches of the 1st thoracic nerve	Dorsal scapular nerve, acces sory nerve
Jianzhongshu (SI 15)		Dorsal scapular nerve
Tianchuang(SI 16)	Great auricular nerve, lesser occipital nerve	
Tianrong (SI 17)	Great auricular nerve, branches of facial nerve	
Quanliao (SI 18)	Branches of facial nerve	
Tinggong (SI 19)	Auriculotemporal nerve, branches of facial nerve	

Table 2.7 Acupoints of the Stomach Meridian of Foot Yangming (ST)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Chengqi (ST 1)	Infraorbital nerve, facial nerve	
Sibai (ST 2)	Infraorbital nerve, facial nerve	
Juliao (ST 3)	Infraorbital nerve, facial nerve	
Dicang (ST 4)	Facial nerve	
Daying (ST 5)	Branches of facial nerve	
Jiache (ST 6)	Great auricular nerve, facial nerve	Masseteric nerve
Xiaguan (ST 7)	Branches of facial nerve	
Touwei (ST 8)	Supraorbital nerve	
Renying (ST 9)	Plexus formed by cervical cutaneous nerve and cervical branch of the facial nerve	Sympathetic trunk
Shuitu (ST 10)	Cervical cutaneous nerve	
Qishe (ST 11)	Cervical cutaneous nerve	
Quepen (ST 12)	Supraclavicular nerves	

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Qihu (ST 13)	End of the 1st intercostal nerve	Trunk of the 1st intercostal nerve
Kufang (ST 14)	End of the 2nd intercostal nerve	Trunk of the 2nd intercostal nerve
Wuyi (ST 15)	End of the 3rd intercostal nerve	Trunk of the 3rd intercostal nerve
Yingchuang (ST 16)		Trunk of the4th intercostal nerve
Ruzhong (ST 17)		Trunk of the 5th intercostal nerve
Rugen (ST 18)	Lateral anterior cutaneous branch of the 5th intercostal nerve	Trunk of the 5th intercostal nerve
Burong (ST 19)		Trunk of the 7th intercostal nerve
Chengman (ST 20)	The 7th intercostal nerve	
Liangmen (ST 21)	Lateral anterior cutaneous branch of the 8th intercostal nerve	
Guanmen (ST 22)	Lateral anterior cutaneous branch of the 9th intercostal nerve	Ends of the 9th intercostal nerve
Taiyi (ST 23)	Same as ST 22	Ends of the 9th intercostal nerve
Huaroumen (ST 24)		Ends of the 9th intercostal nerve
Tianshu (ST 25)	Lateral anterior cutaneous branch of the 10th intercostal nerve	Ends of the 10th intercostal nerve
Wailing (ST 26)	Lateral anterior cutaneous branch of the 11th intercostal nerve	Ends of the 11th intercostal nerve
Daju (ST 27)		Trunk of the subcostal nerve
Shuidao (ST 28)	Lateral anterior cutaneous branch of the subcostal nerve	Lateral branch of the iliohypo gastric nerve
Guilai (ST 29)		Trunk of the lateral cutaneous branch of the ilioinginal nerve
Qichong (ST 30)	Genitofemoral nerve	
Biguan (ST 31)	Lateral femoral cutaneous nerve	Branch of the femoral nerve
Futu (ST 32)	Same as ST 31	Same as ST 31
Yinshi (ST 33)	Same as ST 31	Same as ST 31
Liangqiu (ST 34)	Same as ST 31	Same as ST 31
Dubi (ST 35)	Infrapatollar branch of the saphenous nerve	Articular branch of the common peroneal nerve
Zusanli (ST 36)	Saphenous nerve, superficial peroneal nerve	Trunk of the deep peroneal nerve
Shangjuxu (ST 37)	Same as ST 36	Same as ST 36
Tiaokou (ST 38)	Same as ST 36	Same as ST 36
Xiajuxu (ST 39)	Same as ST 36	Same as ST 36
Fenglong (ST 40)	Same as ST 36	Same as ST 36
Jiexi (ST 41)	Superficial peroneal nerve	Same as ST 36
Chongyang (ST 42)	Same as ST 41	Same as ST 36
Xiangu (ST 43)	Same as ST 41	Same as ST 36
Neiting (ST 44)	Superficial peroneal nerve, deep peroneal nerve	Trunk of the deep peroneal nerve
Lidui (ST 45)	Same as ST 44	

Table 2.8 Acupoints of the Gallbladder Meridian of Foot Shaoyang (GB)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Tongziliao (GB 1)	Facial nerve	
Tinghui (GB 2)	Great auricular nerve, trunk of the facial nerve	
Shangguan (GB 3)	Facial nerve	
Hanyan (GB 4)	Supraorbital nerve	
Xuanlu (GB 5)	Facial nerve	
Xuanli (GB 6)	Facial nerve	
Qubin (GB 7)	Auriculotemporal nerve	
Shuaigu (GB 8)	Auriculotemporal nerve, greater occipital nerve	
Tianchong (GB 9)	Greater occipital nerve	
Fubai (GB 10)	Greater occipital nerve	
Touqiaoyin (GB 11)	Greater occipital nerve, lesser occipital nerve	
Wangu (GB 12)	Lesser occipital nerve	
Benshen (GB 13)	Supraorbital nerve	
Yangbai (GB 14)	Supraorbital nerve, supratrochlear nerve	
Toulinqi (GB 15)	Supraorbital nerve	
Muchuang (GB 16)	Supraorbital nerve	
Zhengying (GB 17)	Supraorbital nerve, greater occipital nerve	
Chengling (GB 18)	Greater occipital nerve	
Naokong (GB 19)	Greater occipital nerve	
Fengchi (GB 20)	Lesser occipital nerve	
Jianjing (GB 21)	Branches of axillary nerve	Radial nerve
Yuanye (GB 22)	Lateral cutaneous branch of the 4^{th} intercostal nerve, long thoracic nerve	
Zhejin (GB 23)	Lateral branch of the 4^{th} intercostal nerve	
Riyue (CB 24)	The 9^{th} intercostal nerve	
Jingmen (GB 25)	The 11^{th} intercostal nerve	
Daimai (GB 26)	The 12^{th} intercostal nerve	
Wushu (GB 27)	Iliohypogastric nerve	
Weidao (GB 28)	Ilioinguinal nerve	
Juliao (GB 29)	Lateral femoral cutaneous nerve	
Huantiao (GB 30)	Inferior gluteal nerve	Sciatic nerve
Fengshi (GB 31)	Lateral femoral cutaneous nerve	Muscular branch of the femoral nerve
Zhongdu (GB 32)	Lateral femoral cutaneous nerve	Muscular branch of the femoral nerve
Yangguan (GB 33)	Lateral femoral cutaneous nerve	
Yanglingquan (GB 34)	Sural nerve	Common peroneal nerve

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Yangjiao (GB 35)	Sural nerve, superficial peroneal nerve	Common peroneal nerve
Waiqiu (GB 36)	Superficial peroneal nerve, lateral sural cutaneous nerve	Common peroneal nerve, deep peroneal nerve
Guangming (GB 37)	Superficial peroneal nerve	Deep peroneal nerve
Yangfu (GB 38)	Superficial peroneal nerve, sural nerve	Deep peroneal nerve
Xuanzhong (GB 39)	Superficial peroneal nerve	
Qiuxu (GB 40)	Superficial peroneal nerve, sural nerve	Deep peroneal nerve
Zulinqi (GB 41)	Sural nerve	Lateral plantar nerve
Diwuhui (GB 42)	Sural nerve	
Xiaxi (GB 43)	Sural nerve	Lateral plantar nerve
Zuqiaoyin (GB 44)	Sural nerve	

Table 2.9 Acupoints of the Bladder Meridian of Foot Taiyang (BL)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Jingming (BL 1)	Supratrochlear and infratrochlear nerve	
Cuanzhu (BL 2)	Anastomotic branch of the supra trochlear nerve and supraorbital nerve	
Meichong (BL 3)	Supratrochlear nerve	
Quchai (BL 4)	Trochlear nerve	
Wuchu (BL 5)	Frontal nerve	
Chengguang (BL 6)	Frontal nerve	
Tongtian (BL 7)	Greater occipital nerve	
Luoque (BL 8)	Greater occipital nerve	
Yuzhen (BL 9)	Greater occipital nerve	
Tianzhu (BL 10)	Greater occipital nerve	
Dazhu (BL 11)	Medial branch of the posterior branches of the 1st thoracic nerve	Lateral branch of the posterior branches of the 1st thoracic nerve, 2 – 3 upper lateral branches
Fengmen (BL 12)	Medial branch of the posterior branches of the 2nd thoracic nerve	Lateral branch of the posterior branches of the 2nd thoracic nerve, 2 – 3 upper lateral branches
Feishu (BL 13)	Medial branch of the posterior branches of the 3rd thoracic nerve	Lateral branch of the posterior branches of the 3rd thoracic nerve, 2 – 3 upper lateral branches
Jueyinshu (BL 14)	Medial branch of the posterior branches of the 4th thoracic nerve	Lateral branch of the posterior branches of the 4th thoracic nerve, 2 – 3 upper lateral branches

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Xinshu (BL 15)	Medial branch of the posterior branches of the 5th thoracic nerve	Lateral branch of the posterior branches of the 5th thoracic nerve, 2 – 3 upper lateral branches
Dushu (BL 16)	Medial branch of the posterior branches of the 6th thoracic nerve	Lateral branch of the posterior branches of the 6th thoracic nerve, 2 – 3 upper lateral branches
Geshu (BL 17)	Medial branch of the posterior branches of the 7th thoracic nerve	Lateral branch of the posterior branches of the 7th thoracic nerve, 2 – 3 upper lateral branches
Ganshu (BL 18)	Medial branch of the posterior branches of the 9th thoracic nerve	Lateral branch of the posterior branches of the 9th thoracic nerve, 2 – 3 upper lateral branches
Danshu (BL 19)	Medial branch of the posterior branches of the 10th thoracic nerve	Lateral branch of the posterior branches of the 10th thoracic nerve, 2 – 3 upper lateral branches
Pishu (BL 20)	Medial branch of the posterior branches of the 11th thoracic nerve	Lateral branch of the posterior branches of the 11th thoracic nerve, 2 – 3 upper lateral branches
Weishu (BL 21)	Medial branch of the posterior branches of the 12th thoracic nerve	Lateral branch of the posterior branches of the 12th thoracic nerve, 2 – 3 upper lateral branches
Sanjiaoshu (BL 22)	Lateral branch of the posterior branches of the 10th thoracic nerve	Lateral branch of the posterior branches of the 1st lumbar nerve, 2 – 3 upper lateral branches
Shenshu (BL 23)	Lateral branch of the posterior branches of the 1st lumbar nerve	Lateral branch of the posterior branches of the 1st lumbar nerve, 2 – 3 upper lateral branches
Qihaishu (BL 24)	Lateral branch of the posterior branches of the 2nd lumbar nerve	
Dachangshu (BL 25)	Posterior branch of the 3rd lumbar nerve	
Guanyuanshu (BL 26)	Posterior branch of the 5th lumbar nerve	Posterior branch of the 5th lumbar nerve
Xiaochangshu (BL 27)	Lateral branch of the posterior branches of the 1st sacral nerve	
Pangguangshu (BL 28)	Lateral branches of the posterior branches of the 1st and 2nd sacral nerves	

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Zhonglushu (BL 29)	Lateral branches of the posterior branches of the 1st – 4th sacral nerves	
Baihuanshu (BL 30)	Inferior gluteal nerve, lateral branches of the posterior branches of the 1st – 4th sacral nerves	
Shangliao (BL 31)	Posterior branch of the 1st sacral nerve	
Ciliao (BL 32)	Posterior branch of the 2nd sacral nerve	
Zhongliao (BL 33)	Posterior branch of the 3rd sacral nerve	
Xialiao (BL 34)	Posterior branch of the 4th sacral nerve	
Huiyang (BL 35)	Coccygeal nerve	
Chengfu (BL 36)	Posterior femoral cutaneous nerve	Sciatic nerve
Yinmen (BL 37)	Posterior femoral cutaneous nerve	Sciatic nerve
Fuxi (BL 38)	Posterior femoral cutaneous nerve	Common peroneal nerve
Weiyang (BL 39)	Lateral sural cutaneous nerve	Common peroneal nerve
Weizhong (BL 40)	Medial sural cutaneous nerve, posterior femoral cutaneous nerve	Tibial nerve
Fufei (BL 41)	Lateral branches of the posterior rami of the 1st and 2nd thoracic nerves	Dorsal scapular nerve
Pohu (BL 42)	Medial cutaneous branches of the posterior rami of the 2nd and 3rd thoracic nerves	Lateral branches of the posterior rami of the 2nd and 3rd thoracic nerves and the dorsoscapular nerve
Gaohuang (BL 43)	Medial cutaneous branches of the posterior rami of the 2nd and 3rd thoracic nerves	Lateral branches of the posterior rami of the 2nd and 3rd thoracic nerves and the dorsoscapular nerve
Shentang (BL 44)	Medial cutaneous branches of the posterior rami of the 4th and 5th thoracic nerves	Lateral branches of the posterior rami of the 4th and 5th thoracic nerves and the dorsoscapular nerve
Yixi (BL 45)	Medial cutaneous branches of the posterior rami of the 5th and 6th thoracic nerves	Lateral branches of the posterior rami of the 5th and 6th thoracic nerves
Geguan (BL 46)	Medial branch of the posterior branches of the 6th thoracic nerve	Trunk of the 7th thoracic nerve
Hunmen (BL 47)	Medial branch of the posterior branches of the 7th thoracic nerve	Trunk of the 9th thoracic nerve
Yanggang (BL 48)	Medial branch of the posterior branches of the 8th thoracic nerve	Trunk of the 10th thoracic nerve
Yishe (BL 49)	Medial branch of the posterior branches of the 10th thoracic nerve	Trunk of the 11th thoracic nerve

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Weicang (BL 50)	Medial branch of the posterior branches of the 11th thoracic nerve	Trunk of the 12th thoracic nerve
Huangmen (BL 51)	Medial branch of the posterior branches of the 12th thoracic nerve	Lateral branch of the posterior branches of the 1st lumbar nerve
Zhishi (BL 52)	Same as BL 51	Same as BL 51
Baohuang (BL 53)	Cutaneous branches of superior gluteal nerve	Superior gluteal nerve
Zhibian (BL 54)		Inferior gluteal nerve, Posterior femoral cutaneous nerve
Heyang (BL 55)	Medial sural cutaneous nerve	Tibial nerve
Chengjin (BL 56)	Medial and lateral sural cutaneous nerves	Tibial nerve
Chengshan (BL 57)	Medial and lateral sural cutaneous nerves	Tibial nerve
Feiyang (BL 58)	Lateral sural cutaneous nerve	
Fuyang (BL 59)	Lateral sural cutaneous nerve	
Kunlun (BL 60)	Superficial peroneal nerve, sural nerve	Tibial nerve
Pucan (BL 61)	Sural nerve	
Shenmai (BL 62)	Superficial peroneal nerve, sural nerve	
Jinmen (BL 63)	Lateral dorsal cutaneous nerve of foot	Muscular branch of the lateral plantar nerve
Jinggu (BL 64)	Sural nerve, lateral dorsal cutaneous nerve of foot	Same as BL 63
Shugu (BL 65)	Same as BL 64	Same as BL 63
Zutonggu (BL 66)	Same as BL 64	
Zhiyin (BL 67)	Same as BL 64	

Table 2.10 Acupoints of the Spleen Meridian of Foot Taiyin (SP)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Yinbai (SP 1)	Superficial peroneal nerve	Medial plantar nerve
Dadu (SP 2)	Superficial peroneal nerve	
Taibai (SP 3)	Superficial peroneal nerve, saphe nous nerve	Medial plantar nerve
Gongsun (SP 4)	Same as SP 3	Medial plantar nerve
Shangqiu (SP 5)	Same as SP 3	
Sanyinjiao (SP 6)	Saphenous nerve	Tibial nerve
Lougu (SP 7)	Saphenous nerve	Tibial nerve
Diji (SP 8)	Saphenous nerve	Tibial nerve
Yinlingquan (SP 9)	Saphenous nerve	Tibial nerve

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Xuehai (SP 10)	Intermediate femoral cutaneous nerve	Muscular branch of the femoral nerve
Jimen (SP 11)	Intermediate femoral cutaneous nerve	Femoral nerve, saphenous nerve
Chongmen (SP 12)	Anterior and lateral femoral cutaneous nerve	Femoral nerve
Fushe (SP 13)	Lateral femoral cutaneous nerve	Femoral nerve
Fujie (SP 14)		End of the 11th intercostal nerve
Daheng (SP 15)	The 11th intercostal nerve	End of the 10th intercostal nerve
Fuai (SP 16)	The 10th intercostal nerve	End of the 9th and 11th inter costal nerves
Shidou (SP 17)	Cutaneous branch of the 5th inter costal nerve	Trunk of the 5th intercostal nerve
Tianxi (SP 18)	Cutaneous branch of the 4th inter costal nerve	Trunk of the 4th intercostal nerve
Xiongxiang (SP 19)	Cutaneous branch of the 3rd inter costal nerve	Trunk of the 3rd intercostal nerve
Zhourong (SP 20)	Anterior thoracic nerve	Trunk of the 2nd intercostal nerve
Dabao (SP 21)	Lateral cutaneous and posterior branch of the 5th intercostal nerve	Trunk of the 6th intercostal nerve

Quote from article of Department of Anatomy, Shanghai First Medical College (1973).

Table 2.11 Acupoints of the Liver Meridian of Foot Jueyin (LR)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Dadun (LR 1)	Superficial peroneal nerve, deep peroneal nerve	
Xingjian (LR 2)	Saphenous nerve, superficial nerve	
Taichong (LR 3)	Saphenous nerve, superficial nerve	
Zhongfeng (LR 4)	Saphenous nerve, medial dorsal cutaneous nerve of foot	
Ligou (LR 5)	Saphenous nerve	
Zhongdu (LR 6)	Saphenous nerve	Tibial nerve
Xiguan (LR 7)	Saphenous nerve	Tibial nerve
Ququan (LR 8)	Saphenous nerve, medial femoral cutaneous nerve	
Yinbao (LR 9)	Saphenous nerve, medial femoral cutaneous nerve, anterior femoral cutaneous nerve	Anterior branch of the obturator nerve, femoral nerve
Zuwuli (LR 10)	Genitofemoral nerve, anterior femoral cutaneous nerve	Anterior branch of the obturator nerve
Yinlian (LR 11)	Genitofemoral nerve, lateral femoral cutaneous nerve	Anterior branch of the obturator nerve

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Jimai (LR 12)	Ilioinguinal nerve	Anterior branch of the obturator nerve
Zhangmen (LR 13)		Trunk of the 10th intercostal nerve
Qimen (LR 14)	Lateral cutaneous branch of the 8th intercostal nerve	Trunk of the 8th intercostal nerve

Table 2.12 Acupoints of the Kidney Meridian of Foot Shaoiyin (KI)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Yongquan (KI 1)	Medial plantar cutaneous nerves	Medial plantar nerve
Rangu (KI 2)	Medial plantar cutaneous nerves, saphenous nerve	Medial plantar nerve
Taixi (KI 3)	Saphenous nerve	Tibial nerve
Dazhong (KI 4)	Saphenous nerve	Tibial nerve
Shuiquan (KI 5)	Saphenous nerve	Tibial nerve
Zhaohai (KI 6)	Saphenous nerve	Tibial nerve
Fuliu (KI 7)	Saphenous nerve, medial sural cutaneous nerve	Tibial nerve
Jiaoxin (KI 8)	Saphenous nerve	Tibial nerve
Zhubin (KI 9)	Saphenous nerve, medial sural cutaneous nerve	Tibial nerve
Yingu (KI 10)	Saphenous nerve, medial femoral cutaneous nerve	Tibial nerve
Henggu (KI 11)	Lateral cutaneous branches of ilioinguinal nerve	
Dahe (KI 12)		Lateral branches of the ilioing uinal nerve
Qixue (KI 13)	Anterior cutaneous and lateral bran ches of the iliohypogastric nerve	Lateral cutaneous branch of the iliohypogastric nerve
Siman (KI 14)	Anterior cutaneous and lateral bran ches of the 12th intercostal nerve	The 12th intercostals nerve
Zhongzhu (KI 15)	Anterior cutaneous and medial bran ches of the 11th intercostal nerve	
Huangshu (KI 16)	Anterior cutaneous and medial bran ches of the 10th intercostal nerve	Terminal branch of the 10th intercostal nerve
Shangqu (KI 17)	Anterior cutaneous branch and medial branches of the 9th intercostal nerve	Terminal branch of the 9th intercostal nerve
Shiguan (KI 18)	Anterior cutaneous and medial branches of the 9th intercostal nerve	Terminal branch of the 9th intercostal nerve
Yindu (KI 19)	Terminal branch of the 8th inter costal nerve	
Futonggu (KI 20)	Terminal branch of the 8th inter costal nerve	

(Continued)

Acupoints	Subcutaneous nerves	Deep-layer nerves
Youmen (KI 21)		Anterior branch of the 7th intercostal nerve
Bulang (KI 22)		Trunk of the 6th intercostal nerve
Shenfeng (KI 23)	Anterior cutaneous and medial branches of the 5th intercostal nerve	Trunk of the 5th intercostal nerve
Lingxu (KI 24)	Anterior cutaneous and medial branches of the 4th intercostal nerve	Trunk of the 4th intercostal nerve
Shencang (KI 25)	Anterior cutaneous and medial branches of the 3rd intercostal nerve	Trunk of the 3rd intercostal nerve
Yuzhong (KI 26)	Anterior cutaneous and medial branches of the 2nd intercostal nerve	Trunk of the 2nd intercostal nerve
Shufu (KI 27)	Medial and intermediate branches of the supraclavicular nerve	Trunk of the 1st intercostal nerve

Following this work, another study (Jiang, 1960) at the Shanghai Traditional Chinese Medical College showed that among 309 acupoints of the 12 meridians, the needles directly touched the trunks of the nerves at 152 acupoints (49.19%). In the remaining 157 acupoints (50.81%), the nerve trunks were within 0.5 cm diameter of the acupoints. Furthermore, Shi (1962) at Xuzhou Medical College, China, also confirmed that among all the 361 acupoints on the entire body, there are 205 acupoints (56.79%) near the nerve trunks, 104 acupoints (28.81%) near the trunks of the cutaneous nerves, and 122 acupoints near to the trunks of the deeper nerves. All these results strongly suggest that the peripheral nerves form the basis of the acupoints and the 12 meridians.

Some studies also indicated the relationship between the distribution of acupoints and the muscle tendon. Xiao (1959) found that 62.50% of the meridian acupoints were located at the dividing position of the muscle with ingress of trunks or branches of the peripheral nerves, and other 37.50% of acupoints were located at either the median or the muscle tendon enthesis. Gunn and Milbrandt (1980) studied the structural features of 70 acupoints, and validated their structural features and classified them mainly into three types. Half of the acupoints studied (35/70) were located at the moving points of the muscles, which are just the muscle-nerve junction adjacent to the skin and very sensitive to electrostimulus. This type of acupoints includes Yangbai (GB-14), Hegu (LI-4), Waiguan (SJ-5), Quchi (LI-11), Sanyinjiao (SP-6), and Shu acupoints on the back. Furthermore, 14 acupoints among the 70 studied were located at the intersection of the bilateral superficial nerves on the median sagittal line of the body. These acupoints include those of Conception Vessel (CV) and Governing Vessel (GV) meridians. Lastly, the remaining 21 acupoints studied, such as Xiaguan (ST-7), Jingming (UB-1), Fengchi (GB-20), Huantiao (GB-30), and Yanglingquan (GB-34) were located at the nerve plexus or branches of the superficial nerve. These investigations suggest that needles activate the sensory nerves that arise in the muscles, and are also consistent with the findings that stimulation of the muscle afferents is important for producing analgesia. When some sites of the body are painful or sensitive to pain stimulus, needling at those sites is usually recommended (so-called "Ashi" points in Chinese). Usually, trigger points can be found outside the muscle bellies, in skin, scars, tendons, joint capsules, ligaments, and periosteum. The most common trigger points are located on (or near) the following acupoints: Naoshu (SI-10), Tianzong (SI-11), Bingfeng (SI-12), Quyuan (SI-13), Jianzhongshu (SI-15), Naohui (SJ-13), Jianliao (SJ-14), Fengmen (UB-12), Feishu (UB-13), Jueyinshu (UB-14), Xinshu (UB-15), Dushu (UB-16), Geshu (UB-17), Zhonglushu (UB-29), Chengfu (UB-36), Yinmen (UB-37), Fuxi (UB-38), Weiyang (UB-39), Weizhog (UB-40), Fufen (UB-41), Yanggang (UB-48), Yishe (UB-49), Wushu (GB-27), Weidao (GB-28), Juliao (GB-39), Huantiao (GB-30), etc. (Qiu and Chen 1992; Li 2003).

Thus, we believe that acupoints are very closely associated with nerves, muscles, tendon, blood vessels, lymph, and other tissues near the site. However, nerve signals generated in the site are considered to be the primary component of the acupuncture-elicited message. In other words, the peripheral nerves form the main basis of the acupoints (Figs. 2.1 and 2.2).

2.3.2 General Histological Features of Acupoints

Microscopic studies of the acupoints further revealed the morphological basis of the acupoints and the mechanisms of sensation and effect of acupuncture. Though acupoints only comprise known structures such as nerves, vessels, lymph, muscles, and tendons, there exist relative specificity of the histological features of the acupoints when compared with the non-acupoints (Nakazo 1987). For example, under the acupoint Zusanli (ST-36), the subcutaneous tissues have smaller tissue space on the superficial fascia layer, and larger tissue space on the muscular and deep fascia layers than the non-acupoints. In addition, they have more branches of little vessels than the non-acupoints. While reciprocal chiasm and anastomosis of the micro-vessels are observed to form compact capillary network at the acupoint Zusanli (ST-36), the little vessels are observed to distribute into sparsate arboreal branch at the non-acupoints (Pan 1979; Pan and Zhao 1986).

Histological studies on acupoints show that they have abundant and manifold nerve endings, nerve tracts, nerve branches, and various kinds of special receptors distributed at the epidermis, dermis, subcutaneous fascia, muscular layer, and vascular tissues of acupoints. However, major differences in the variety, quantity, and style of the combination of tissues at different acupoints could be observed at acupoints. For example, there exist crescent or little orbicular free nerve endings among the metrical cells of the epidermis at the acupoints of the finger tips; and hair follicle receptor, free nerve endings, Ruffini corpuscles, Krause corpuscles and Pacini's corpuscles at the acupoints with pelages (Wang et al. 1985). Furthermore,

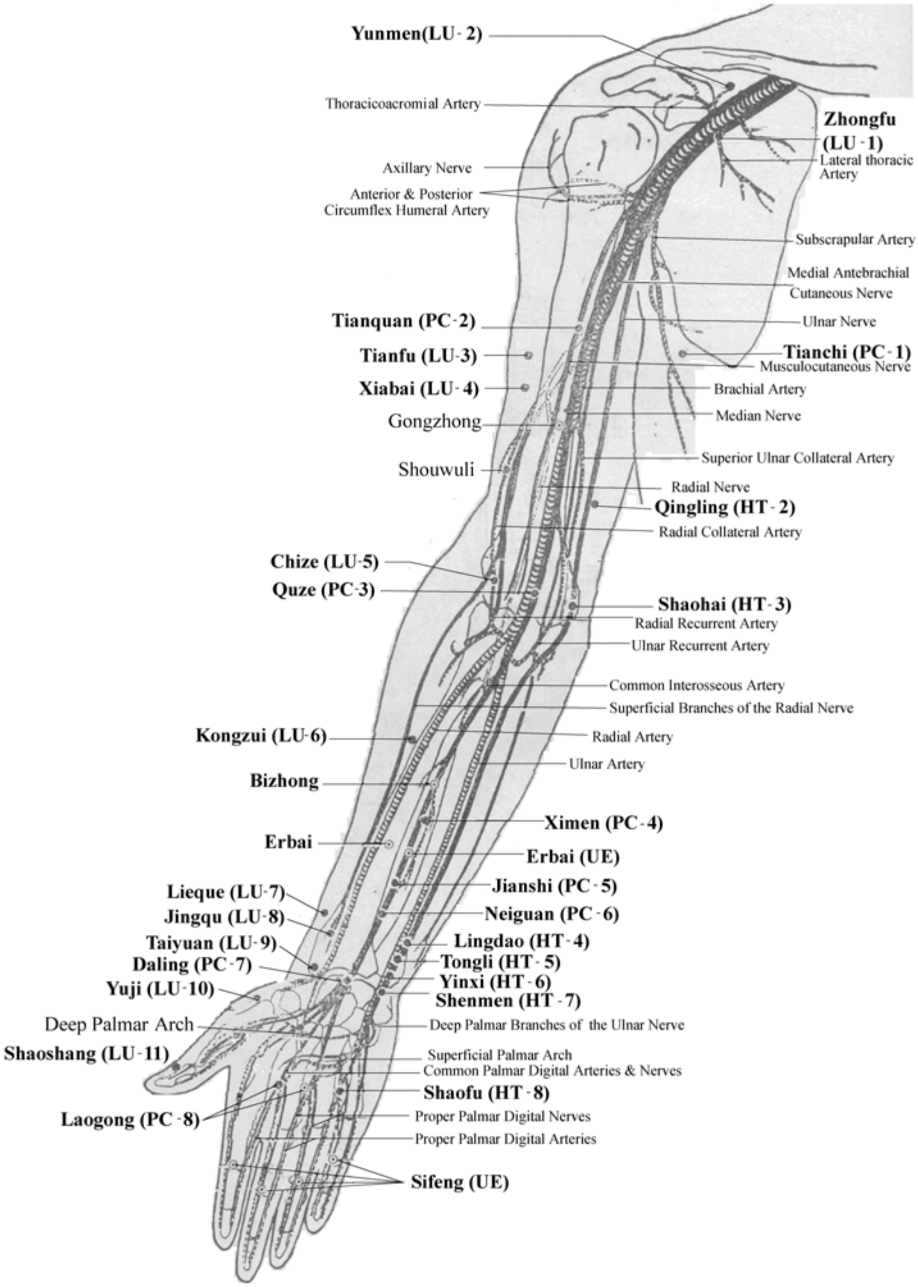

Figure 2.1 Schematic diagram of the positional projection of some acupoints on the nerves and vessels anterior to the upper limb and posterior to the lower limb. Note that the peripheral nerve tracts and branches go through most acupoints (modified from figures of Yan, 1988).

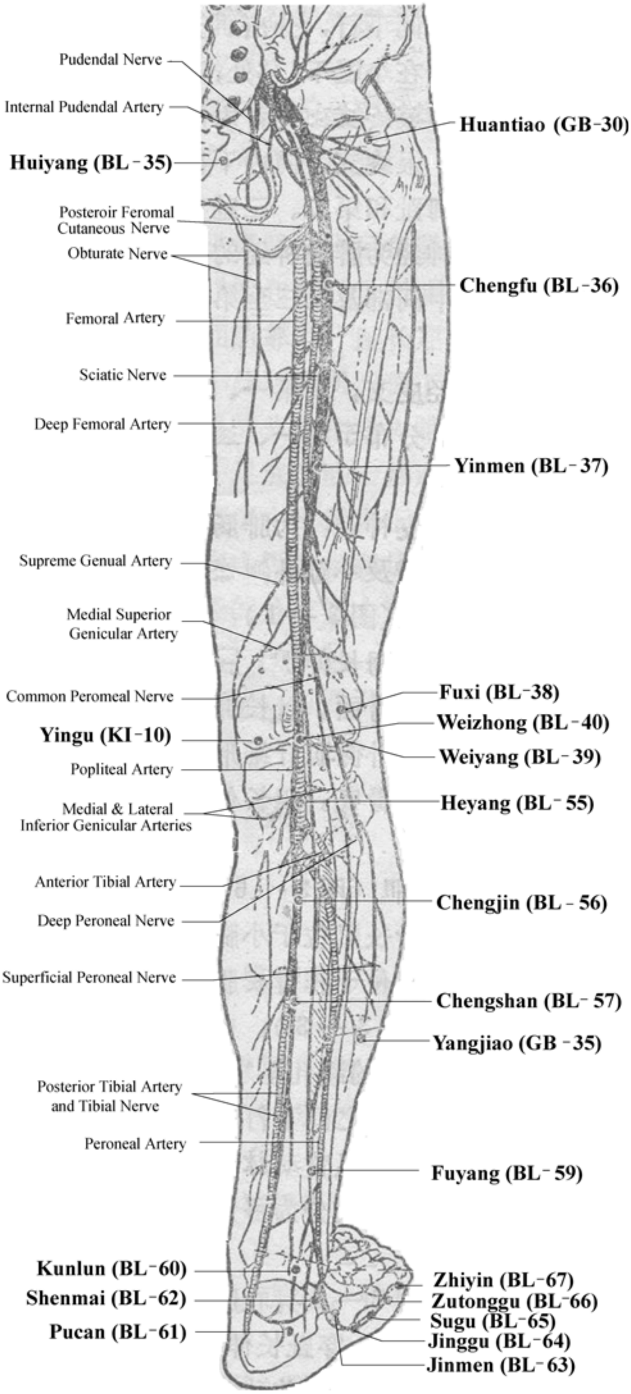

Figure 2.1 (Continued)

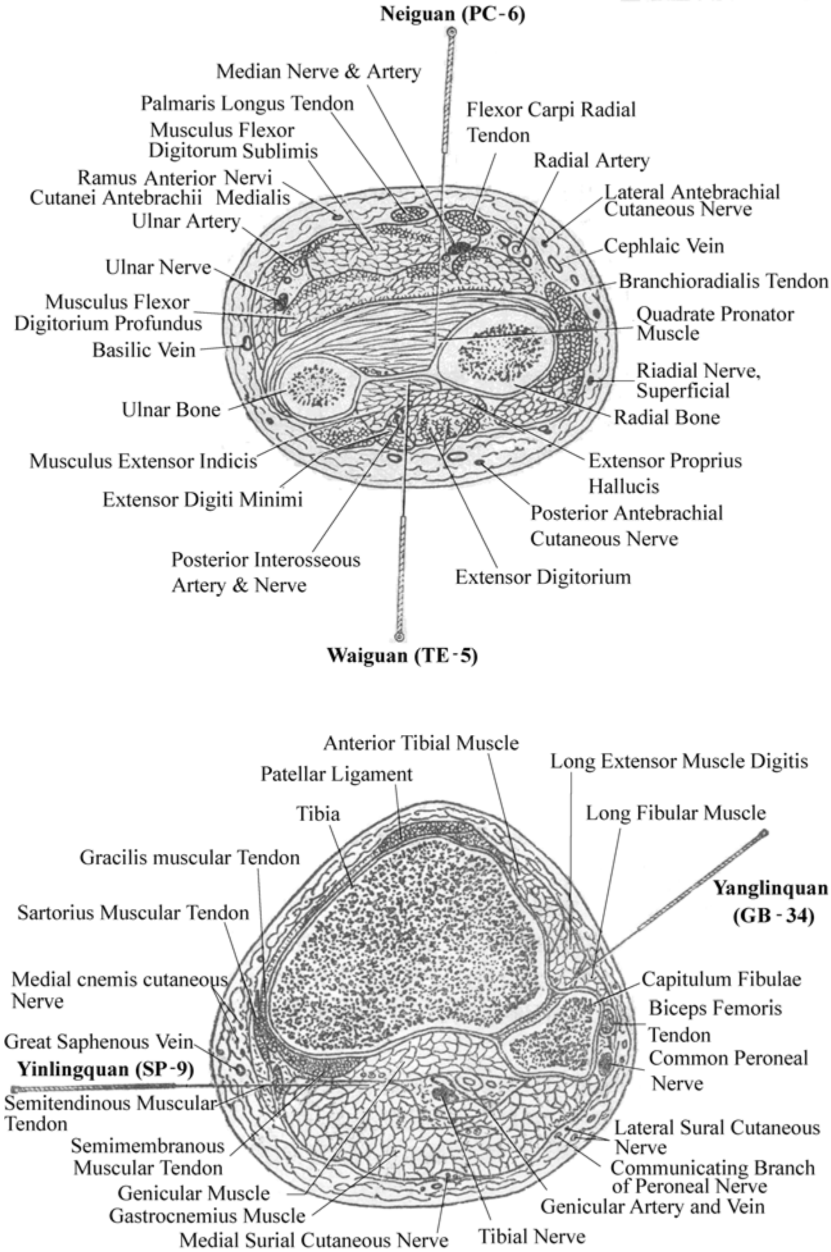

Figure 2.2 Schematic transverse section of the acupoints Neiguan (PC-6, top) and Yanglingquan (GB-34, bottom) showing the structures punctured by the acupuncture needles (modified from figures of Yan, 1988).

Meissner corpuscles and free nerve endings can be chiefly observed at the acupoints of toes, such as Yinbai (SP-1) and Dadun (LI-1). Under acupoints with capilli, hair follicle receptors, various kinds of free nerve endings, Ruffini corpuscles, Meissner corpuscles, Krause corpuscles, and lamellated corpuscles are mainly evident. At acupoints with thick muscles, there usually exist muscle spindle, nerves, and vessels. Collectively, it seems that all the acupoints are the locus where there are concentrated known histological structures, such as vessels, nerve tracts, nerve branches, free nerve endings, and various kinds of receptors; however, the non-acupoints do not appear to exhibit these characters (Cao 1979; Pan 1979; Pan and Zhao 1986).

Lin et al (1994) observed the microstructures of 29 acupoints, such as Zusanli (ST-36), Sanyinjiao (SP-6), Taixi (KI-3), Neiguan (PC-6), Yangchi (TE-4) in the limbs of 41 patients who had amputated extremity or other surgical operation on the limbs. They found that in the area of the acupoints that produced needling sensation, there were mainly neurostructures, such as little nerve bundles, free nerve endings, nerve trunk and branches, Vater-Pacini corpuscles, and muscle spindles. Furthermore, the small nerve bundles and free nerve endings were observed to be the main structures, and the nerve fibers were mainly Ⅱ, Ⅲ, and Ⅳ fibers.

2.3.3 Microanatomic Examination of Acupoints

As early as in 1958, we and other investigators (Zhou PH, Huang DK and others; please refer to the Appendix), using microanatomic methods, observed that the nerve network was highly distributed at acupoints and the surrounding tissues.

In general, the 21 acupoints studied showed homologous skin structures, that is, all the acupoints exhibited structures such as epidermis, dermis and hypodermis structures, and structures of muscles and tendons in the deep layer. However, in the microstructures among the different parts of the skin, major differences were observed in the thickness of every layer, orientation, and density of the fiber arrangement, size and number of nerves and vessels. The superficial and deep layer at all the acupoints scattered had different nerve bundles, nerve plexus, and nerve endings. Furthermore, around the sweat glands, blood vessels, and hairs, the nerve endings were much denser. Many nerve endings formed spiral structures, while some were reticular. In addition, many types of nerve microstructures could be observed, such as nerve plexus at hair follicle, muscular spindle, and racemose nerve endings (Figs. 2.3a, b). It is worth emphasizing that at the superficial acupoints, such as Shaoshang (LU-11), the touch corpuscles were abundant in its superficial tissues (Fig. 2.3c). On the other hand, at deep acupoints like Hegu (LI-4), the nerve fibers were observed to be distributed abundantly at deep-layer tissues (Fig. 2.3d).

Some researchers (Hu and Zhao 1980; Nakazo 1987) compared the amount of nervous fibers at the acupoints with that at the non-acupoints in the dermatic tissue

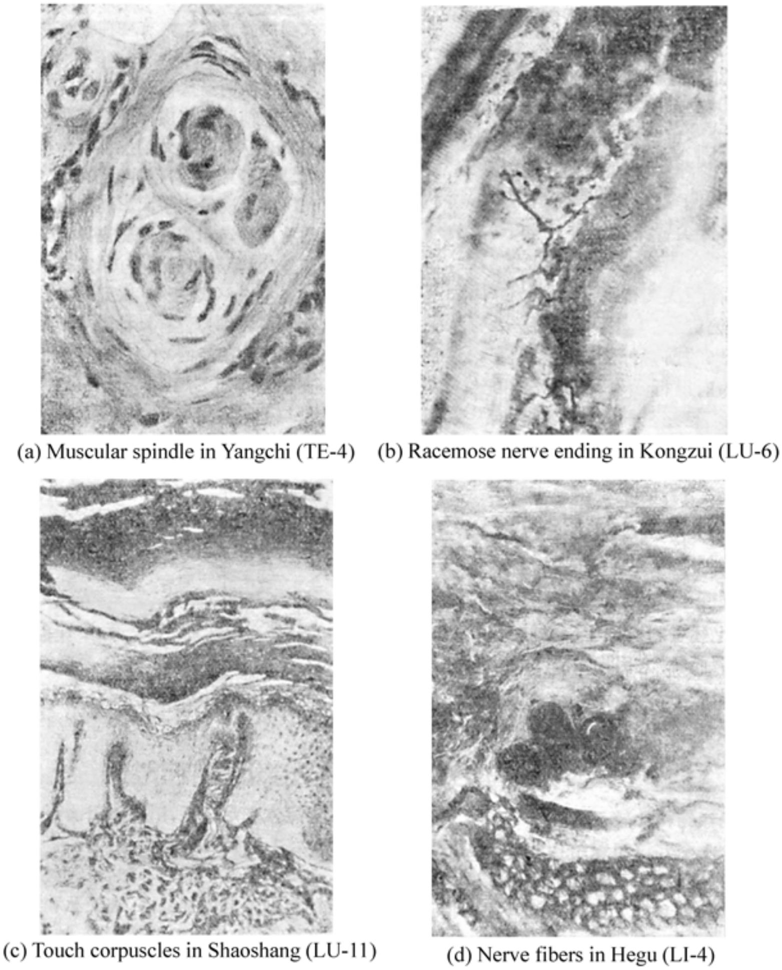

Figure 2.3 Microanatomic examination of four different acupoints. Note that there are abundant receptors and effector apparatus, such as free nerve endings, Ruffini corpuscles, Meissner corpuscles, Krause corpuscles, lamellated corpuscles, muscle spindle, etc. (Quoted from the article of Department of Anatomy, Shanghai First Medical College, 1973)

of both the humans and animals, using light microscopy and electromicroscopy. They found that the ratio of the density of the nervous fibers between the acupoints and non-acupoints were 7.22:5.26 (about 1.4:1). When compared with the components of the non-acupoints, the acupoints were observed to comprise additional nervous settings among the skin, subcutaneous tissue, and muscular layer, such as special receptors, free nervous ending, nerve bundles, and nerve plexus. Kelner (1966) observed 12,000 continuous slices of eleven acupoints and found that the acupoints were positions of obviously localized effectors and receptors. One receptor was observed to dominate only 2.80 mm^2 of the dermatic size at the area of the acupoints, while that at the area of non-acupoints was 12.83 mm^2. There were very significant differences observed between the area of acupoints and non-acupoints.

Han (1996) showed that acupoints are endowed with additional nerve fibers including pressure and stretch receptors, and have more myelinated group II fibers in their innervation, when compared with the non-acupoints. Lu et al (1979, 1983, 1986) found that in the area of Zusanli (ST-36), there are 1550 myelinated fibers and 577 non-myelinated fibers, at a ratio of 2.7:1. On the other hand, in the non-acupoint area, only 640 myelinated fibers and 860 non-myelinated fibers were observed, at a ratio of 0.7:1. They also showed that the ratio of $A_{\alpha,\beta,\gamma}$ to A_{δ} in Zusanli (ST-36) is 3.1:1, while that in the non-acupoint is 1.61:1. It seems that the myelinated fibers in the acupoints are much more than that in the non-acupoints.

In 1984, Dung listed ten structures that are found in the vicinity of acupoints. They include large peripheral nerves (the larger the nerve, the better), nerves emerging from a deep to a more superficial location, cutaneous nerves emerging from a deep fascia, nerves emerging from bone foramina, motor points of the neuromuscular attachments (the site where a nerve enters the muscle mass, which may occur a few centimeters along the nerve and then divides into smaller branches), blood vessels at the vicinity of the neuromuscular attachment, along a nerve composed of the fibers of varying diameters, bifurcation points of the peripheral nerve, ligaments (muscle tendons, joint capsules, facial sheets, collateral ligaments) rich in nerve endings, and suture lines of the skull. Thus, his data confirm that no particular structure dominates at the acupoints, and the major correlate is the presence of a nerve, either in the large nerve bundles or the nerve ending.

A report by Heine (1988) also revealed that 80% of the acupoints correlate with the perforations in the superficial fascia of the cadavers. Through these holes, a cutaneous nerve vessel bundle was observed to penetrate to the skin.

More details about the structure underneath the acupoints have been described in some anatomical atlases of the acupoints (Yan 1988; Zhang 1990; Zhu 1998; Li 2003). All these data suggest that (1) the acupoints on the face and forehead regions are located along the terminal or the cutaneous branches of the trigeminal nerve and facial nerve and (2) the typical spinal nerves have six cutaneous branches that reach the skin of the body wall in the thorax and abdomen on the trunk, and the acupoints are mostly related to the ulnar nerve, median nerve, and radial nerve on the forearm and hand.

2.3.4 Morphological Basis of Sensation of Acupuncture at Acupoints

When the needles are manipulated and retained in the acupoints by experienced Chinese doctors, the patients as well as the acupuncturists can feel a typical sensation called "*De-Qi*". This sensation is subjective and is described by patients as numbness, pressure sensation, heaviness, soreness, or distention. In addition, a feeling of heat or coldness can also be experienced. On the other hand, the acupuncturists may mostly experience a heavy and tensional feel. The *De-Qi* sensation differs among the patients, and is also dependent on the place of needling. It is more pronounced when the point is located in the peripheral muscles or when the distal points of the hand or feet are needled. It is also associated with the feeling of insertion, which is generally felt in the deep layers of the tissue. Often, the *De-Qi* sensation radiates along the channel, especially when the distal points are needled. This phenomenon is called “propagated sensation along the channel”. From the 1970s to 1980s, numerous studies on this phenomenon that generally occurs in 5% – 10% of the patients, were carried out in China. Several methods of needle stimulation have been shown to evoke propagated sensations along the channels. Indeed, the efficacy of acupuncture treatment is considered to essentially depend on the sensation of *De-Qi* induced by the needle stimulation (lifting, thrusting, rotation, clockwise or counterclockwise, etc.) (Zhang 1990; Qiu and Chen 1992).

However, the exact tissue setting that is related to these various kinds of feelings is difficult to judge from the morphological studies. Nevertheless, through studies employing the methods of morphology, myoelectricity of acupoint, separation of fine nerve tract, etc., researchers have found some clues for the basis of the sensation of acupuncture.

Dense distribution of muscle spindles has been observed at some acupoints, such as Hegu (LI-4) and Neiguan (PC-6), with thick muscles, which are related to the sensations of the acupuncturist’s hand (Zhu 1998). Acupoints near the tendons, such as Kunlun (BL-60) and Quze (PC-3), mostly comprise Picinian corpuscles, while acupoints like Chengshan (BL-57) at the juncture of the muscle and tendon mainly contain Golgi tendon organ. Furthermore, Xiyan (Ex-36) and other acupoints at the articular capsules mainly comprise Ruffini corpuscles. Usually, acupoint stimulus to the nerves, vessels, tendon and periosteum, and muscles, mainly induces a feeling of numbness, soreness, sourness, and sourness as well as distend, respectively. The connective tissues are considered to be the main structure to accept a stimulus of the acupuncture. Furthermore, numerous mast cells are observed to regularly array around the micro-vessels, capillary, nerve endings, and nerve plexus at the acupoints. In addition, the activation of mast cells by the stimulus may also be related to the sensation and effect of acupuncture (Popov 2001).

When manipulating the needles to obtain the *De-Qi* sensation, the acupuncturist’s hand may experience the sensation of heaviness, tightness, non-smoothness, and stagnation. It has been validated (Zhu 1998) that these strengthened feelings mainly occur at the acupoints with thick muscles, such as the acupoints of Hegu (LI-4), Neiguan (PC-6), and Zusanli (ST-36). Histological observations show that the muscle spindles are the main receptive settings at the acupoints with thick muscles. The intrafusal fiber is observed to accept the impulse derived from the γ-efferent fiber of the spinal cord, contract, and subsequently release myoelectricity to induce contraction of the local muscles.

Some researchers (Pan 1979; Shi and Zhang 1996) have found that the sensation of needling at the acupoint of Hegu (LI-4) is derived from the deep-layer structure, and have testified that the muscle spindles at this acupoint should be receptors of the needling stimulus. Therefore, the structure of Hegu (LI-4) point is considered to involve both the somatic and the vegetable nerves. In the area of Neiguan (PC-6), the receptors of the needling sensation are observed to be located at the quadrate pronator muscle, along with the distributed adrenergic and cholinergic fibers at the arteriolar circumference, hypodermic, and muscular tissues (Liao et al. 1979).

2.3.5 Other Morphologic Research on Acupoint

Redundant micro-vessels are also observed to be distributed at the acupoints, and there exists plexus of sympathetic nerve on the wall of the vessels (Zhu 1998; Li 2003). When manipulating the needle, the afferent impulse of the acupuncture signal can stimulate the efferent sympathetic nerve on the vessels and activate the vascular smooth muscles. Thus, the micro-vessels at the local acupoints may be partially involved in the effect settings of the acupuncture.

There has been evidence showing the relationship between the acupoints and blood vessels, as well as the autonomic nerve in the wall of the blood vessels. Huge et al (2000) showed that among the 361 acupoints of the entire body, 58 acupoints (16.07%) are located near the main stem of the arteries, and 87 acupoints (24.10%) are near the stem of the superficial veins. For example, Zusanli (ST-36) of Stomach meridian of Foot-Yangming is observed to be located just at the converging points of the vascular branch of the nerve at the anterior tibial artery, which is derived from both the common peroneal nerve and the deep tibial nerve. Fuliu (KI-7) of Spleen meridian of Foot-Shaoyin is observed to comprise the anastomotic ramus of the vascular nerve of the tibial nerve at the anterior tibial artery. Laogong (PC-8) has been found to comprise the anastomotic ramus of the vascular nerve derived from both the median nerve and cubital nerve. Furthermore, Hegu (LI-4) is found to contain the vascular branch of the nerve derived from the common palmar digital nerve of the thumb. All these facts indicate the somatic nerves' connection with the plexus of the vegetative nerve around the vessels or the insertion into the vascular wall to form the anastomotic ramus or the converging point under the acupoints. They may be the key points or pathway linking the functional connections between the somatic and vegetative nerves. Furthermore, these facts may also explain the cause of the sensation of *De-Qi* concomitant with the effect of the vegetative nerve.

Moreover, some investigators noticed the features of three-dimensional construction of acupoints as well as the characters of the extracellular matrix of the acupoints (Yu et al. 1996a, 1996b).

Taken together, an acupoint is very likely to be a complicated structure comprising nerve endings, receptors, vessels, connective tissues, and other tissue/cells with nerve signals being the cause of acupuncture sensation.

2.4 Neural Connection Between Meridian-Point and Viscus

According to the theories of TCM, acupoints and meridians are associated with *Zang-Fu* (viscus; internal organs). The correlation between the meridian-points and viscera is also known as the body-surface connection with viscera (Cheng 1990), and refers to the bidirectional relationship between the meridian-points and viscera. In other words, the pathological or physiological change in the viscera can be reflected by the corresponding meridian and acupoints on the body surface, which in turn, stimulate certain meridian or acupoints that can adjust the physiological function or pathological change in the corresponding viscera (Li 2003).

On comparing the correlation between the meridian-points and viscera with the relationship between the meridian-points and peripheral nerves, we can see that the meridian-points and viscera are closely correlated through the peripheral distribution of the nerves. The theory of correlation between the meridian- points and viscera may be adapted based on the current knowledge of the nervous system.

First, the mutual internal and external meridians are observed to be closely related to their distribution in the peripheral nerves.

(1) Lung Meridian of Hand-Taiyin and Large Intestine Meridian of Hand-Yangming are closely related to the musculocutaneous and the radical nerves. The tip of the needle is inserted into the trunk of the radical nerve at the points of Quchi (LI-11) and Chize (LU-5). The anastomotic branches of the two nerves are found at the point of Lieque (LU-7). The superficial branch of the radical nerve arises from the point of Lieque (LU-7) and goes to Yangxi (LI-5). Furthermore, the branch of the lateral antebrachial cutaneous nerve is observed to come from Lung Meridian of Hand-Taiyin distributed at Pianli (LI-6). These distributions correspond to the parlance of "*Fu*-organs following to *Zang*-organs and meridians of *Fu*-organs going along superficial and external". The acupoints of Lung Meridian of Hand-Taiyin from Tianfu (LU-3) to Shaoshang (LU-11), except for Shaoshang (LU-11), are mostly consistent with the distribution of the trunk of the musculocutaneous nerve. Along the Large Intestine Meridian of Hand-Yangming, one can observe the trunks of the dorsal antebrachial cutaneous nerve of the radical nerve from Shouwuli (LI-13) to Pianli (LI-6), branch of the lateral brachial cutaneous nerve from Wenliu (LI-7) to Yangxi (LI-5), and superficial branch at the points of Yangxi (LI-5) and Hegu (LI-4).

(2) Heart Meridian of Hand-Shaoyin and Small Intestine Meridian of Hand-Taiyang are the internal and external meridian, respectively. One can observe the ulnar and medial antebrachial cutaneous nerve distributed along both the meridians. The trunk of the lateral antebrachial cutaneous nerve comes across the Heart Meridian of Hand-Shaoyin from Qingling (HT-2) to Shenmen (HT-7). The stem of the ulnar nerve passes through the Heart Meridian of Hand-Shaoyin from Jiquan (HT-1) to Shaochong (HT-9), except for Shaohai (HT-3). There are the branches of the medial antebrachial cutaneous nerve distributed at Xiaohai (SI-8) of Small Intestine Meridian of Hand-Taiyang, and the trunk of the ulnar nerve distributed at its deep layer.

(3) Pericardium Meridian of Hand-Jueyin and Sanjiao Meridian of Hand-Shaoyang are related to the internal and external meridian, respectively. The branches of the medial antebrachial cutaneous nerve distributed along both the meridians, and many acupoints of the two meridians are observed to be related to the palmar interosseous nerve of the median nerve in the deep layer. On the head, both the facial and auriculotemporal nerves are distributed on the two meridians. Furthermore, there exist branches of the median nerve distributed along the Pericardium Meridian of Hand-Jueyin from Quze (PC-3) to Zhongchong (PC-9), branches of the medial antebrachial cutaneous nerve at the superficial layer, and branches of the lateral cutaneous nerves at the acupoints of Ximen (PC-4), Jianshi (PC-5), and Neiguan (PC-6). The branches of the median and the palmar interosseous nerves in the deep layer from Ximen (PC-4) to Neiguan (PC-6) can also be observed. By inserting the needles at Neiguan (PC-6), one can touch the dorsal interosseous nerve and reach Waiguan (TE-5) of Sanjiao Meridian of Hand-Shaoyang. From Sidu (TE-9) to Yangchi (TE-4) of Sanjiao Meridian of Hand-Shaoyang, there exist the dorsal antebrachial cutaneous nerve distributed on their superficial layer, or the medial antebrachial cutaneous nerve at the acupoints of Huizong (TE-7) and Sidu (TE-9). In addition, there exist branches of the ulnar nerve from Guanchong (TE-1) to Yangchi (TE-4), and the distributed branches of dorsal interosseous nerve in the deep layer from Sidu (TE-9) to Waiguan (TE-5).

(4) Stomach Meridian of Foot-Yangming and Spleen Meridian of Foot-Taiyin are observed to be related to the internal and external meridian, respectively. Both the saphenous nerve and superficial peroneal nerves are distributed on the two meridians. In addition, Kidney Meridian of Foot-Shaoyin and Bladder Meridian of Foot-Taiyang are observed to be related to the internal and external meridian, respectively, comprising tibial-nerve distribution.

According to the “internal and external” theory of TCM, diseases are considered to invade the human body and progress internally or externally through the correlated meridians. Thus, diseases related to the internal meridian can be treated using both internal and external meridians. On the other hand, the “external” diseases can also be treated using external and internal meridians.

Second, the relationship between the distribution of Shu and Mu points, and their correlative viscera are observed to be closely associated with the distribution of the peripheral nerves. Shu points on the back and nape parts, and Mu points on the chest and abdomen parts can be differentiated into *Yin* and *Yang*: Mu points belong to *Yin*, and the Shu points belong to *Yang*. In Table 2.13, the relationship of the segmental nerve distribution between the correlative organs and Mu and Shu points, based on the phenomenon of segmental distribution of the nerves in the human organs, is listed.

Table 2.13 Relationship of the neural segmental distribution between the correlative organs and the Mu and Shu points

Organs	Spinal Segments	Shu Points		Mu points	
		Acupoints	Segments	Acupoints	Segments
Lung	$C_3 - T_4$	Feishu (BL 13)	T_{1-3}	Zhongfu (LU 1)	T_1
Pericardium		Jueyinshu (BL 14)	T_{2-4}	Danzhong (CV 17)	T_4
Heart	T_{3-4}	Xinshu (BL 15)	T_{3-5}	Juque (CV 14)	
Liver	T_{7-10}	Ganshu (BL 18)	T_{7-9}	Qimen (LR 14)	T_8
Gallbladder	T_{7-10}	Danshu (BL 19)	T_{8-10}	Riyue (GB 24)	T_9
Spleen	T_{6-11}	Pishu (BL 20)	T_{9-11}	Zhangmen (LR 13)	T_{10}
Stomach	T_{6-9}	Weishu (BL 21)	T_{10-12}	Zhongwan (CV2)	T_9
Sanjiao		Sanjiaoshu (BL 22)	$T_{11} - L_1$	Shimen (CV 5)	T_{11}
Kidney	$T_{12} - L_1$	Shenshu (BL 23)	$T_{11} - L_1$	Jingmen (GB 25)	T_{11}
Large intestine	T_{11-12}	Dachangshu (BL 25)	L_3	Tianshu (ST 25)	T_{10}
Small intestine	T_{9-11}, L_{1-3}	Xiaochangshu (BL 27)	S_1	Guanyuan (CV 4)	T_{12}
Bladder	$T_{11} - L_2$	Pangguangshu (BL 28)	S_{1-2}	Zhongji (CV 3)	$T_{12} - L_1$

C: cervical nerve; T: thoracic nerve; L: lumber nerve; S: sacral nerve.

2.4.1 Segmental Nerve Innervation Between Meridian-Points and Viscera

Neuroanatomical studies have demonstrated that the distribution of meridian-points are closely related to the segmental innervation. In the studies on the relationship between the locations and indications of the acupoints on the trunk of the body and the neural segments, it was found that the nerves of the trunk are segmental and arranged almost annularly, and that the Back-Shu and Front-Mu points and the points of the CV meridian are identical with the internal organs to which these points pertain and govern in the neural segments. For instance, Zhongfu (LU-1), the Front-Mu point of the lung, and Feishu (BL-23), the Back-Shu point of the lung, are both controlled by the first-fifth segments of the thoracic nerves and the nerves that control the lung come from the same neural segments. Tanzhong

(CV-17), controlled by the fourth neural segment of the thoracic nerve, is indicated in diseases of the respiratory system. This shows that the points and their corresponding internal organs have an identity in the neural segments.

The alignments of the acupoints on the ventral and dorsal trunk present the neurotaxis are shown in Fig. 2.4. The characteristic alignments of the acupoints of the eight meridians are as follows:

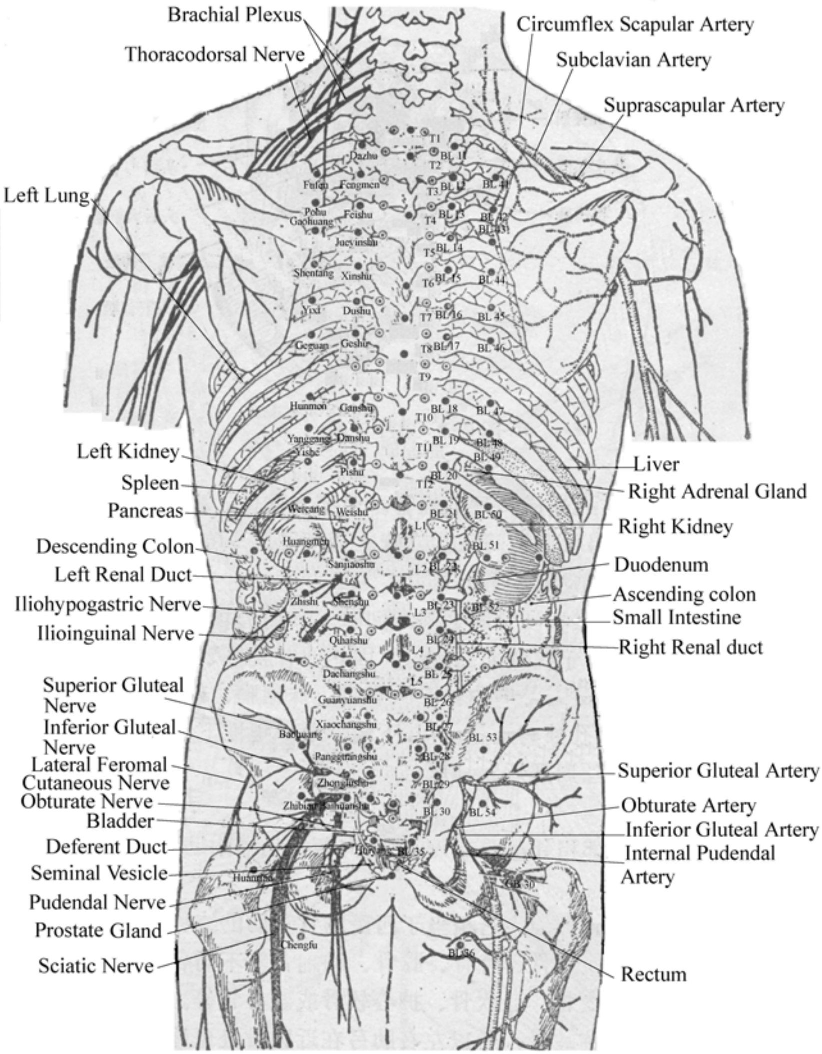

Figure 2.4 Schematic diagram of the relationship between acupoints and distribution of cutaneous nerve, and their dominant viscera on the dorsal trunk. Note that the connection between the meridian point and viscera is closely related to the segmental innervations and the convergence of somatic and autonomic nerves at the same spinal segments (modified from figures of Yan, 1988).

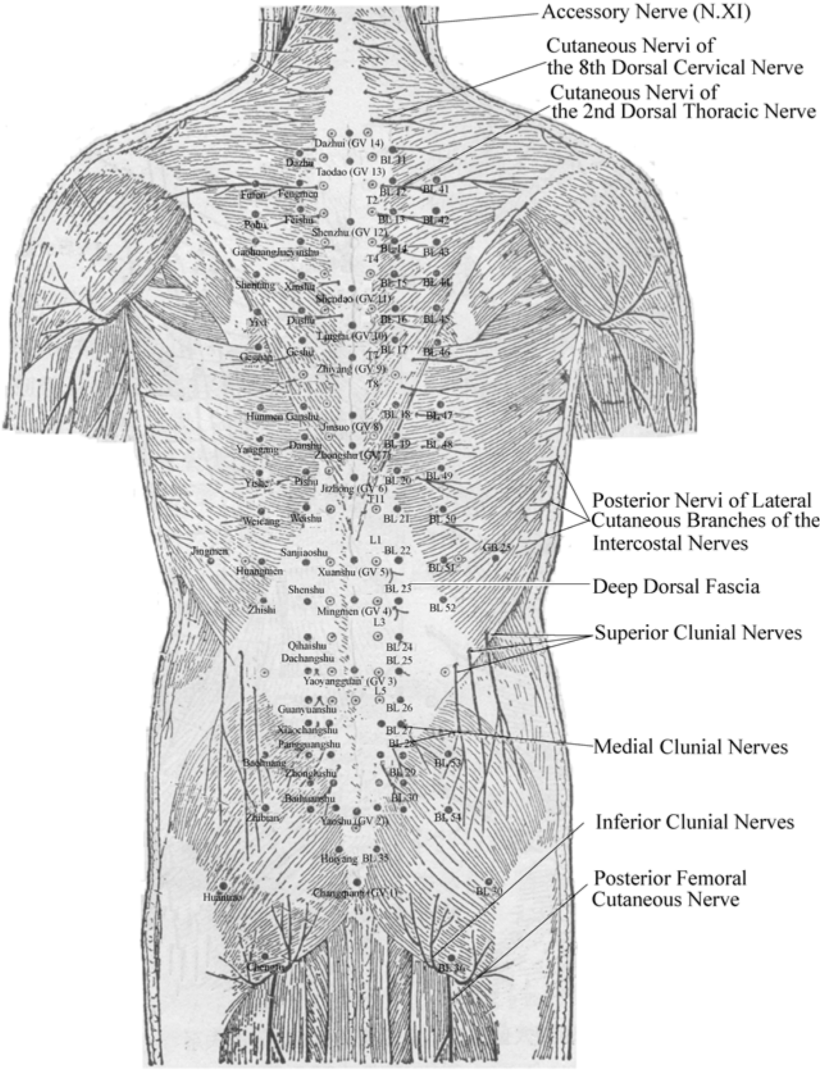

Figure 2.4 (Continued)

(1) Acupoints of the CV Meridian are located at the midline of the abdomen, where the juncture of the terminal of the anterior cutaneous branches of the bilateral thoracic nerve is distributed. The alignments of the acupoints are very identical with the distribution of the anterior cutaneous branches of the thoracic nerve.

(2) Abdominal acupoints of the Kidney Meridian of Foot-Shaoyin, the Stomach Meridian of Foot-Yangming, and the Spleen Meridian of Foot-Taiyin are located in a parallel array near the anterior cutaneous branches of the cutaneous nerve bilateral to the midline of the abdomen. As the lateral branch of the anterior cutaneous branches of the cutaneous nerve on the abdomen is shorter, the acupoints of the

three meridians are observed to lie nearer to the midline of the abdomen. However, when the three meridians go up to the thorax, the lateral branches of the thoracic nerves extend longer, and owing to the enlargement of the thoracic cage, the alignment of the acupoints of the three meridians move away from the midline laterally.

(3) Similar to the alignment of those on the abdomen, the acupoints of the GV meridian and the Urinary-bladder Meridian of Foot-Taiyang lie in a parallel array on the midline and both sides on the back, and are very identical with the distribution of the posterior cutaneous branches of the thoracic nerve.

(4) The distribution of nerves on the ventral and dorsal trunk presents the primitive neurotome. Apparently, alignments of the acupoints on the trunk are very identical with the segmental innervation.

The alignments of the acupoints on the four limbs is associated with the nerve segments. As the nerve segments of the four limbs are the extension of the primitive nerve segments along the longitudinal axis of the limbs, unlike the obvious segmental characters of the nerve segments on the trunk, every meridian on the limbs are located at one or two nerve segments. For example, the Lung Meridian of Hand-Taiyin is distributed along the radial to the upper limbs, which includes the spinal segment of $C_{5\ 6}$. The Heart Meridian of Hand-Shaoyin is distributed along the ulnar to the upper limbs, corresponding to the spinal segment of T_1. The Pericardian Meridian of Hand-Jueyin is distributed intermediately, including the spinal segment of $C_{7\ 8}$. Another example is the distribution of acupoints of the Heart Meridian of Hand-Shaoyin from the aspects of the nerve segments. This meridian is situated just at the segment of the upper thoracic spinal cord ($T_{1\ 3}$), and the sensory fibers of the somatic nerves of the medial upper limbs also enter the dorsal horn of the upper thoracic spinal cord. The primary center of the sympathetic nerve of the heart is also located at the upper thoracic spinal cord. As both these sensory fibers and sympathetic nerves converge at the dorsal horn of the upper thoracic spinal cord, acupuncturing the acupoints of the Heart Meridian of Hand-Shaoyin can affect the functioning of the heart through the segment of the upper thoracic spinal cord.

The relationship between the therapeutic efficacy and particular acupoints further shows that the meridians are closely related to the neural segments. For instance, the points of the Heart Meridian of Hand-Shaoyin may be used to treat diseases of the heart, lung, and trachea. The same meridian passes through the medial aspect of the tip of the little finger, and the medial aspect of the forearm and the chest. The skin of these areas where the meridian passes is controlled by the first-third neural segments of the thoracic nerves. This indicates that these areas and the heart, lung, and trachea are under the domination of the same neural segments. Another example is the long branches of the intercostal nerve that descend for several segments. According to the orientation of the sensation of needling and the range of indications of the acupoints, there exists considerable coherency between the segmental nerve distribution of the acupoints and that of the organs.

With regard to the Spleen Meridian of Foot-Taiyin, all the acupoints at the calf are observed to be related to the saphenous and tibial nerves, and belong to the nerve segments of $C_{3\ 4}$ and $S_{1\ 3}$ of the spinal cord. These nerve segments are also vegetal nerve segments that dominate the celiac and pelvic organs. The traits of the meridian may be related to its special morphological structure, which might explain the possibility of the treatment of the internal-organ diseases by puncturing or moxibusting the superficial acupoints.

The relationship between the meridian-points and the peripheral nerves is different from that between the body trunk and limbs. On the body trunk, the nerves are segmental and arranged almost annularly, and occasionally, are vertical. Table 2.14 shows the relationship between the main acupoints of the CV Meridian and the nerve segments of the correlative organs.

Table 2.14 Relationship between the main acupoints of the CV meridian and the nerve segments of the correlative organs

Acupoints	Nerve Segments	Correlative Organs	Nerve segment
Danzhong (CV 17)	T_4	Trachea, lung	$C_2 - T_4$
Jiuwei (CV 15)	T_6	Stomach	T_{6-9}
Zhongwan (CV 12)	T_8	Stomach	T_{6-9}
Qihai (CV 6)	T_{11}	Intestine, reproductive organ	T_{10-12}
Shimen (CV 5)	T_{11}	Uterus, kidney, bladder	$T_{10} - L_2$
Guanyuan (CV 4)	T_{12}	Uterus, kidney, bladder	T_{10-12}

We also observed that thin branches of the anterior and lateral cutaneous branches of the intercostal nerves overlapped with each other, and some fibers anastomosed to form the nerve plexuses. The positions of these plexuses correspond to the lines of the Spleen, Stomach, and CV Meridians. This phenomenon may interpret the reason for the radiating nature of the needling sensation along the meridian path.

2.4.2 Convergence of Afferent Signals of Meridian-Points and Viscera in the Central Nervous System

To explore the overlapping and anastomosed relationships of the segmental distribution of the afferent neurons of the organs of heart, stomach, liver, and gallbladder, etc., Tao et al (1989, 1991) employed the horseradish peroxidase (HRP) tracing technology to study the sensory neural segment of eleven acupoints, namely, Neiguan (PC-6), Jianshi (PC-5), Shaohai (HT-3), Zusanli (ST-36), Taichong (LR-3), Qimen (LR-14), Liangmen (ST-21), Ganshu (BL-18), Pishu (BL-20), Sibai (ST-2), and Hegu (LI-4). They found that after injected HRP into the acupoint of Neiguan (PC-6), the segments $C_6 - T_1$ emerged HRP-labeled cells, suggesting that the segments of the afferent neurons of Neiguan (PC-6) are $C_6 - T_1$. At the same time, the HRP-labeled neurons were found at the anterior horns of the spinal cord of segments $C_6 - T_1$. Among these HRP-labeled neurons, most were middle- and small-sized cells. Using the same method, they found that the segments of the afferent neurons of Jianshi (PC-5) are $C_7 - T_1$; Shenmen (HT-7), $C_6 - T_2$; Shaohai (HT-3), $C_6 - T_2$; Zusanli (ST-36), $T_{10\ 12}$, $L_{1\ 7}$, and $S_{1\ 3}$; Taichong (LR-3), T_{12}, $L_{1\ 7}$, and $S_{1\ 3}$; Qimen (LR-14), $T_{5\ 8}$; Liangmen (ST-21), $T_5 - L_2$; Ganshu (BL-18), $T_6 - L_1$; Pishu (BL-20), $T_6 - L_1$; and Hegu (LI-4), $C_{5\ 8}$. Interestingly, more large and middle neurons were labeled by the HRP at the acupoints of Zusanli (ST-36) and Ganshu (BL-18). They also showed that the HRP-labeled neurons were located at the semilunar ganglion of the trigeminal nerve as well as the nuclei of the facial and oculomotor nerves, after injected the HRP into the acupoint of Sibai (ST-2), which may possibly explain the reason for using this acupoint to treat syndromes of pain of the trigeminal nerve and paralysis of the facial nerve.

Tao and Zhang (1993) also used the HRP-tracing method to study the segmental distribution of the afferent nerve of the visceral organs. They found that the ganglion neuron of the segments $C_{4\ 8}$, $T_{1\ 12}$, and Wenliu (LI-7) were labeled by HRP, when it was injected into the anterior and posterior wall of the stomach, as well as the pylorus and cardia. It implied that the segments of the sympathetic afferent nerves of the stomach are $C_{4\ 8}$, $T_{1\ 12}$, and associated with Wenliu (LI-7). Wenliu (LI-7) is also overlapped and anastomosed with the segments of the afferent nerve of the acupoint Zusanli (ST-36) ($T_{10\ 12}$, $L_{1\ 7}$, $S_{1\ 3}$). This overlapped and anastomosed relationship provides the morphologic basis for the acupuncture treatment of the diseases of stomach and intestines by puncturing the acupoint Zusanli (ST-36). Similarly, there is an overlapped and anastomosed relationship between the afferent nerve of the heart (segment $C_8 - T_{10}$) and the acupoints Neiguan (PC-6) ($C_6 - T_1$), Jianshi (PC-5) ($C_7 - T_1$), Shenmen (HT-7) ($C_6 - T_2$), and Shaohai (HT-3) ($C_6 - T_2$). Similar relationships were found between liver ($T_3 - T_{12}$ and L_1) and acupoints Qimen (LR-14) ($T_{5\ 8}$), Liangmen (ST-21) ($T_7 - L_2$), and Ganshu (BL-18) ($T_6 - L_1$). Based on the overlapped and anastomosed relationship between the segments of the afferent nerve of the visceral organs and some special acupoints, we may at least partially explain the aspect of the morphologic basis of stimulating the acupoints to treat diseases of the visceral organs.

Other experiments (Tao and Li 1993; Tao and Ren 1994) also validated the phenomena that afferent fibers of the body surface and the relative viscera converge at the same neuron. Using double-labeling technology, researchers (Tao and Ren 1995) found double-labeled cells at $T_{2\ 5}$. After labeling the heart nerve with true blue (TB), the second intercostal nerve with bisbenzimide (Bb), the wall of the bladder with fast blue (FB), and the tibial nerve with nuclear yellow (NY), the double-labeled cells were observed at the spinal segment of the dorsal horn of L_6. These phenomena imply that the effect of acupuncture on the visceral function may occur at the lower center (spinal cord), and that the sensory impulse of the acupoints or the peripheral nerves activated by acupuncture could affect the sensation and function of the viscus through the efferent branches of the axons. In addition, by using the methods of neural degeneration and lesion techniques, researchers also found that the nucleus of the brainstem, hypothalamus, and cortex play an important role in the relationship between the meridian-point and viscus.

2.5 Afferent Nerve Fibers and Afferent Pathway of Acupuncture Signal

Abundant data suggest that acupuncture signal is transmitted mainly by somatic sensory nerves with afferent fibers of sympathetic nerves being involved in activity of some acupoints (Li 2003). Lu et al (1979, 1983, 1986) studied the distribution of myelinated and non-myelinated fibers at acupoint area of Zusanli (ST-36), and found that the ratio of the number of myelinated fibers to non-myelinated fibers was about 2.7:1, and that of the number of thick fiber (myelinated fiber of type Ⅱ (diameter 6~12 μm, 52%) and type Ⅰ (>12 μm, 22%) to thin fiber (type Ⅲ, <5 μm, 26%) was 3:1. They concluded that one structural feature of acupoint of Zusanli (ST-36) was more myelinated fibers than unmyelination fibers at acupoints of Zusanli (ST-36), and especially more type Ⅱ fibers. For structural feature of acupoint Rongquan (K-1), there were many receptors at side of muscular mantle and fiber, such as free nerve ending, muscular spindle, and so on.

Collectively, the area of an acupoint is observed to contain free nerve ending, Vater-Pacini corpuscles, and muscle spindle. The nerve fibers are of types Ⅰ, Ⅱ, and Ⅲ, with type Ⅱ being the major type. Furthermore, the acupoints and meridians are observed to be closely related to the peripheral nerves.

2.5.1 Acupuncture Signal and Afferent Nerve Fibers

Many researchers believe that the main effect of acupuncture is mediated by the afferent nerve signal through the somatic nerve, along with the afferent elements of some sympathetic nerve (Bishop and Landau 1958; Chiang et al. 1973; Chan 1984; Pomeranz 1986). For example, the afferent pathway of Zusanli (ST-36) is observed to be the peroneal nerve (Lu et al. 1979). Chiang et al (1973) validated that the effect of acupuncture analgesia with Hegu (LI-4) was mediated by the afferent signal through the deep somatic nerve, because it was unaffected by the blockage of cutaneous nerve. Pomeranz and Chiu (1976) also confirmed that the effect of acupuncture analgesia with Hegu (LI-4) only appeared in the integrity of the radial nerve, and that the effect of Neiguan (PC-6) on analgesia and pressure-boost were eliminated by the dissection of the median nerve. Furthermore, after dissection of the infraorbital nerve, the effect of Renzhong (GV-26) on anti-shock and pressure-boost was also eliminated (Lu et al. 1979). These observations suggest that the sensory fibers of the somatic nerve serve as an afferent pathway of acupuncture. On the other hand, many studies show that the acupuncture could induce activation of the internal organs. For example, needling Zusanli (ST-36) was observed to induce change in the movement of the intestines, implying that a part of the fiber of the sympathetic nerve may have participated in the transmission of the acupuncture effect.

In 1978, Toda and Ichioka reported that type Ⅱ afferent fibers were sufficient for acupuncture analgesia in rats. In addition, Pomeranz (1986) also found that type Ⅱ afferent fibers were adequate to produce acupuncture analgesia. Some researchers believed that the acupoint maps were essential for localizing the sites where the best *De-Qi* could be achieved (i.e., location of type Ⅱ and Ⅲ muscle afferent fibers). Lu (1983) showed that type Ⅱ and Ⅲ afferent fibers were important for acupuncture analgesia in rabbits and cats because diluted procaine (0.1%) blocked type Ⅳ fibers and had no effect on acupuncture analgesia, while ischemic blockade (or anodal blockade) of type Ⅱ and Ⅲ fibers eliminated acupuncture analgesia.

In 1985, Wang et al carried out some observational experiments on human subjects using direct microelectrode recordings from single fibers in the median nerve, and performed acupuncture on the distal side. They observed that during *De-Qi*, numbness was related to the activation on type Ⅱ muscle afferent fibers; heaviness, distension, and aching were owing to the activation of type Ⅲ fibers; and soreness was related to the activation of type Ⅳ non-myelinated fibers. The acupuncturists also noticed that when the patient got the *De-Qi* sensation, the muscle grabbed the needle.

Although there is still disagreement on the relationships between the afferent effect of the acupuncture and the fiber type of the somatic nerves (Zhu 1998), anatomical and electrophysiological evidence lead us to the conclusion that afferent fibers of type Ⅱ and Ⅲ are responsible for transmitting the acupuncture signal. The acupoints might possibly be the loci of type Ⅱ and Ⅲ fibers. However, there is also evidence showing that all type Ⅰ, Ⅱ, Ⅲ, and Ⅳ fibers may participate in the signal transmission of acupuncture. Some studies showed that electroacupuncture mainly stimulate the fibers of type Ⅱ and Ⅲ fibers, while acupuncture manipulation mainly stimulate the fibers of type Ⅲ and Ⅳ, producing feeling of sourness, numbness, distention, and weightiness. More studies are needed to clarify this important issue.

2.5.2 Acupuncture Signal Transmission Pathway

Currently, many researchers consider that impulse induced by acupuncture transmits to the spinal cord to the interneurons, and then, the second impulse transmits to the upper nerve center along the lateral funiculus of the ventral spinal cord (Tao 1989;

Lin et al. 1991; Huge et al. 2000). Previous studies on this issue showed, for example, that the effect of acupuncture was eliminated by the dissection of dorsal funiculus of the spinal cord, and that acupuncture analgesia and adjustment of visceral function were eliminated by the dissection or destruction of the lateral funiculus of the bilateral ventral spinal cord. In patients with syringomyelia, owing to the destruction of concatenation of conduction tract of thermic sense and the ventral lateral funiculus, both the effect and sensation of the acupuncture disappeared. Acupuncture signals entering the posterior horn of the spinal cord were also observed to influence the neurons of the anterior and lateral horns to initiate soma-viscus reflex or soma-soma reflex, thus, adjusting the pain reaction and activation of viscus through sympathetic fibers or γ-efferent fibers. All these facts demonstrate that acupuncture signals affect the neurons of the posterior horn after entering the spinal cord, and then transmit upward through the ventral lateral funiculus.

Through transmission from the spinal cord, the signals enter the brain, and are exchanged in the thalamus, and then projected upward to the cerebral cortex, to produce the sensation of acupuncture. If the connection between the cortex and axons of the sensory neuron of the thalamus is interrupted, then the patients may not be able to ascertain the location of the sensation of acupuncture.

Thus, the signal of acupuncture can be transmitted to the CNS through the peripheral afferent pathway and be integrated into the brain, finally, sending therapeutic signals via the efferent pathway (also see Chapter 3).

2.6 Concluding Remarks

There have been numerous theories concerning the meridians and acupoints. However, none has been supported by convincing evidence, except for the data from neurobiological research. Extensive studies with current techniques have demonstrated that the peripheral nervous system forms the basis of the so-called meridians and acupoints, while CNS processes the acupuncture signal. Substantial data have shown that meridians and acupoints are closely associated with the peripheral nerves. Furthermore, the nerves distributed at the acupoints and their correlative organs have been observed to belong to the same spinal segment, or within the range of the nerve segments belonging to the correlative organs. There have been differences (e.g., thickness and orientation of the fibers, thickness of the tissue layer, etc.) observed among various acupoints, though they have similar tissue structures, such as epidermis, dermis, and hypodermis. With respect to the nerves, the acupoints have been observed to differ not only in the density of the nerve distribution and thickness of the nerve fibers under every acupoint, but also in the shape of the nerve endings. Owing to these differences, the puncturing methods and puncturing deepness vary from one acupoint to another. Accordingly, the reflection of *De-Qi* is also observed to be different, depending on the acupoints punctured. The effect of a given acupoint on the body is observed to be at least partly related to the structural traits and its location.

However, there are also some unresolved issues in the neuroanatomic studies regarding the relationship between the nerves and meridians (Sun et al. 2002). For example, there has been no consistency, to some extent, between the segments of some organs and those of the distribution of acupoints that are effective for the organs (e.g., small intestine and Xiaochangshu (BL-27); bladder and Pangguangshu (BL-28); and stomach and Zusanli (ST-36)). Another example is the meridians on the head, such as Gallbladder Meridian of Foot-Shaoyang and Sanjiao Meridian of Hand-Shaoyang. Significant mismatch has been observed between the nerves and these meridians. Hence, further investigations are needed to clarify these issues. Therefore, before we try to fully understand the mystery of acupoints and meridians, it may be valuable to retain the meridian theory in mind for efficient clinical practice and laboratory research. It is possible that there are issues that we cannot understand with our present knowledge. Hence, if we dismiss this ancient theory, we may lose some important information about the nature of acupuncture and guideline for the clinical practice.

Note: Most contents of Section 3 in this chapter (The neuroanatomic basis of acupoints) have been written based on the original studies by Drs. Zhou PH, Huang DK (the second author of this chapter), and others at the Shanghai First Medical College (now Fudan University Shanghai Medical College) from 1958 to 1960. The original article was informally and partially published in Chinese in 1959, 1960 and 1973. Also refer to the Appendix at the end of this book.

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3 Neural Transmission of Acupuncture Signal

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Summary Acupuncture, one of the most prevalent methodologies of Traditional Chinese Medicine (TCM), has been used in Asian countries for curing numerous diseases for thousands of years. However, the true mechanisms underlying the effectiveness of acupuncture are still under debating. The meridian model based on TCM has been used so far, for guiding the practice of acupuncture. In this model, acupuncture is believed to treat the diseased organ of the patient by balancing the *Yin* and *Yang* conditions that are regulated by an energy substance (*Qi*) flowing constantly through the whole meridian, a network connecting all the organs of the body. Therefore, in the acupuncture treatment, it is crucial to select special acupoint(s) along the meridian that links the diseased organs, as well as to modulate the *Qi* flowing in the meridian through the induction of the needling sensation (*De-Qi*). On the other hand, a neurobiological model established in the recent decades, has supported the notion that an important mechanism of acupuncture in curing diseases is mediated by the nervous system. Stimulation by needles at acupoints is considered to initiate acupuncture signals through the nerve fibers (e.g., A_β and A_δ) innervated at the deep tissue near the acupoints. The acupuncture signal is transmitted through the central nervous system, which activates and integrates with the neurons located in broad areas, such as those in the cortex, limbic system, brainstem, spinal cord, which in turn, regulate other systems. The nerve-mediated model provides us a better explanation regarding the biological mechanisms of acupuncture signal transmission in the body which has been broadly documented by both *in vivo* and *in vitro* studies under controlled conditions. In this chapter, we will review in particular, the research concerning the influence of acupuncture-elicited signals in the nervous system and how the neural pathways mediate the therapeutic effects of acupuncture.

Keywords *acupuncture signal, afferent nerves, autonomic nervous system, central nervous system, transmission*

3.1 Introduction

Acupuncture therapy has been practiced in China and other Asian countries for more than two thousand years. Modern clinical research has confirmed the impressive therapeutic effect of acupuncture on numerous human ailments, such as controlling pain, nausea, and vomiting. However, the biological mechanisms of acupuncture are still under debate. In Traditional Chinese Medicine (TCM), the mechanism of acupuncture therapy is explained by a meridian model. According to this model, acupuncture is believed to treat the diseased organs by modulating two conditions known as *Yin* and *Yang*, which represent all the opposite principles that people find in the universe, both inside and outside the human body. *Yin* and *Yang* complement each other, and are subjected to changes between each other. The balance of *Yin* and *Yang* is thought to be maintained by *Qi*, an energy substance flowing constantly through the meridian, a network connecting all the organs of the body. The illness, according to this theory, is the temporary dominance of one principle over the other, owing to the blockade of the *Qi* from flowing through the meridian under certain circumstance. The axiom of "No stagnation, No pain" in TCM summarizes this concept. Thus, the goal of acupuncture treatment is to restore the balance of *Yin* and *Yang* conditions in the diseased organ(s). This theory has been considered to be useful to guide this ancient therapy, such as carrying out diagnosis, deciding on the principle, and selecting the acupoints. However, neither *Qi* nor meridian can be detected under a controlled condition in the animal model or in humans, using current scientific technology. Thus, the meridian-mediated theory is still a mystery.

In the past 50 years, extensive efforts have been taken to explore the biological mechanisms and its significance in acupuncture, using modern technologies. The successful results of the tests, ranging from animal experiments to clinical analysis, clearly support the neurobiological hypothesis of acupuncture in regulating multiple systems including the hormonal and immune system. Hypothetically, the acupuncture signal is initiated at the acupoints surrounding the nerve terminals, and is transmitted to the intro- and super-spinal regions, following the afferent nerve fibers. In the central nervous system, the acupuncture signal is believed to regulate the activity of the neurons in certain brain areas (i.e., the cerebral cortex, the limbic system, the hypothalamus, the brainstem descending control system, etc.) by directly or indirectly controlling the activity of the target organs through the efferent nerve and neural-endocrine mechanism. Indeed, through controlled experiments, a chain of events triggered by the mechanical stimulation at the acupoints with needling or its electrical equivalent (electro-acupuncture) can be traced. For instance, in the human or animal model, the acupuncture-induced unit discharges of neurons could be recorded using electrophysiological methods, the level of synthesized and/or the release of a neurotransmitter or its receptor can be measured by biochemical assays, and the activity of a brain area owing to acupuncture can be monitored by noninvasive functional imaging methods, thus, investigating the association of acupoint-brain activity. The fact that acupuncture could activate or inhibit specific brain areas associated with functions of nociceptive, cardiovascular, and vision, suggests that a number of neural circuits and substrates are specifically involved in the therapeutic effect of acupuncture. Among them, the limbic system which mediates both the neural-endocrine system and the brainstem-descending control-spinal cord in the acupuncture analgesia has been perhaps the most extensivelystudied. The neural pathways, as shown in Fig. 3.1, may partially elucidate the regulatory effect of acupuncture in improving the pathological actions caused by the internal environmental dysfunctions, such as in the situations of pain, cardiovascular diseases, and substance abuse.

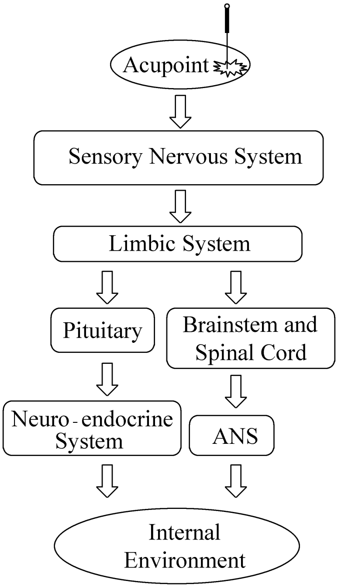

Figure 3.1 The nerve-medial acupuncture signal transmission model. The diagram shows that one of the mechanisms of acupuncture is regulation of the autonomic nervous activity that modulates the body homeostasis. The acupuncture signal is first transmitted to the central nervous system via the sensory nervous system (including afferent fibers, thalamus, cerebral cortex, etc.), especially to the limbic system, in which the signal is integrated among the neurons that control the activity of the autonomic nervous system and endocrine system. ANS, autonomic nervous system.

Understanding of the biological mechanisms is essential to comprehend the acupuncture therapy and the theory of meridian in TCM. However, the biological mechanisms underlying acupuncture are yet to be fully understood. Neither the meridian model nor the neurophysiological model could completely elucidate all the findings obtained from the clinical tests and research, and both the theories have their shortcomings and limitations. In this chapter, we will discuss whether (1) the neural signal initiated by stimulation of acupoint could influence in the activation of numerous neural pathways in the central and peripheral nervous systems; and (2) the activation changes of those neural pathways underlie the therapeutic effect of acupuncture.

3.2 Initiation of Acupuncture Signal

Acupuncture signals for curing the diseases, elicited by the stimulation of acupoints, have been claimed and described by the researchers and clinicians in favor of either the meridian model of TCM or the neurobiological model. Even though arguing remains about the biological mechanisms underlying the initiation of acupuncture signal at the acupoint, it has been well documented that certain patterns of acupuncture signals evoked by the stimulation of acupoint are crucial for treating various diseases. A most significant phenomenon regarding the initiation of acupuncture signal is the needling sensation (*De-Qi*) generated by the stimulation of acupoint. The results obtained from the clinical observation and research experiment indicate that the selection of acupoint, modality, frequency, intensity, and timing plays an important role in generating the needling sensation and thus, determining the effectiveness of acupuncture. In the following sections, we will first discuss about the factors that affect the initiation of acupuncture signal, and then, determine whether there is any neural mechanism underlying the needling sensation.

3.2.1 Acupoint-Selection Impact on the Pattern of Brain-Area Activity

More than 400 acupoints, including their size and depth, have been classified according to their origin of meridian, functional significance, and localization in the body, by the State Supervision Bureau of Technology of China and World Health Organization (WHO). The specificity of acupoints is an important issue, as the effectiveness of acupuncture is largely dependent on the acupoint (single or multiple) selected. Numerous evidences from electrophysiological recordings of the unit response of the neurons to the acupoint stimulation, microinjection of compounds (such as agonist or antagonist that specifically bind to a neurotransmitter receptor) into the brain area, or destruction of certain brain nucleus have revealed that manipulation of neuronal activation in certain brain areas could significantly change the functional effect of the acupoint stimulation, indicating an existence of an acupoint-brain activation relationship during acupuncture. Furthermore, recently developed functional methods, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) enable the monitoring of the brain-area activity triggered by needling at the acupoint. As the noninvasive testing methods, fMRI and PET can be used to test the brain activation in the conscious patients, normal subjects, or animal models under acupuncture manipulation. Investigations using these methods have demonstrated that different brain-area activities could be evoked by needling, which have been designated as real acupuncture or sham acupuncture in both human and animal models.

The selection of sham acupuncture in fMRI is mostly based on the non-meridian points (Cho et al. 1998), superficial tactile stimulation (Hui et al. 2000), or both (Yoo et al. 2004). The sham acupuncture group may demonstrate no or very little effect mostly on the somatosensory areas, as observed in the studies using fMRI. Wu et al (2002) compared the real electro-acupuncture with three other acupuncture control groups, namely, mock electro-acupuncture (no stimulation), minimal electro-acupuncture (superficial and light stimulation), and sham electro-acupuncture (same stimulation as real electro-acupuncture but applied at non-meridian points). In this study, the real electro-acupuncture by needling at the acupoint of Yanglingquan (GB-34) was observed to elicit significantly higher activation in the hypothalamus and primary somatosensory-motor cortex, and lower activation in the rostral segment of the anterior cingulate cortex, than the sham electro-acupuncture. On comparing the minimal electro-acupuncture with mock electro-acupuncture, the minimal electro-acupuncture was observed to elicit significantly higher activation over the medial occipital cortex. Furthermore, single-subject analysis showed that superior temporal gyrus (encompassing the auditory cortex) and medial occipital cortex (encompassing the visual cortex) frequently respond to minimal electro-acupuncture, sham electro-acupuncture, or real electro-acupuncture.

For example, Neiguan (PC-6) is an acupoint relevant for the management of nausea, including vestibular-related motion sickness, and is usually selected for the treatment of cardiovascular disorders also. Acupuncture of Neiguan (PC-6) was observed to selectively activate the left superior frontal gyrus, anterior cingulate gyrus, and dorsomedial nucleus of the thalamus. Furthermore, acupuncture-specific neural substrates in the cerebellum were also evident in the declive, nodulus, and uvula of the vermis, quadrangular lobule, cerebellar tonsil, and superior semilunar lobule. The MR-signal changes, often observed during the acupuncture of analgesic points, were not observed in this study (Yoo et al. 2004). Using fMRI and a word-generation paradigm, significant activation was observed in the left and right inferior frontal gyri (BA-44, 45), as well as in the left superior temporal gyrus (BA-22, 42). Electrical stimulation of either one of the two language-implicated acupoints, Sanyangluo (TE-8) and Yamen (GV-15), without the word-generation paradigm in the same cohort, produced significant activation in the right inferior frontal gyrus (BA-44, 46) and the left and right superior temporal gyri (BA-22, 42), respectively (Li et al. 2003). Thus, fMRI studies demonstrated that stimulation of different acupoints could modulate the activity of different sets of brain areas, which is consistent with acupoint-brain activation observed previously using invasive methods.

3.2.2 Acupuncture Modality: Manual or Electrical?

There is no standard acupuncture modality defined yet. Currently, manual and electrical are the two dominate methods. Several experiments voluntary using fMRIs have been designed to study the effects of different acupuncture modalities on acupoint-brain activation. Both manual and electro-acupuncture have been found to modulate fMRI signals in the brain areas (Kong et al. 2002; Li et al. 2003); however, they displayed distinct brain activation patterns. This implies the recruitment of different brain mechanisms. Kong (2002) showed that electro-acupuncture at Hegu (LI-4) mainly produced increased fMRI signals in the precentral gyrus, postcentral gyrus/inferior parietal lobule, and putamen/insula; while, manual needle manipulation produced prominent decreases in the fMRI signals in the posterior cingulate, superior temporal gyrus, and putamen/insula. This suggests that different brain network (a different set of brain areas) may be involved during manual or electro-acupuncture stimulation. Furthermore, an overlapped acupoint-brain activation pattern was also reported by Napadow et al (2005). By comparing the major effects of the electro-acupuncture at different frequencies (2 or 100 Hz) with the manual acupuncture at the acupoint of Zusanli (ST-36), they found that, in general, electro-acupuncture (particularly at low frequency) produced more widespread fMRI signal increases than the manual acupuncture did. On the other hand, both acupuncture stimulations produced more widespread responses than the placebo-like tactile control stimulation.

Another modalitiy, laser needles, has also been described (Siedentopf et al. 2002; Litscher et al. 2004). Acupuncture with laser needle is painless and do not any tactile optical stimulation. The advantage of a patient being unaware of the acupunctural stimulation helps the researchers to perform true double-blind studies in acupuncture research (Litscher et al. 2004). Studies on healthy subjects indicate that laser acupuncture (Siedentopf et al. 2002) has the effect of inducing the activity of visual-related areas by stimulating vision-related acupoints, similar to other acupuncture modalities.

3.2.3 Wave Forms, Frequency, Intensity, and Timing

Electro-acupuncture has the power of setting stimulation frequency and intensity objectively and quantifiably. It has been found that 2 or 100 Hz electro-acupuncture stimulation can induce analgesia via distinct central mechanisms. Low-frequency acupuncture is observed to release endorphins (enkephalin and β-endorphin), while high-frequency acupuncture is found to release dynorphin. In an fMRI experiment reported by Zhang (2003), the average fMRI signals in the bilateral secondary somatosensory area and insula, as well as contralateral anterior cingulate cortex and thalamus were observed to be positively correlated with the electro-acupuncture induced analgesic effect across the subjects in either 2 or 100 Hz frequency. Positive correlations were observed in the 2 Hz group in the contralateral primary motor area, supplementary motor area, and ipsilateral superior temporal gyrus, while negative correlations were found in the bilateral hippocampus. In the 100 Hz group, positive correlations were observed in the contralateral inferior parietal lobule, ipsilateral anterior cingulate cortex, nucleus accumbens, and pons, while negative correlations were detected in the contralateral amygdala. Electro-acupuncture with low frequency (2 Hz), as described by Napadow et al (2005), produced a more widespread of fMRI-signal than those of high frequency (100 Hz) and placebo-like tactile control stimulation. For example, only low-frequency electro-acupuncture was observed to produce signal increases in the pontine raphe area. The results indicate that distinct brain activation patterns elicited by either low or high frequency, though overlapped, are displayed, suggesting that the functional activities of certain brain areas, correlated with the effect of electro-acupuncture, are frequency-dependent.

In traditional acupuncture practice, the intensity of acupuncture could be enhanced by different methods including the rotation of acupuncture stimulation. An fMRI study by Fang et al (2004) compared the non-rotating with the rotating stimulation method of two real acupoints Taichong (LR-3) and Qiuxu (GB-40), and one sham point in 15 healthy subjects. The rotating of the needle was observed to strengthen the effects of the acupuncture only at the real acupoints, by activating the secondary somatosensory cortical areas, frontal areas, the right side of the thalamus, and the left side of the cerebellum. No such effects of the needling technique were seen while stimulating the sham point. In addition, the results from the studies in healthy humans using fMRIs after the stimulation of acupoints indicated that the stimulation of acupoints can induce the activity change in specific set of brain area(s).

The duration of acupuncture stimulation is also important for the disease treatment, and there is no restriction with respect to the time of the stimulation. In general, at least 10 min is required for the production of the therapeutic effects of acupuncture, with the maximal effect caused from 30 min to a few hours of acupuncture. The therapeutic windows are numerous, broadly ranging from hours to days based on the patient's condition and the acupuncture methodology selected. Moreover, acupuncture treatment has a cumulative effect. A prolonged therapeutic effect of acupuncture is thought to be caused by the increased release of endogenous opioid in the endocrine system. Traditional practitioners suggest that initial treatments should be 1 – 2 times per week, until the patient's body begins to maintain the desired balance. Subsequently, the treatment can be continued weekly, every other week, or monthly. However, there is still a lack in the follow-up study with the functional imaging method in the patients treated with different paradigms of acupuncture. According to the clinical practice, some patients eventually have just a seasonal "tune-up". With a still unknown mechanism, acupuncture will cause a reduced effect in curing diseases by tolerance of the patients to the acupuncture treatment.

3.2.4 Transduction of Acupuncture Signal in the Afferent Nerves

As discussed earlier, acupuncture signal could modulate the activation of neural pathways. Than, what is the mechanism by which acupuncture signal is initiated by needling of the acupoint(s)? In the recent years, many studies have been carried out to demonstrate the transmission of acupuncture signal in the afferent nerves. Attention has been paid particularly to explore the biological mechanism of a special needling sensation (*De-Qi*), the experience of the needling sensation is considered commonly as an indicator of the effectiveness of the acupuncture procedure. The needling sensation experienced by the patient during acupuncture includes numbness, heaviness, and radiating paraesthesia along the pathways of the meridians. However, the biological mechanism of needling sensation still remains unclear. Zhou et al (1979) demonstrated an anatomical association of meridians, especially where the acupoints are located, with the distribution of peripheral nerves. These data provided indirect anatomical evidences of the structural relationship of the meridian with the peripheral nerves in terms of the acupoint distribution, and support the idea that the acupuncture signal may be initiated at the nerve fibers surrounding the acupoints.

To study the biological basis of the needling sensation during acupoint stimulation, the needling sensations of 168 affected points were evaluated and compared with that of 131 normal points in 76 patients with various neurological diseases (Department of Physiology and Acupuncture Research Group, Shanghai First Medical College 1973; Chen et al. 1986). The needling sensation was absent at all points in the affected regions in patients with complete brachial plexus and spinal transactional lesions. Patients with spinal motor neuron disease, myopathy, and deep sensory deficits such as Tabes dorsalis involving the posterior column were able to feel the needling sensations at all the affected points. The after-effects of the needling sensations in patients with Tabes dorsalis disappeared quickly. whereas in patients with Syringomyelia involving anterior commissure or posterior horn in the spinal cord, the needling sensation was markedly weakened or completely absent, together with reduced pain and thermal deficits (Fig. 3.2). Thus, these results indicate that the impulses of needling sensations are ascended mainly through the ventrolateral funiculi, in which pain and temperature sensations are

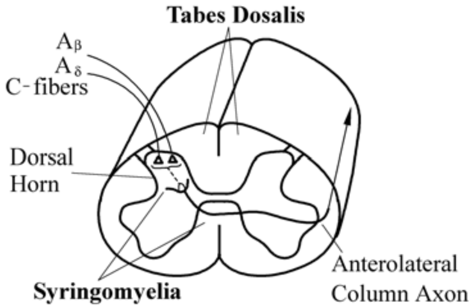

Figure 3.2 Diagram showing the damaged areas in spinal cord of the patient with Tabes dorsalis and Syringomyelia.

conducted upward to the brain. The needling sensations and acupuncture effects are observed to be closely related to the structural and functional integrity of the pathway conducting pain and temperature sensations.

After realizing that the needling sensation is closer to the deep muscle pain, Chiang et al (1973), with procaine (2%), blocked either the cutaneous nerves that innervate the skin tissue or the muscular nerves underlying the same point to test the hypothesis. They founded that the blockade of the cutaneous nerves did not affect the needling sensations and acupuncture analgesia caused by stimulation at Hegu (LI-4). However, the blockade of the muscular nerves eliminated the needling sensation and acupuncture analgesia. They further reported that the afferent impulses for the needling sensation and acupuncture analgesia were transmitted mainly via the deep nerves that innervate the deep fasciae, tendinous sheaths, muscles, and periostea.

Other studies extended the findings that acupuncture activity accompanied by the needling sensation is likely to pass to A_β (type II) (Pomeranz and Paley 1979), A_δ (type III) (Chiang et al. 1975; Lu 1983), and possibly even C fibers (Li et al. 2002). Toda (2002) reported a significant correlation between the amplitude of A_β fibers in the compound action potentials of ulnar, median, and raduak nerves elicited by electro-acupuncture at Hegu (LI-4), and the degree of suppression of the jaw-opening reflex. The experiment revealed greater suppressive effect after the stimulation of Hegu (LI-4) than that of the two non-meridian points.

Recently, clinic trials have also provided evidences that support the idea that needling of muscle produces better therapeutic effect of acupuncture on patients suffering from segments of pain (Molsberger et al. 2002), low back pain (Melchart et al. 2003), or shoulder myofascial pain (Ceccherelli et al. 2001), than needling of skin and subcutaneous tissue. These deep acupunctures are observed to be better at all times, and this underlines the importance of stimulating the afferent nerves in muscle with needling sensation for the control of pain.

Various evidences yielded from histology, electrophysiology, immunohistochemistry, molecular signal transduction, functional imaging, etc., have thus implied that the afference of acupuncture information, at least parts of it, depends on the peripheral nervous system. The detailed mechanism of how the acupuncture signal is initialized at an acupoint still needs to be delineated.

3.3 Integration of Acupuncture Signal in the Central Nervous System

A great number of evidences have revealed that various brain areas are affected by acupoint stimulation. However, how are they involved in producing the therapeutic effect of acupuncture? There are ample evidences that support the notion that various neural pathways in the central and peripheral nervous systems are activated and integrated during acupuncture. Such regulated neural pathways may integrate into a neural network to modulate the internal environmental dysfunctions that cause symptoms like pain, cardiovascular diseases, and substance abuse. As the analgesic effect of the acupuncture is perhaps the most well studied, in this section, acupuncture analgesia will be taken as an example to introduce how the various neural pathways in the central nervous system are regulated by the stimulation of acupoint, and work together to modulate the nociceptive signals.

A brief summary about the neuronal circuitry for acupuncture analgesia is characterized and provided in Fig. 3.3. The signals triggered by the acupuncture have been demonstrated to activate the endogenous analgesia system, as well as integrate and suppress the nociceptive signals along the nociceptive pathway at different levels of the central nervous system. At least, it includes the areas of the spinal cord, reticular formation, nuclei raphe, locus coeruleus, periaqueductal gray (PAG), arcuate nucleus, preoptic area of hypothalamus, thalamus, caudate nucleus, accumbens, amygdala, hippocampus, and cortex. Thus, the overall effect of the acupuncture analgesia depends on a dynamic balance between the neuronal activities at different levels of the central nervous system. Three neuronal circuitries are believed to play essential roles in acupuncture analgesia, and therefore, have been extensively studied in terms of understanding the biological mechanisms underlying the acupuncture analgesia. These neuronal circuitries are located at the spinal cord, lower brainstem, and mesolimbic area.

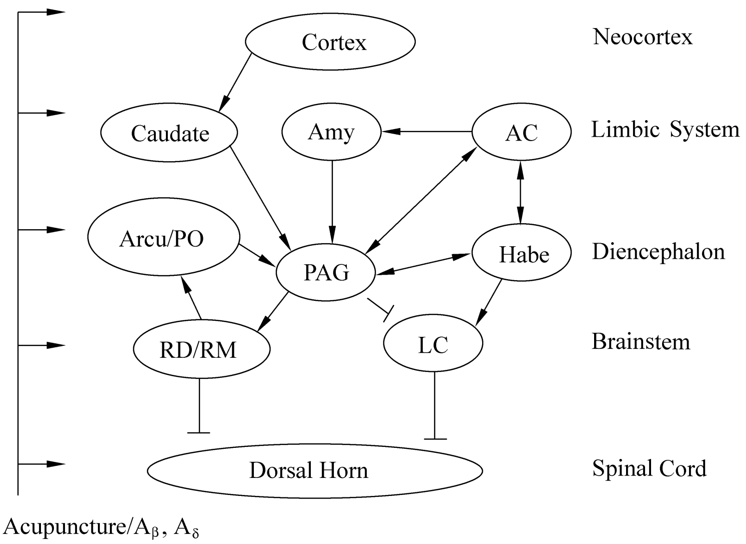

Figure 3.3 Schematic diagram of the possible neural pathways involved in acupuncture analgesia. AC, nucleus accumbens; Amy, nucleus amygdala; Arcu, arcuate nucleus of hypothalamus; Habe, nucleus habenula; LC, locus coeruleus; PAG, periaqueductal gray; PO, preoptic area of hypothalamus; RD/RM, nucleus raphe dorsalis/nucleus raphe magnus.

3.3.1 Integration of Nociceptive and Acupuncture Signals in the Spinal Cord and the Gate Control Theory

The gate control theory of pain, proposed by Melzack (Melzack and Wall 1962), illustrates that the perception of physical pain is modulated by the interaction between different neurons. Afferent fibers, that bring noxious stimulation signals to the brain, comprise the myelinated A_{δ} fiber and the small non-myelinated slow C fiber, while the large-diameter A_{β} fibers are non-nociceptive and could inhibit the effects of firing by C fibers. Some areas of the laminae in the dorsal horn of the spinal cord are observed to receive both the pain stimuli from the C fibers and the non-nociceptive input from A_{β} fibers, where the non-nociceptive fibers indirectly inhibit the effects of the pain fibers, thus, "closing a gate" to the transmission of their stimuli (Kandel et al. 2000). On the other hand, in other parts of the laminae, the pain fibers also inhibit the effects of non-nociceptive fibers, thus "opening the gate". In the model, an inhibitory connection exists with A_{β} and C fibers, which could form a synapse on the same "projection neuron", as well as with an inhibitory interneuron that also forms a synapse on the projection cell. The activation of the interneuron will inhibit the projection cells and reduce the pain signal to the brain. The C fiber's synapse can inhibit the inhibitory interneuron, indirectly increasing the projection cell's chance of firing. On the other hand, the A_{β} fiber forms an excitatory connection with the inhibitory interneuron, thus, decreasing the projection cell's chance of firing. Like the C fiber, the A_{β} fiber also has an excitatory connection on the projection neuron. Thus, depending on the relative rates of firing of C and A_{β} fibers, the firing of the nonnociceptive fiber may regulate the firing of the interneuron and projection neuron, and the transmission of pain stimuli to the brain (Kandel et al. 2000). The gate control theory not only explains that the peripheral nervous system has centers at which pain stimuli can be regulated, but also shows how the stimulus that activates only the non-nociceptive nerves can also inhibit pain (Fig. 3.4).

Hypothetically, scientists speculated that during acupuncture analgesia, non-nociceptive A_{β} and A_{δ} fibers are selectively stimulated to produce inhibition of the activation of the projection cells and thereby, lessening pain. Indeed, on the primary afferent substance, P fibers seem to contain presynaptic opioid receptor. It was found that the electrical stimulation of the sensory nerves with intensities that elicit C and A_{δ} fibers may increase the release of P-like immunoreactive material, while the stimulation of the enkephalinergic neurons with low frequency may inhibit the release of the P substance from the primary afferent nociceptive neurons. Further observations imply that the circulating opioid peptides, stimulation of enkephalinergic interneuron by activating A_{β} fiber, or administration of opiate drug, could inhibit the release of P substance and the transmission of action potentials evoked by noxious stimuli. The fact that the signals of the noxious and acupuncture are integrated by the local circuitry within the spinal cord may explain the partial mechanisms produced by acupuncture analgesia.

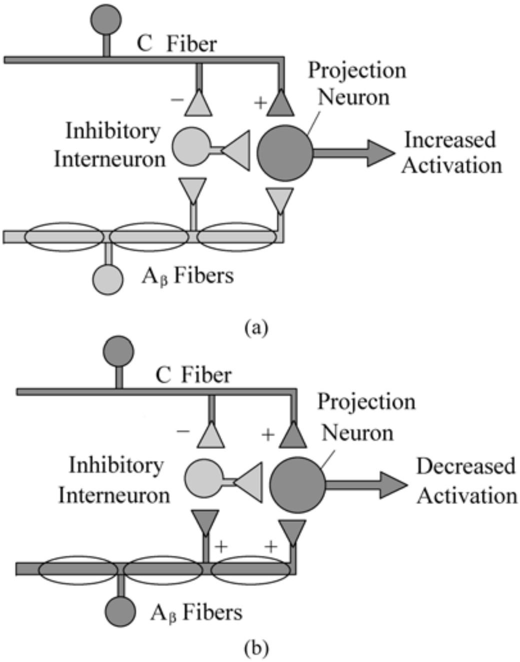

Figure 3.4 The "gate" hypothesis of pain control. The hypothesized interneuron activated by A_β fibers acts as a gate, primarily controlling the transmission of pain stimuli conveyed by C fibers to higher centers.

3.3.2 Effects of Brainstem and Descending Control on Acupuncture Analgesia

As shown in Fig. 3.5, numerous studies indicate that stimulation of system descending from the brainstem to the spinal cord could induce stronger analgesia (Fields and Basbaum 1978, 1979). Among these is the PAG that surrounds the third ventricle and the cerebral aqueduct of the ventricular system. Stimulation of this area produces analgesia by activating the descending pathways of the raphespinal serotonergic neurons and coerulospinal noradrenergic neurons that directly and/or indirectly inhibit the nociceptors in the laminae of the spinal cord (Kandel et al. 2000). It also activates the opioid receptor-containing parts of the spinal cord.

In general, raphespinal serotonergic neurons exercise a tonic inhibition on the spinal nociceptive reflexes. However, the maximal antinociceptive effect obtained by the pharmacological stimulation of serotonergic receptors in both intact and spinal animal model, by intraventricular or intrathecal application was far from beyond the analgesic effect of morphine microinjection or electrical stimulation in the PAG (Fields and Basbaum 1978). Acute lesions of nucleus raphe magnus

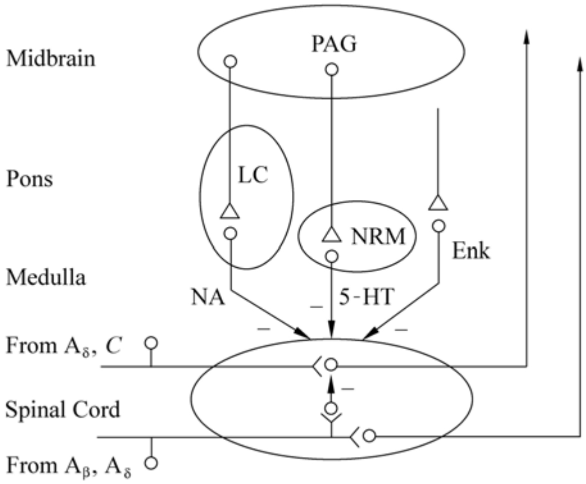

Figure 3.5 Regulation of nociceptive signal in the spinal cord by brainstem and the descending control system. On entering the dorsal horn, the signals are inhibited via opioid receptor located presynaptically on the primary afferent nociceptive neurons. Activation of the descending serotonergic (5 HT) and noradrenergic (NA) neurons evoked by either electric stimulation of PAG, LC, or NRM or microinjection of opiates has an inhibitory action upon the transmission of action potential by noxious stimuli. Some other area of enkephalin in the brainstem and/or circuitry may also block the primary afferent nociceptive neurons, presynaptically. Other non nociceptive impulse and/or those of the acupuncture via A_β and A_δ fiber may also inhibit the nociceptive impulse mediated by the inhibitory interneuron, some of which may be enkephalinergic. Enk, enkephalin neuron; LC, locus coeruleus; PAG, periaqueductal gray; NRM, nucleus raphe magnus.

(Proudfit 1979) also do not eliminate the analgesic effect of morphine. Furthermore, the opiate receptor antagonist, naloxone, does not eliminate the analgesic effects of serotonergic receptor agonists (Berge and Hole 1980). The moderate antinociceptive effect of raphespinal serotonergic neurons implicate that there is at least one more descending system mediating this strong analgesic effect. There are increasing evidences suggesting that the descending noradrenaline pathways also participate in spinal modulation of nociceptive information. Stimulation of brainstem nuclei from which noradrenergic neurons originate has analgesic effects (Segal and Sandberg 1977). Serotonergic and noradrenergic stimulation as well as opiate receptor stimulation might produce analgesia through different systems. Moreover, morphine clearly produces analgesic effects in the spinal cord, acting on the sites caudal to a spinal transection, and this is neither seemed to be mediated via serotonergic receptor nor the noradrenaline receptor.

Similarly, by stimulating, destroying brain nuclei, or using electrophysiological methods to record the unit discharges of neurons, it was also found that numerous brain areas such as the spinal cord, reticular formation, nucleus raphe magnus, nucleus raphe dorsalis, locus coeruleus, and PAG play a role in acupuncture analgesia. Microinjecting in those areas or intrathecal injection of either serotonergic or noradrenergic compounds was observed to regulate the acupuncture analgesia which is mediated by their respective receptor. In addition, the release of numerous neurotransmitters, such as opioid peptides in PAG and noradrenaline in locus coeruleus was revealed to be regulated by acupuncture. The evidences imply that the neural pathways of the descending control system in the brainstem are also involved in the acupuncture analgesia.

3.3.3 The Limbic System and Acupuncture Analgesia

The limbic system is central for acupuncture effectiveness, regardless of the specific acupuncture modality (manual or electro-acupuncture). The limbic system includes many structures in the cerebral cortex and sub-cortex of the brain, and functions by influencing the endocrine system and the autonomic nervous system. Amygdala, hippocampus, cingulate gyrus, fornicate gyrus, hypothalamus, mammillary body nucleus accumbens, orbitofrontal cortex, and olfactory bulb are generally considered to be a part of the limbic system.

Needle manipulation has demonstrated a more regionally specific and quantifiable effect on the relevant structures of the animal brain, including the cortex, caudate nucleus, nucleus accumbens, amygdala, and hypothalamus. Most of the areas involved in acupuncture analgesia are the limbic system itself or those connected with the area of the limbic system directly.

Han et al (1987) pointed out that the mesolimbic inhibitory loop (Fig. 3.6) is crucial for acupuncture and morphine analgesia. Mesolimbic loop includes the areas of nucleus accumbens, amygdala, habenula, and PAG, which are limbic areas involved in the effects of acupuncture mentioned earlier. The loop modulates the outputs of PAG to the descending control system, and is an important structure for analgesia.

Investigation of the neuronal correlates of the acupuncture in human brain sites is limited to using the above mentioned invasive experimental methods. Noninvasive functional imaging methods, such as fMRI and PET have been used to study the relationships between particular acupoints and changes in the correlated brain-area activities. Hegu (LI-4) and Yanglingquan (GB-34) have been extensively used for acupuncture analgesia in both clinical tests and animal research. Stimulation of the Hegu (LI-4) point in animal studies has been found to release opioid-like peptides from the limbic system, such as the hippocampus (Zhu et al. 1990) and PAG (Zhang et al. 1981). The inhibition of fMRI signals in the hippocampus (Hui et al. 2000) and PAG (Liu et al. 2004) has been observed by stimulation of Hegu (LI-4). However, stimulation of Yanglingquan (GB-34) has been observed to significantly increase the fMRI signals in the hypothalamus and primary somatosensory-motor cortex (Wu et al. 2002). As mentioned in Section 3.1 of this chapter, Neiguan (PC-6) is an acupoint relevant in the management of nausea, including vestibular-related motion sickness, and is therefore, usually selected for the treatment of cardiovascular disorders. Acupuncture of Neiguan (PC-6) is observed to selectively activate the left superior frontal gyrus, anterior cingulate gyrus, and dorsomedial nucleus of thalamus.

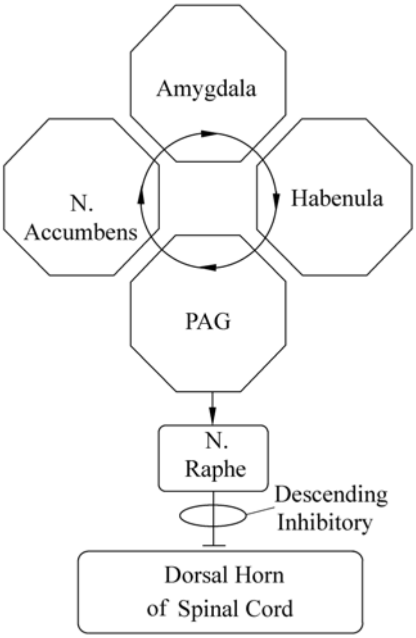

Figure 3.6 Mesolimbic loop of analgesia. PAG, periaqueductal gray.

Moreover, using this noninvasive testing method in human subjects to explore the acupoint-brain activity correlation with the needling sensation, Hui et al (2000) reported that through stimulation of the Hegu (LI-4) point, the inhibition of fMRI signals were found in the limbic system of most normal subjects, especially in those who have experienced needling sensations. The phenomenon was also observed using PET. Hsieh (1998) reported that acupuncture needling sensations was associated with the activation of the hypothalamus and cerebellar vermis when compared with the sham group.

3.4 Neurobiological Mechanism of Acupuncture in Autonomic Nervous System

The results of numerous research and clinical observations have revealed that the biological basis of the acupuncture is partly through the regulation of the autonomic functions by the mechanisms of intraspinal and/or super spinal mechanisms.

3.4.1 Structure and Function of Autonomic Nervous System

The autonomic nervous system is a part of the peripheral nervous system and is composed of the sympathetic and parasympathetic nervous systems, functioning primarily in contrast to each other, and plays an important role in the emotional life. The autonomic functions are controlled by the spinal cord, brainstem, hypothalamus, and cerebral cortex (Fig. 3.7). The cortical control of the autonomic functioning is mainly via the limbic system such as hypothalamus, which is barely conscious. The acupuncture mechanism underlying the regulation of the autonomic nervous system has been observed by many investigations through its impact on the cortical control systems, especially the limbic system.

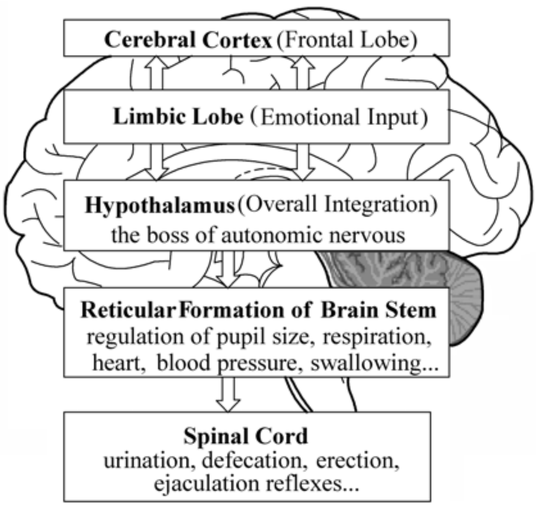

Figure 3.7 Control over the autonomic nervous system by the central nervous system. Control over the autonomic nervous system is exercised by the spinal cord, brainstem, hypothalamus, and cerebral cortex.

It is not a surprise that hypothalamus has an important role in mediating the therapeutic effect of acupuncture, not only because of the link of the hypothalamus to the autonomic system by the projections to the (lateral) medulla, where the cells that drive the autonomic systems are located, but also owing to the fact that hypothalamus controls the neural-endocrine system by sending the axons directly to the posterior pituitary underneath, and that the neurons of the hypothalamus secrete peptides that regulate the release of the anterior pituitary hormones. Thus, the main function of the hypothalamus is homeostasis. Factors such as blood pressure, body temperature, fluid, electrolyte balance, and body weight are held to a precise value called the set-point, although this set-point can migrate over time, from day to day, and is remarkably regulated by hypothalamus. For the purpose of homeostasis, hypothalamus receives a variety of inputs including those from the spinal cord and the other regions of the limbic system.

The function of the sympathetic nervous system appears to prepare the body for the different kinds of vigorous organ activities associated with “fight or flight”, That is, running from danger or preparing for violence. The primary function of the parasympathetic nervous system is to bring the body back from the emergency status created by the sympathetic nervous system. Some scientists believe that the activity of the sympathetic nervous system represents the *Yang* status, while that of the parasympathetic nervous system indicates the *Yin* status. The theory speculates that acupuncture modulates the *Yin* and *Yang* status is directly or indirectly mediated through the regulation of the autonomic nervous system.

Autonomic nervous system also deals with the visceral sensory neurons, as well as the visceral and somatic pain fibers that travel along the same afferent pathways, explaining the phenomenon known as the referral pain. In this event, visceral pain is considered as somatic. For example, heart attack is manifested as upper thoracic and left arm pain.

3.4.2 Acupuncture Signal Regulating Activation of Autonomic Nervous System

The theory that acupuncture signals transmitted to the brain areas interact with the neurons at different levels of the cortical controlling system (neural and/or endocrine), which control the outflow of the sympathetic nervous system (Fig. 3.8), has been vigorously examined in the animal models (Cao 2002). For example, our previous results showed that electro-acupuncture could induce the release of endogenous opioid peptides from PAG and hypothalamus (Zhang et al. 1981; Zhu et al. 1990). During acupuncture analgesia, the release of adrenaline was monitored dynamically in some sympathetic nervous system, controlling areas such as the Locus coeruleus, PAG, nucleus raphe magnus, and dorsal horn of spinal cord. The results have supported the notion that acupuncture inhibits sympathetic activities associated with nociceptive stimulation, which may explain a mechanism in which acupuncture plays a favorable role in reducing the pain (Cao et al. 1983).

Interestingly, acupuncture stimulation can induce both inhibition and activation effects on the structures of brain such as the visual cortex. While some studies indicated the increase of activity in the visual areas after the vision-related acupoint BL-1-67 (Cho et al. 1998; Siedentopf et al. 2002) is stimulated, Li et al (2003) showed both an increase in the activity of the visual cortex in ten subjects and a decrease in the other eight. Shen (2001) described a study in which the stimulation of the visual-related acupoint in the visual cortex of twelve participants resulted in increased signals in four subjects, but decreased signals in eight. The participants were classified into *Yin* or *Yang* groups, where patients in the *Yin* group were defined to have deficient blood circulation, and those in the *Yang* group were considered to have an overabundance when they receive acupuncture by a traditional practitioner. The participants in the *Yin* group demonstrated increased signals, while those in the *Yang* group showed decreased signals. Thus, a biological basis for *Yin* and *Yang* status is considered to exist, and some researchers believe that acupuncture has a homeostatic effect on both the sides.

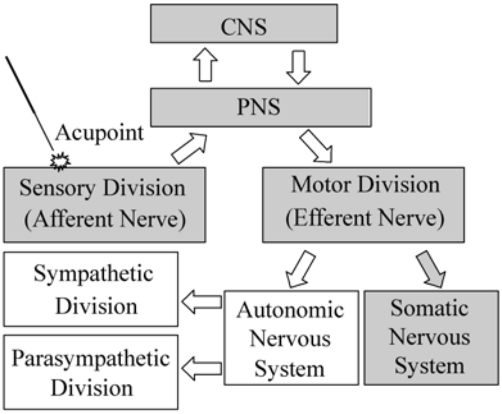

Figure 3.8 The therapeutic effect of acupuncture on the target organs is mediated by the sympathetic and parasympathetic nerve of the autonomic nervous system.

3.4.3 Therapeutic Effects of Acupuncture Mediated Through Autonomic Nervous System

Cao et al (1983) reported that patients under pneumonectomy with acupuncture anesthesia demonstrated marked changes in pain threshold, pain-tolerance threshold, galvanic skin reflex, finger plethysmogram, and skin temperature measured at the palm and fingers. Further analysis of individual variation in acupuncture analgesia indicated that those with high pain-tolerance threshold, rising skin temperature, and inhibition of pain responses in the finger plethysmogram and galvanic skin activity during acupuncture can exhibit a good analgesic effect (Department of Physiology and Acupuncture Research Group, Shanghai First Medical College 1973), which suggests that acupuncture enables inhibition of the functional activity of the sympathetic nervous system. The analysis also demonstrated that even though acupuncture is able to elevate the pain, warmth threshold, and pain-tolerance threshold, only the pain-tolerance threshold is observed to be correlated well with the efficacy of the acupuncture analgesia, which also supports the notion that the limbic system might play an important role in acupuncture.

Apart from acupuncture anesthesia, acupuncture is practiced to regulate the functions of the heart and vascular systems that are well controlled by the autonomic nervous system. The usage of acupuncture in this field includes modulation of heart rate (Meng 2004) and blood pressure (Smith 1992; Ballegaard et al. 1995), and elevation of the sympathetic activity in heart failure (Middlekauff et al. 2004). Sympathetic activation during acute mental stress was eliminated after acupuncture (Middlekauff et al. 2002), even though the regulatory effect had to be obtained through proper acupuncture needling technique. Li (2002) also reported a neural pathway of the therapeutic effect of acupuncture on cardiovascular disease. Electro-acupuncture was observed to activate the arcuate nucleus in the hypothalamus, which sends the excitatory projections to the ventral PAG and, in turn, to the nucleus raphe obscurus. Excitation of nucleus raphe obscurus neurons was observed to inhibit the cardiovascular neurons in the rostral ventrolateral medulla by activating the opioid, γ-aminobutyric acid (GABA), and serotonergic receptors to reduce the sympathetic outflow, which ultimately exerts the therapeutic effect of the acupuncture (Fig. 3.9).

Through regulation of the vagus nerve that supplies parasympathetic fibers to all the organs, except the adrenal glands and the sympathetic nervous system, acupuncture can regulate the respiratory system. For instance, relaxation of bronchioles for asthma is usually achieved by stimulation at the Ding Chuan (MDC-1), Zhongfu (LU-1), and Feishu (BL-13) acupoints. Other regulatory functions mediated by the autonomic nervous system, which can be influenced by acupuncture, include suppression of stomach spasms (Chiu 2002), correcting urine retention, increasing white blood cells and platelet counts, etc. Furthermore, it was found that patients with a suppression of the sympathetic nerve system could successfully ovulate after acupuncture treatment (Yu 2002).

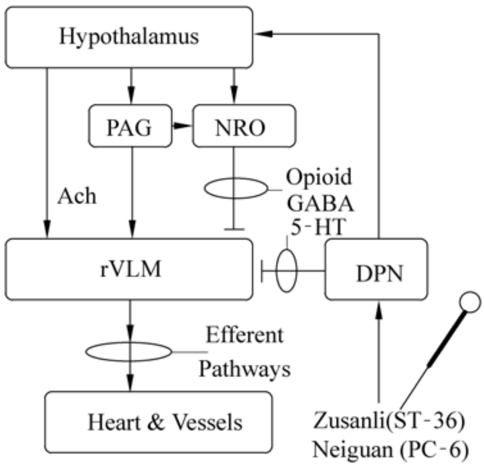

Figure 3.9 Neural pathway of the electro-acupuncture effect on cardiovascular neurons in rVLM. Electro acupuncture at Zusanli or Neiguan acupoints using low current and low frequency activates the DPN and MN underneath, which stimulate the pathway and release opioid, GABA, and 5 HT to inhibit the rVLM. DPN, deep peroneal nerve; NRO, nucleus raphe obscurus; rVLM, rostral ventrolateral medulla; PAG, periaqueductal gray.

3.5 Concluding Remarks

Invasive and/or noninvasive animal experiments or clinical tests have revealed that: (1) the initiation of acupuncture signals by needling at specific acupoints is, at least partially, mediated by the nerve fibers innervated to the deep tissue underlying the acupoint sites; (2) the transmission of acupuncture signals is likely through A_β, A_γ, and possibly C-related fibers; and (3) the intraspinal and superspinal controlling systems, such as the limbic system, hypothalamus, descending control system, play an important role in regulating the activity of the autonomous nervous system during acupuncture.

Acupoint-brain activity analysis using invasive and/or noninvasive experiments has demonstrated immensely complicated activation patterns of the brain areas by acupuncture. For example, either fMRI signal decreases or increases in the same area with same acupoint could be observed, and there exists brain area overlap after activation of different acupoint stimulation. The differences even contradict observations may be due to the subject's physiological condition, the acupuncture method selected, such as acupoints, modality, intensity, frequency, etc. Therefore, although evidences from *in vivo* and *in vitro* indicate that a large number of brain areas and neural pathways play an important role in medicated therapeutic effect of acupuncture. The biological mechanism concerning the therapeutic effect of acupuncture is still largely unknown.

To unveil the underlying biological mechanisms, various acupuncture parameters according to the treatment intention need to be identified in a controlled physiological condition. As these mechanism concerns cannot be easily studied in humans, animal models have to be employed. The molecular imaging technology has been developed recently, which enables to study the molecular processing dynamically with a noninvasive imaging method in animal models under needling manipulations. Therefore, the use of this method in animal model may provide novel insights into the central and/or peripheral processes during acupuncture, and may lead to the improvement of this ancient therapy.

Acknowledgements

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4 Acupuncture-Induced Activation of Endogenous Opioid System

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Summary It has been accepted that acupuncture at certain points on the body induces analgesia/anesthesia and therapeutic effects on certain diseases. The mechanistic research demonstrates that acupuncture effects are mediated by the central neurotransmitters. Among them, the endogenous opioid peptides (EOP) play an important role in acupuncture effects. In general, acupuncture activates the EOP system by influencing the release and synthesis of EOP, and regulating the function and expression of their corresponding receptors. Although previous data were mostly obtained from the studies on acupuncture analgesia and anesthesia, it is very likely that acupuncture-induced activation of the EOP system may induce multiple effects on the body, as EOP system broadly participates in the physiological function and pathophysiologic process.

Keywords *enkephalin, β-endorphin, dynorphin, release, opioid receptors*

4.1 Introduction

Endogenous opioid peptides (EOP) are the opioid-like peptides in the brain. In 1970s, two group (Hughes 1975; Snyder and Matthysse 1975) independently reported that the brain extracts mimicked ability of morphine to inhibit electrically induced contractions of the mouse vas deferens, with these effects being blocked by naloxone, suggesting the existence of EOP in the brain. After the isolation and amino acid sequence analysis of two enkephalin pentapeptides, i.e. methionine-enkephalin (Met-enkephalin, Tyr-Gly-Gly-Phe-Met) and leucine-enkephalin (Leu-enkephalin, Tyr-Gly-Gly-Phe-Leu) in 1975 (Hughes 1975), β-endorphine, dynorphin, orphanin FQ, endomorphin were found one after the other in 2 decades.

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These opioid peptides produce a variety of physiological functions by binding with different opioid receptors, mainly mu-, delta-, and kappa-opioid receptors (MOR, DOR, and KOR). It has been generally accepted that manual acupuncture and electroacupuncture (EA) can upregulate the opioid system in the central nervous system. In the past 30 years, a number of studies, especially those of acupuncture analgesia and anesthesia, have demonstrated that manual acupuncture/EA increases the opioid activity by increasing the opioid release, enhancing the opioid content, and modulating the expression and function of the opioid receptors.

4.2 Role of Endogenous Opioid System in Acupuncture

As early as in the 1970s, it was revealed that acupuncture could affect the EOP activity that critically participates in acupuncture analgesia. For example, Zou et al (1979a) observed that manual acupuncture/EA at the Zusanli (ST-36) acupoint could increase the content of EOP in rabbit cistern cerebrospinal fluid. He and Dong (1983) observed that during acupuncture analgesia, the opioid activity increased in the human cerebrospinal fluid and the perfusate from certain brain regions. On the other hand, substantial data suggest that simulated EA could exhibit similar effect. Sodipo et al (1981) showed that the simulated EA (electrical stimulation of the superficial peroneal and posterior tibial nerves), similar to the systemic administration of met-enkephalinamide (a synthetic opioid), could inhibit nociceptive discharges. The effects induced by both simulated EA and met-enkephalinamide could be significantly reduced by naloxone, an opioid antagonist.

In our studies on the effect of simulated acupuncture on cardiovascular disorders, we also found that EOP plays an important role in simulated EA-induced inhibition of experimental arrhythmia and pressor response (Xia et al. 1985, 1986, 1989). More recently, other researchers (Li et al. 1997; Xie et al. 1997; Wang et al. 1997; Yu et al. 1999; Yu and Xia 2001; Zhou et al. 2003; You et al. 2005), using EA or simulated EA, also confirmed the important role of EOP in the rectification of experimental arrhythmia, pressor response, and tachycardia. For example, in the rat model of tachycardia, EA ameliorated tachycardia, which could be reversed by the intraperitoneal injection of the opioid receptor antagonist, naloxone (1 mg/kg) or by the intracerebroventricular injection of selective KOR antagonist, nor-binaltorphimine (nor-BNI, 12 nmol) (Yu et al. 1999).

4.3 Acupuncture-Promoted Release of Endogenous Opioids

Accumulating evidence strongly suggests that acupuncture could promote the release of EOP, leading to an increase in the level of EOP in both the central nervous system and peripheral circulation.

4.3.1 Central Release

In clinical studies, several reports consistently showed that manual acupuncture/EA could increase the level of EOP in the cerebrospinal fluid (Sjölund et al. 1977; Chen et al. 1984). Many animal studies showed similar results, i.e., manual acupuncture/EA enhances the pain threshold, which was associated with an increased level of EOP in the cerebrospinal fluid (Zou et al. 1979a; Pert et al. 1981). By measuring the specific subtypes of EOP, Chen et al (1984) found that in 10 patients without the complaint of pain, EA increased the pain threshold and pain tolerance with an increase in β-endorphin-like immunoreactive substances in the cerebrospinal fluid. Wu et al (1983) observed an increase in met-enkephalin in the cistern with increased pain threshold in rabbits, when manual acupuncture was applied to the bilateral Zusanli (ST-36) acupoints.

It seems clear that both manual acupuncture and EA could increase the content of enkephalin and/or β-endorphin in the cerebrospinal fluid, implying an increase in the release of EOP in the central nervous system. Indeed, many studies confirmed this viewpoint. Zou et al (1979b, 1980) found that acupuncture analgesia could be strengthened by applying an inhibitor to inhibit the extracellular degradation of enkephalin in the brain, which was associated with an increase in the level of enkephalin in the striatum, hypothalamus, as well as cerebrospinal fluid in the experimental animals. These observations suggest that acupuncture could promote the release of EOP and enhance the effect of acupuncture. Furthermore, several groups, with the approaches of push-pull perfusion and radioimmunoassay, showed that manual acupuncture/EA could increase the enkephalin level in the perfusate from different brain regions, such as the periaqueductal gray matter and brainstem. For example, Zhou et al (1993) found that EA could increase the release of leu-enkephalin from the reticularis paragigantocellularis lateral. In addition, the release of β-endorphin significantly increased from this nucleus in rats with higher EA efficacy, but not in those with lower efficacy. Furthermore, the release of dynorphin $A_{1\ \ 13}$ was also observed to increase in the same nucleus.

4.3.2 Peripheral Circulation

EA could increase the level of EOP in the plasma (Tang and Han 1979). In the rat model of acute arthritis (subcutaneous injection of Freund's adjuvant into the right ankles), Zhu et al (1993) found that needling at the Huantiao (GB-30) acupoint for 10 min increased the pain threshold by 42.3% (p<0.05) in the inflamed ankles and by only 5.6% in the non-inflamed ones. Systemic administration of naloxone was observed to block the acupuncture effect. Interestingly, local injection of naloxone was also found to antagonize the acupuncture effect. These results suggest that acupuncture may enhance the peripheral opioid activity through an interaction between the EOP and opioid receptors in the inflamed area. Xi et al (1995) examined the changes in the contents of β-endorphin, leu-enkephalin, and noradrenalin in the plasma before and after the induction period of EA anesthesia, general anesthesia, and epidural anesthesia in 63 surgical cases. They found that the levels of β-endorphin and leu-enkephalin increased in the subjects under EA anesthesia, which was significantly different from those under general anesthesia and epidural anesthesia. In contrast, the noradrenalin level in the plasma was not statistically different among the three groups. These results further demonstrate that acupuncture may promote the release of EOP into the peripheral circulation. Recently, Kim et al (2006) also showed that EA could suppress inflammation through a peripheral opioid mechanism. Furthermore, there is evidence showing that the pituitary gland is an importance source for the acupuncture-induced increase in EOP in the peripheral blood.

4.3.3 Frequency-Dependent Release

The parameters of EA stimulation are important for the outcome effect. For example, we observed that simulated EA with low-frequency and low-intensity current could induce an inhibition of the sympathetic reaction, while that of high-frequency and high-intensity current led to an opposite effect. Recently, we also demonstrated that EA-induced brain protection from cerebral ischemia is greatly dependent on the frequency and intensity of the electrical stimulation (Zhou et al. 2007).

Other investigators, especially Dr. Han's group, provided evidence that the release of EOP varies in the brain depending on the frequency of EA stimulation. Fei et al (1987, 1988) found that low-frequency (2 Hz) EA stimulation led to the release of met-enkephalin and β-endorphin in the rat spinal cord. In the human body, simulated EA (transcutaneous nerve stimulation) applied on the hand and leg resulted in a marked increase (367%, $p<0.05$) of met-enkephalin, but not dynorphin in the cerebrospinal fluid (Han et al. 1991). In contrast, high-frequency EA (100 Hz) was observed to promote the release of dynorphin in the rat spinal cord. The relationship between EA frequency and the release of EOP subtypes are schematically shown in Fig. 4.1 (Han 2003, 2004; Han and Wang 1992; Han et al. 1991).

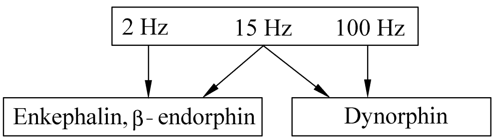

Figure 4.1 EA frequency and potential EOP release.

In the serial studies conducted by Han and others (Wang et al. 1990, 1991; Han and Wang 1992; Han 2003), it was shown that the lesion of the arcuate nucleus of the hypothalamus eliminated analgesia induced by low-frequency EA, but not that induced by high-frequency EA. On the other hand, selective lesion of the parabrachial nucleus attenuated the effects of high-frequency EA, but not those of low-frequency EA. However, the periaqueductal gray matter was a common pathway for both the signals of EA (Fig. 4.2).

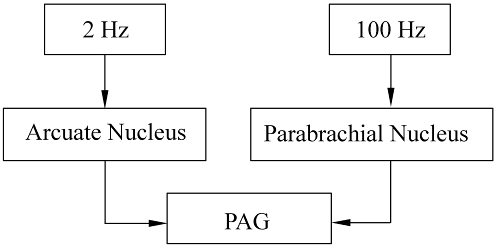

Figure 4.2 Potential pathways of low- and high-frequency EA in the brain. PAG, periaqueductal gray matter.

4.4 Acupuncture-Induced Alteration in the Content of EOP in the Brain

Tang and Han (1979) observed that EA could significantly enhance the EOP activity in the rat brain, and the enhanced activity of EOP was found to be associated with the efficacy of EA analgesia. Owing to the existence of multiple types of EOP, which are differentially distributed in various brain regions, some investigators examined their specific changes in response to acupuncture.

Zou et al (1980) found that EA could induce analgesic effect and increase the enkephalin level in the hypothalamus and striatum by 1.6 – 1.8 times and 1.6 – 1.7 times, respectively (p<0.01), in rabbits. The ratio of leu-enkephalin and met-enkephalin remained unchanged when compared with that of the control group. There was no significant change in the content of enkephalin in other brain regions. In addition, in the rat model, they observed an increase in the contents of enkephalin in several brain regions. In the hypothalamus, the content of met-enkephalin increased by 3.4 times (p<0.01) and that of leu-enkephalin increased by 1.35 times (p close to 0.05). In the striatum, met-enkephalin increased by 3.6 times (p<0.005) and leu-enkephalin increased by 2.1 times (p<0.001). Met-enkephalin also increased in the nucleus accumbens. The ratio of leu-enkephalin and met-enkephalin was very different from that of the control group.

Chen et al (1981, 1983) observed that EA could increase the content of β-endorphin in the rat brain (whole brain sample), which was associated with the acupuncture effect. When the level of β-endorphin in response to EA was higher, the effect was better. This observation suggests that acupuncture could prompt EOP release in the pituitary gland. Furthermore, a study carried out on different brain regions also showed similar results with the highest content of β-endorphin observed in the midbrain, when EA induced the best effect.

Xie et al (1984) determined the levels of met-enkephalin and leu-enkephalin in the brainstem and spinal cord, using radioimmunoassay in rats subjected to EA analgesia, and found that enkephalin significantly increased in the caudate nucleus and hypothalamus, though there was no significant change in the thalamus, lower brainstem, and spinal cord. They also noticed that only the change in the met-enkephalin level, but not leu-enkephalin level, was relevant to the effect of EA analgesia.

Some researchers observed that the time window of EA application could significantly influence the effect of acupuncture on the content of EOP. Wang and Wang (1989a, 1989b) determined the effects of EA on leu-enkephalin in the medulla oblongata, pons, midbrain, hypothalamus, hippocampus, striatum, and cortex of rats at four time points of a day (5:00, 11:00, 17:00, and 23:00; Table 4.1). They observed that EA applied at 5:00 increased the leu-enkephalin level by 34.8% in the hypothalamus and decreased it by 21.4% in the cortex. When EA was applied at 11:00, the level of leu-enkephalin increased in the hypothalamus and hippocampus by 65.3% and 37.0%, respectively. When EA was applied at 17:00, the level of leu-enkephalin increased by 50.1% in the hippocampus. In contrast, EA applied at 23:00 led to a decrease in the leu-enkephalin level (−29.8%) in the hippocampus. Based on these results, it seems that acupuncture at different time points may differentially affect the contents of enkephalin in the brain.

Table 4.1 Effect of EA at different time points on leu enkephalin

	5:00	**11:00**	**17:00**	**23:00**
Hypothalamus	34.8%↑	65.3%↑		
Hippocampus		37%↑	50.1%↑	29.8%↓
Cortex	21.4%↓			

All these observations, though complicated, consistently suggest that manual acupuncture/EA could significantly increase the content of EOP in the central nervous system in most cases. It is worth noting that the hypothalamic arcuate nucleus and pituitary gland are important resources in terms of acupuncture-induced increase in the content of EOP (Zou et al. 1980; Zhu et al. 1984; Yu et al. 1994).

However, in certain conditions, if the rate of EOP release is faster than that of its synthesis, then there is a possibility of an increase in the EOP release with a decrease in the content of EOP in the brain. For example, Pert et al (1981) showed that EA could increase the level of endorphins in the cerebrospinal fluid with concomitant decreases in the basomedial hypothalamus and medial thalamus of β-endorphin-like immunoreactivity as well as endorphin-like radioreceptor activity. These results imply that EA could produce its analgesic action at least partially by activating the endorphinergic circuitry in the central nervous system, resulting in a release and depletion of endorphins in certain brain loci and a concomitant elevation in the cerebrospinal fluid.

The disease status may greatly affect the content of EOP in the brain as well as the effect of acupuncture. In an animal model of shock, Ma et al (1995) determined the contents of enkephalin in the brainstem, diencephalons, hypothalamus, striatum and hippocampus using radioimmunoassay, and observed that the traumatic shock tended to increase the level of leu-enkephalin in all these brain regions, while acupuncture decreased it in the hypothalamus.

Therefore, acupuncture leads to differential changes in the contents of EOP in various brain regions, depending on the status of the body and the condition of acupuncture.

4.5 Acupuncture-Enhanced Expression of Endogenous Opioids

Manual acupuncture/EA-induced increase in the content of EOP may be attributed to many factors, including an increased expression and a decreased degradation. Till date, there are substantial data suggesting that acupuncture signal may enhance the expression or synthesis of EOP in the brain.

Wu et al (1980) found that after central application of cycloheximide, EA-induced increase in met-enkephalin of the striatum and hypothalamus was much less than that in the control, suggesting that the effect of EA is dependent on the newly synthesized enkephalin. Serial studies from Zhou's group at Shanghai Medical University provide more direct evidence for the EA-induced expression of enkephalin (Fan et al. 1997; Da et al. 1997, 1998). They studied the expression of preproenkephalian (PPE) mRNA in hypothalamic arcuate nucleus (AR), periaquedutal grey (PAG) and rostral ventral-medial surface of the medulla oblongate (RVM) of the rats after nociceptive stimulation or EA. Their results showed that the number of PPE-mRNA positive neurons increased with stronger signal staining in these regions after noxious stimulation, suggesting an increased expression of PPE-mRNA. EA increased more expression as compared to that of the rats with noxious stimulation, particularly in AR and RVM (Da et al. 1997). Furthermore, they observed that EA enhanced the expression of PPE mRNA in many brain regions, including the neocortex, hypothalamus, mesencephalon, pons and medulla, especially in nucleus t-ractus solitarii, nucleus reticuaris lateralis, nucleus t-ractus spinalis nervi t-rigemini and RVM (Da et al. 1998). Interestingly, they saw a different change in the spinal cord. Similarly as in the AR-PAG-RVM, the expression of PPE was increased by noxious stimulation. In the group of EA plus noxious stimulation, however, EA attenuated the nociception-induced expression though little change was observed in the control rats subjected to EA (Da et al. 1997).

There are also studies showing that EA-induced expression of EOP is dependent on the frequency of the stimulation (Han et al. 1991; Han 2003; Ji et al. 1993; Guo et al. 1997).

As the expression of EOP involves many biological processes with energy consumption, the effect of acupuncture on the expression of EOP is critically dependent on the cellular condition. Under normal conditions, acupuncture may increase the content of EOP in the brain via the upregulated expression, in addition to the release of EOP. However, in disease states and other abnormal conditions (e.g., in the above-mentioned model of shock), acupuncture may not be able to increase the expression of EOP because of improper function and metabolism of the cells.

4.6 Acupuncture and Opioid Receptors

Opioid receptors (Fig. 4.3) are G-protein-coupled membrane proteins with three major subtypes, i.e., MOR, DOR, and KOR. These receptors are distributed widely and distinctively in the central nervous system. They have a prominent role in brain function, as they regulate the reuptake and feedback of presynaptic transmitter and modulate various functions of the cell membrane.

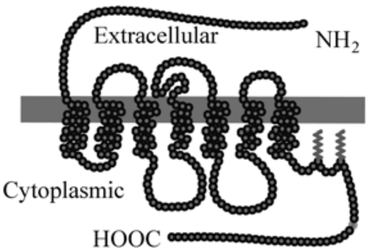

Figure 4.3 Schematics representation of the opioid receptors.

Acupuncture-induced release of EOP activates the opioid receptors, thus leading to cellular and molecular reactions. However, EOP do not have the ability to bind selectively to a specific opioid receptor (Table 4.2). Thus, in a given brain region or neuron, the EOP-mediated function greatly relies on the distribution of the opioid receptors, including the ratio of various opioid receptor subtypes. For example, if only DOR exists in a neuron, then manual acupuncture/EA-induced release of EOP, i.e., β-endorphin, enkephalin, or dynorphin, can only induce a DOR-mediated effect in this particular neuron.

Table 4.2 Relative selectivity of major EOPs and commonly used opioid ligands

	Opioid receptor subtype		
	μ	***δ***	***κ***
EOP			
β endorphin	+++	+++	+++
Leu enkephalin	+	+++	
Met enkephalin	++	+++	
Dynorphin	++	+	+++
Agonist			
Morphine	+++	+	++
Antagonist			
Naloxone	+++	++	++

"+++" strongest binding; "++" strong binding; "+" weak binding; "−" non- or little-binding.

4.6.1 Role of Opioid Receptor Subtypes in Acupuncture Effects

It has been well documented that opioid receptors play a crucial role in many effects induced by manual acupuncture/EA. The simplest and strongest evidence is that many of the acupuncture effects can be eliminated or attenuated by the opioid receptor antagonists (Xia et al. 1985, 1989; Zhao et al. 2002; Tian et al. 2008a, 2008b).

Substantial data show that all the three major opioid receptors are involved in the acupuncture effects. Herz and Millan (1989) employed several approaches to demonstrate that β-endorphin-activated MOR in the periaqueductal gray matter plays an important role in acupuncture analgesia. There are also numerous reports showing that opioid receptor subtypes in the brain and spinal cord are differentially involved in producing acupuncture effects, depending on the experimental conditions and acupuncture effects tested (Fei et al. 1987, 1988; Chen and Han, 1992a, 1992b; Chen et al. 1996; Wu and Chen 1999; Huang et al. 2000; Li et al. 2001).

Han and others (Fei et al. 1987, 1988; Chen and Han 1992a, 1992b; Han 2003), using the method of cross-tolerance, observed that 2 Hz EA-induced analgesia was mediated by MOR and DOR, 100 Hz EA-induced analgesia was mediated by KOR, and 2 – 15 Hz EA-induced analgesia was mediated by the combined action of MOR, DOR, and KOR, in the spinal cord of rats. In another report, Chen et al (1996) showed that the antinociception induced by 2 Hz EA was mediated by both MOR and DOR, while that induced by 100 Hz EA was mediated primarily by KOR. On the other hand, the antinociception induced by 30 Hz EA was mediated by all the three opioid receptors.

It is worth noting that some opioid receptors specifically participate in producing certain acupuncture effect, which varies with the brain regions. For example, MOR and DOR, but not KOR, in the right ventralis lateralis pars medialis of the brainstem, are found to participate in the inhibitory effect of EA on the reflex autonomic response in cats (Li et al. 2001).

4.6.2 Acupuncture and Opioid Receptor Density

Besides enhancing the activity of opioid receptors via an increased release of EOP, acupuncture is observed to even alter the expression of opioid receptors and increase their density in the brain.

Using receptor autoradiography, Gao and He (1996) found that pain stimulation (formalin injection into the rat hind paw) significantly increased the MOR density in several brain areas associated with antinociception, and that EA further increased the MOR density in these regions. In our recent investigation on the mechanism of acupuncture-induced brain protection against cerebral ischemia, we found that cerebral ischemia (middle cerebral artery occlusion) caused brain infarction with a decrease in the DOR density. EA reduced the ischemic infarction and neurological deficits with an increase in DOR density in the cortical region, while naltrindole, a DOR antagonist, completely eliminated EA-induced protection (Tian et al. 2008b), suggesting that EA could protect the brain against ischemic injury via upregulation of DOR.

Some studies indicate that acupuncture-induced changes in the opioid receptor expression could also vary depending on the acupuncture conditions. Wang et al (1998) determined KOR mRNA expression using RT-PCR after EA at 2 or 100 Hz, and observed that one session of EA stimulation had no significant effect on KOR mRNA in the brain and spinal cord, 24 h after EA. Interestingly, acupuncture without electric stimulation for 6 days (30 min/session; one session/day) significantly increased the KOR mRNA in the striatum and amygdala. However, after 3 – 6 sessions of 100 Hz EA stimulation, KOR mRNA significantly decreased in the spinal cord, striatum, and amygdala. In contrast, 2 Hz EA stimulation decreased the KOR mRNA level in the periaqueductal gray matter and striatum, but increased or biphasically changed the KOR mRNA in the spinal cord and amygdala.

Dong et al (1998) investigated the effect of repetitive 100 Hz EA stimulation on the characteristics of KOR binding in several brain regions and the spinal cord of rats, using radio ligand-binding assay. They applied 100 Hz EA once a day (30 min/session) for 7 days. The Bmax of KOR decreased in all the brain regions studied during the development of 100 Hz EA tolerance. In the cortex and pons-medulla, a marked downregulation of KOR occurred within 24 h, and remained at a low level throughout the observation. The Bmax of KOR binding showed a bell-shaped curve in the spinal cord, i.e., upregulation in the first 5 days and downregulation at day 7. In contrast, a slow and steady downregulation was found in the midbrain and striatum. In most of the brain areas, there were no significant changes in the binding affinity of KOR with [^{3}H]-U69593, except for the midbrain, where the KOR-binding density decreased while the binding affinity increased (Kd values declined). These results also show that repeated 100 Hz EA for an "over-long" period could lead to EA tolerance and downregulate KOR in the brain, especially in the midbrain and striatum.

Taken together, it seems that a mild and prolonged stimulation of acupuncture could increase the opioid receptor expression, while a strong and "over-long" stimulation may eventually lead to a decrease in the opioid receptor expression. One of the reasons may be attributed to the release of EOP, because an excessive release of EOP may downregulate their receptors as a mechanism of negative feedback.

4.7 Concluding Remarks

The previous studies have shown that acupuncture-induced effects on EOP vary depending on various factors, such as the subject, status of the organism, regions studied, acupuncture manner (manual acupuncture or EA, stimulation parameters, single or repetitive treatment, lasting period, etc.), and applying window. Nevertheless, considerable data suggest that acupuncture can activate or strengthen the activity of the EOP system in the central nervous system by increasing the release and production of EOP, and by upregulating the opioid receptor expression.

In spite of the fact that most of the data currently available were obtained through the research on manual acupuncture/EA-induced analgesia, the significance of the increased activity of the EOP system is not limited to the modulation of pain because the EOP system is widely distributed in the central nervous system and is directly involved in multiple functions (e.g., cardiovascular regulation and neuroprotection). Furthermore, EOP may indirectly alter various functions in the body by modulating other neurotransmitters. Therefore, it is reasonable to speculate that such major changes in the EOP system can greatly affect the neuronal and other functions in the body via the coordination with cellular signals. Indeed, our recent work has demonstrated that DOR is neuroprotective and plays an important role in the EA-induced brain protection from ischemic injury (Zhang et al. 2000, 2006; Zhao et al. 2002; Ma et al. 2005; Tian et al. 2008a, 2008b; Chao et al. 2009; Yang et al. 2009).

At present, it is not well understood as to how acupuncture produces the therapeutic effects on neurological disorders. A detailed investigation on the role of EOP system in producing acupuncture effects as well as the underlying mechanism may provide unique clues to better understand the mystery of acupuncture. The outcome information may potentially improve the clinical practice of acupuncture and provide novel insights into new solutions to some neurological disorders.

Acknowledgements

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5 Effect of Acupuncture on Neurotransmitters/ Modulators

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Summary Acupuncture research, especially the mechanistic investigations on acupuncture analgesia, has yielded abundant information showing that acupuncture signal, either generated by manual acupuncture or electroacupuncture (EA), remarkably influences the release, synthesis, reuptake, and degradation of the central neurotransmitters/modulators, including monoamines (e.g., serotonin, noradrenalin, and dopamine), acetylcholine (ACh), amino acids, orphanin FQ, substance P, prostaglandin, cholecystokinin-octopeptide-8 (CCK-8), somatostatin, and neurotrophic factors. In general, acupuncture enhances the activity of the endogenous opioid peptides, serotonin, dopamine, ACh, and inhibitory amino acids such as γ-aminobutyric acid (GABA), glycine, taurine, and lactamine, while it attenuates the activity of noradrenalin and excitatory amino acids including glutamate and aspartic acid. A prolonged period of acupuncture may induce excessive production of CCK-8 and deplete some pro-acupuncture substances, thus causing the so-called acupuncture tolerance. Acupuncture also regulates the expression and function of the corresponding receptors. However, the effects of acupuncture on the central neurotransmitters/modulators are dependent on the status of the organism and conditions of acupuncture (e.g., stimulation parameters and acupoints), and vary from region to region in the central nervous system. Although these data were largely obtained from the studies on acupuncture analgesia, it is reasonable to presume that acupuncture is capable of modulating the brain functions through the regulation of central neurotransmitters/modu-lators, because all the acupuncture-influenced neurotransmitters/modulators participate directly or indirectly in neural regulation in almost all aspects.

Keywords *neurotransmitters, modulators, monoamines, acetylcholine, amino acids*

5.1 Introduction

Acupuncture on the body can generate an afferent signal of the nerves, which has the ability to initiate the central signal process involving multiple neurotransmitters/modulators at different levels in the central nervous system (see Chapters 2 and 3). Because of the unique nerve distribution and afferent pathway (see Chapter 2), specific acupoints, when stimulated by acupuncture or other approaches, may activate/inhibit certain neurotransmitters and modulators in various pathways. Indeed, past investigations have shown that acupuncture could greatly influence the activities of many neurotransmitters and modulators, including endogenous opioid peptides, monoamines, acetylcholine (ACh), and amino acids. This chapter will summarize the progress in this field, except for the endogenous opioid peptides, which has been presented in Chapter 4. Owing to numerous earlier studies, we will make succinct description of the cited studies and present plumpish information in this short chapter.

5.2 5-hydroxytryptamine

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter synthesized in the serotonergic neurons that are mainly located in the median regions of the brain. Its synthesis and metabolism are schematically shown in Fig. 5.1. Under normal conditions, the level of serotonin is dependent on the intake of tryptophan (TRP) and the degradation by monoamine oxidase (MAO). In the central nervous system, serotonin is believed to play an important role in the regulation of body temperature, mood, sleep, vomiting, sexuality, and appetite.

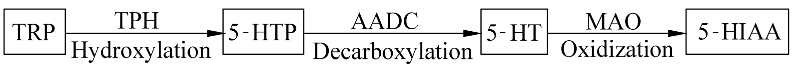

Figure 5.1 Schematic representation of 5-HT synthesis and degradation pathway. TRP, Tryptophan; TPH, tryptophan hydroxylase; 5 HTP, 5 hydroxytryptophan; AADC, aromatic L amino acid decarboxylase; 5 HT, 5 hydroxytryptamine; MAO, monoamine oxidase; 5 HIAA, 5 hydroxyindole 3 acetic acid.

Acupuncture has been shown to induce a therapeutic effect by increasing the activity of 5-HT system in the central nervous system. Early studies (Han et al. 1980) showed that acupuncture analgesia could be enhanced or attenuated by the increment or decrement of the 5-HT level, respectively, in the central nervous system. We (Xia and Li 1984; Xia et al. 1985) found that simulated EA (low-frequency and low-intensity stimulation of deep peroneal nerve) could attenuate sympathetic cardiac arrhythmia induced by hypothalamic stimulation, which was found to be associated with an increase in the 5-HT activity in the periaqueductal gray matter and median regions of the brainstem. Zhu et al (1990b) and Mo et al (1994, 1995) also demonstrated that 5-HT in these areas plays an important role in EA analgesia.

5.2.1 Acupuncture-Induced Increase in Central 5-Hydroxytryptamine Activity

Several studies have shown that acupuncture can increase the levels of 5-HT and its metabolite (5-hydroxyindole-3-acetic acid, 5-HIAA) in the brain, indicating an increase in the 5-HT activity. Jin et al (1979) reported that in rats under EA analgesia, the levels of 5-HT and 5-HIAA, especially the latter, significantly increased in the brain， suggesting an increased turnover rate of 5-HT in response to acupuncture. After EA and pestle-acupuncture stimulation at the acupoint "Zusanli (ST-36)", the levels of 5-HT and 5-HIAA were found to increase mainly in the interbrain and endbrain. Furthermore, Ye et al (1979, 1980) showed that after EA at the acupoints along the DU meridian, the level of 5-HT significantly increased in the nuclei of median raphe and the nearby areas of the brainstem. Other studies also showed that acupuncture could increase the content of 5-HT and 5-HIAA in the cerebral cortex, brainstem, and even in the peripheral circulation, which lasted for at least 30 min (Shi and Wu 1983; Zhao and Zhu 1988; Chen et al. 2003). In the midbrain, both 5-HT and 5-HIAA markedly increased in the caudate putamen, while 5-HT tended to increase in the nigra substance with a significant increase in 5-HIAA. Furthermore, Xu et al (1984) showed that EA could significantly increase the contents of 5-HT and 5-HIAA in the periaqueductal gray matter, nuclei of median raphe, and spinal cord.

An increase in 5-HIAA, the metabolite of 5-HT, is considered to be one of the indices for 5-HT release, and the above-mentioned studies suggest that EA could strengthen the activity of the serotonergic neurons by increasing the 5-HT release. Indeed, we observed that simulated EA could significantly increase the level of 5-HIAA in the cerebrospinal fluid, suggesting an extracellular increase in 5-HIAA level (Xia et al. 1989a, 1989b). By administering 5-HT liberator, fenfluramine, in the rats, EA could promote the release of 5-HT as well as dopamine in the ventral part of the periaqueductal gray matter (Sun et al. 2003).

In addition to the enhanced utilization of 5-HT in the nervous system, several studies have also suggested that acupuncture could increase the content of 5-HT in most regions of the brain. This may be partially attributed to an increase in the 5-HT synthesis. There is evidence showing that acupuncture is capable of accelerating the synthesis of 5-HT (Shi and Wu 1983). On the other hand, acupuncture may reduce 5-HT degradation (Han et al. 1980).

Thus, taken together, acupuncture seems to increase the central 5-HT activity in most cases.

5.2.2 Acupuncture Regulation of 5-Hydroxytryptamine Activity in Certain Physiological and Pathophysiologic Conditions

The effect of acupuncture on 5-HT activity may vary in some circumstances, especially in pathophysiologic conditions. Lu et al (1989) observed that when rats developed typical allergy arthritis, the hypothalamic content of 5-HT was higher than that of the control. In the rats that formed allergy arthritis again after reserpinization, the level of 5-HT was still higher in the hypothalamus, and EA was observed to decrease the levels of 5-HT in the hypothalamus of these rats. Huang et al (1998) observed a major change in the plasma 5-HIAA with the circadian rhythm. The effect of acupuncture on 5-HIAA varied with the circadian rhythm. In a study on the effect of acupuncture on obesity, Wei and Liu (2002) showed that the levels of TRP and 5-HIAA increased, but the level of 5-HT decreased, in the raphe nuclei of the obesity group when compared with those in the normal group. Interestingly, acupuncture was found to increase the level of 5-HT and decrease the contents of TRP and 5-HIAA with no significant changes in the levels of dopamine and noradrenalin in the same subjects, suggesting a specific effect of acupuncture on 5-HT system in certain conditions.

In addition, other neurotransmitters and hormones may influence the effect of acupuncture on 5-HT system, and among them, adrenocorticotropic hormone (ACTH) is believed to play an important role in the regulation of 5-HT system. Zhu et al (1984) observed that after the removal of rat pituitary gland, acupuncture did not markedly increase the pain threshold and failed to enhance the contents of 5-HT and 5-HIAA in the brain. The injection of ACTH restored acupuncture-induced analgesia with an increase in the contents and conversion ratio of 5-HT.

5.2.3 Acupuncture and 5-Hydroxytryptamine Receptors

Most of the previous studies have focused on the role of 5-HT receptors in acupuncture by determining the effects of 5-HT receptor agonists and antagonists on the acupuncture efficacy. For example, Kim et al (2005) found that intrathecally injected methysergide (a 5-HT receptor antagonist) could significantly reverse the acupuncture-induced antinociception, suggesting that acupuncture-induced antinociception is produced by the activation of 5-HT receptors. Owing to the presence of multiple subtypes of 5-HT receptors, Takagi and Yonehara (1998) examined the effects of intravenous injection of various 5-HT antagonists on EA-induced analgesia in rabbits, and observed that 5-HT_1 except 5-HT_{1A}, 5-HT_2 except 5-HT_{2A} and 5-HT_3 receptors, were involved in the EA-induced analgesia. On the other hand, activation of 5-HT_{1A} and 5-HT_{2A} receptors attenuated the EA effect, suggesting differential roles of 5-HT receptor subtypes in EA effects. Chang et al (2004) also reported the differential roles of 5-HT_{1A}, 5-HT_2, and

5-HT_3 in EA analgesia based on the results of antagonists. However, their results were somewhat different from those of Takagi and Yonehara (1998), and this difference could be attributed to the different experimental conditions between their studies. Till date, the roles of various 5-HT receptor subtypes in acupuncture are not yet clear, although there are many reports based on the applications of 5-HT agonists and antagonists.

Mo et al (1994, 1995) determined the binding density of 5-HT receptors in different brain areas of rats, using receptor autoradiography after needling at the acupoint "Zusanli" (ST-36). They showed that the 5-HT receptor density decreased in the cerebral cortex, hippocampus, striatum, and spinal cord after the onset of significant analgesia by needling at the acupoint "Zusanli" (ST-36). We speculate that this decrease in 5-HT receptor density might reflect the downregulation of the 5-HT receptor expression as a negative feedback, because of increased 5-HT release and enhanced activation of the 5-HT receptors. However, the effect of acupuncture may have differential effects on the central and peripheral 5-HT receptors. Tian et al (2006) reported the effect of EA on 5-HT_{4A} receptor expression in the colon mucosa, using semi-quantitative immunohistochemistry. Their results showed that EA could significantly increase the expression of 5-HT_{4A} receptor in rats with chronic visceral hypersensitivity.

It is generally accepted that acupuncture could promote 5-HT release and activate 5-HT receptors. However, few studies have been carried out in the past to elucidate the precise roles of 5-HT receptor subtypes in acupuncture, including their function and expression in acupuncture.

5.3 Noradrenalin

Noradrenalin, adrenaline, and dopamine belong to the category of catecholamine neurotransmitters. They are all synthesized from the same precursor, tyrosine. The precursor tyrosine is transformed into dopamine by tyrosine hydroxylase, and the dopamine is subsequently transformed into noradrenalin by dopamine-β-carboxylase.

Noradrenalin is an important neurotransmitter of the post-ganglion sympathetic nerves and many central neurons, such as those in the locus ceruleus and hypothalamus. The released noradrenalin exhibits its effect by interacting with the adrenergic receptors. This interaction is terminated by noradrenalin reuptake into the presynaptic neuron and its degradation by MAO, or by the extracellular catechol-o-methyltransferase. Tyrosine hydroxylase and MAO are observed to critically regulate the level of noradrenalin in neurons.

Earlier investigations, including our studies (Xia and Li 1984; Xia et al. 1985, 1989a, 1989b), have shown that all these substances are actively involved in acupuncture-induced activities in the brain.

5.3.1 Acupuncture Reduction of Noradrenalin Release and Content in the Brain

Using push-pull perfusion and radioenzymatic assay in rabbits, Xu et al (1984) found that during EA analgesia, the release of noradrenalin significantly decreased in the noradrenalin ascending pathway in the locus ceruleus, periaqueductal gray matter, and raphe magnus nucleus, although the release significantly increased in the A1 nucleus of the noradrenalin descending pathway. It is believed that EA could reduce the release of noradrenalin in most of the brain regions.

Acupuncture also decreases the content of noradrenalin in the brain. For example, through biochemical determination, Jin et al (1979) showed that acupuncture could decrease the content of noradrenalin in the rat brain. There has been evidence demonstrating that EA could attenuate the fluore- scence intensity of noradrenalin in the nucleus ceruleus of rats. Wang et al (1994a, 1994b) investigated the role of noradrenalin in reticularis paragigantocellularis lateral nucleus (RPGL) in EA-induced analgesia, using push-pull perfusion and high-performance liquid chromatography (HPLC)-electrochemical detection. They observed that after 20 min of EA, the pain threshold increased significantly, which was associated with a marked decrease in the content of noradrenalin and its metabolite, methoxy-hydroxyphenylglycol (MHPG), in the perfusate. Some investigators suggest that acupuncture may change the rate of noradrenalin utilization and synthesis (Han et al. 1979).

In an obese rat model, acupuncture also reduced the level of noradrenalin in the lateral hypothalamic area when inducing weight reduction. However, acupuncture may induce diverse effects in different brain areas in terms of the content of noradrenalin. Using histochemistry, Wei et al (1983a, 1983b) observed stronger noradrenalin staining in the posterior nucleus of the hypothalamus, lateral hypothalamic area, and intermediolateral nucleus of the spinal cord, after acupuncture treatment, while no significant change was found in the medial preoptic area of the hypothalamus and dorsal motor nucleus of the vagus nerve.

5.3.2 Effect of Endogenous Opioid Peptides on Noradrenalin During Acupuncture

There are several lines of evidence suggesting that the acupuncture effect on noradrenalin is regulated by the endogenous opioid peptides. Zhu et al (1984) showed that after the injection of glutamic acid sodium in the newborn rats to destroy arcuate nuclei, a major source of β-endorphin, acupuncture analgesia was significantly attenuated and the content of noradrenalin was higher in the brain of the experimental group than that in the control group. Destruction of the arcuate nuclei along with the removal of pituitary gland, which greatly reduced the level of β-endorphin in the brain, further attenuated acupuncture analgesia and increased the content of noradrenalin in the brain. β-endorphin is presumed to inhibit noradrenalin during acupuncture. Our previous studies also suggest that simulated EA may reduce the activity of noradrenalin system in the brain via the activity of endogenous opioid peptide (Xia et al. 1989b).

5.3.3 Acupuncture and Noradrenergic Receptors

There are two major subtypes of noradrenergic receptors, i.e., α- and β-receptors, which play different roles in acupuncture effects. Zhu et al (1990a) observed that microinjection of noradrenalin (0.5 μg/unilateral) into the preoptic area could attenuate acupuncture analgesia. Wang et al (1994a, 1994b) compared the effects of noradrenergic α-receptor antagonist, phentolamine, β-receptor antagonist, propanolol, and non-selective agonist, noradrenalin, on acupuncture by microinjecting them into RPGL in rats. They observed that phentolamine could strengthen acupuncture analgesia, while noradrenalin could antagonize it. However, propanolol did not show any effect on acupuncture analgesia. These results suggest that α-receptors in RPGL may be involved in pro-acupuncture effect, but the role of β-receptors needs to be clarified. Recently, Baek et al (2006) demonstrated that bee-venom acupuncture, although not a traditional acupuncture or EA, could relieve inflammatory pain in collagen-induced arthritis, and showed that the antinociceptive effect of bee-venom acupuncture could be mediated by the α_2-adrenergic receptor.

Till date, however, the noradrenalin receptor mechanism underlying acupuncture effects is not yet well understood. Currently, there is no convincing evidence to demonstrate the effect of acupuncture on the expression of noradrenergic receptors, though some reports suggest that acupuncture could alter the expression of noradrenergic receptors in the lung tissues of guinea pigs with asthma (Chen et al. 1996) and in the polycystic ovaries of the rat model (Manni et al. 2005).

5.4 Dopamine

Dopamine serves as a neurotransmitter of some peripheral nerves and central neurons in many regions, including the substantia nigra, hypothalamus, midbrain, and ventral tegmental area. Dopaminergic neurons uptake tyrosine and convert it to 3, 4 hydroxy-phenylalanine by the action of tyrosine hydroxylase, and subsequently to dopamine by the action of dopa decarboxylase. After the release, dopamine binds to the dopaminergic receptors for the functional activity and is cleaned-up by the reuptake and enzymatic destruction.

5.4.1 Acupuncture-Induced Alteration in Dopaminergic Activity

An early study showed that EA at the acupoints along the DU meridian could significantly increase the contents of dopamine and the main metabolite, homovanillic acid, in the caudate putamen, suggesting that acupuncture could strengthen the activity of the dopaminergic neurons. Wang et al (1991) reported that EA could increase the pain threshold and the level of dopamine in the brainstem. Some later studies (Hou et al. 2002) also demonstrated that acupuncture could significantly affect the dopaminergic activity.

However, previous literature is contradictory. Jin et al (1979) showed that during EA analgesia, the content of dopamine showed no appreciable changes in the brain. Zhu et al (1990a) also reported that EA could not induce any significant change in the release of dopamine in the preoptic area of the hypothalamus. However, Kim et al (2005) showed that acupuncture at the specific acupoint "Shenmen" (HT-7), but not at the control points "TE-8" and tail, could significantly decrease the dopamine release in the nucleus accumbens.

The effect of acupuncture on the dopaminergic system may vary with the brain regions and acupuncture conditions. Hence, different patterns of dopamine release and content after acupuncture could be observed, which should be clarified in future studies.

5.4.2 Effect of Other Neurotransmitters on Dopaminergic Activity during Acupuncture

Wang et al (1991) showed that EA could significantly increase the pain threshold and the contents of 5-HT and dopamine in the brainstem, and decrease that of noradrenalin in the endbrain. These effects could be eliminated by pre-injecting naloxone, an opioid receptor antagonist, suggesting that EA could regulate the monamine neurotransmitters and thus induce analgesia through the function of opioid receptors. Yoon et al (2004) demonstrated that acupuncture at the specific acupoint "Shenmen" (HT-7), but not at the control points (PC-6 or tail), could significantly decrease the dopamine release in the nucleus accumbens. This effect was completely prevented by SCH 50911 (a GABA antagonist). These results suggest that the effect of acupuncture on the dopaminergic activity may be achieved through the regulation of other neurotransmitter systems. The differential EA effects observed in different brain regions may be partially attributed to the differences in the integrated activities of various neurotransmitter systems in these regions.

5.4.3 Acupuncture and Dopaminergic Receptors

Gao et al (1998) tested the effect of some agonists and antagonists of dopaminergic receptors on the rat flick model, to determine the role of D1 and D2 receptors in acupuncture analgesia. They found that the intrathecal administration of D2 receptor agonist, LYI71555, or D1/D2 receptor agonist, apomorphine, increased the pain threshold and potentiated acupuncture analgesia. In contrast, D1 receptor agonist, SKF38393, had no effect on the acupuncture effect. Intrathecal administration of D1 receptor antagonist, SCH23390, or D2 receptor antagonist, sulpiride, was observed to attenuate acupuncture analgesia. These results suggest that D2 receptor may be involved in pain modulation and its activation may enhance acupuncture analgesia.

EA likely alters the expression of dopaminergic receptors in the central nervous system. Gao et al (1998) detected the changes in the central D1 and D5 receptor mRNA at 10 and 24 h after EA, using in-situ hybridization and autoradiography. They observed that the D1 and D5 receptor mRNA in the spinal cord increased after EA, especially at 24 h after EA. The results demonstrate that EA could enhance the expression of central D1 and D5 receptors. In contrast, there are also studies showing that EA could attenuate the upregulation of dopamine receptors in disease states. For example, Lin and Lin (2000) determined the change in the D2 receptors and their relationship with the dopamine content in the hemi-parkinsonian rats before and after EA treatment. They observed that 6-hydroxy-dopamine lesion in the substantia nigra and ventral tegmental areas could induce an upregulation of the striatal D2-binding sites. EA treatment was found to elevate the DA level of the injured side of the striatum and prevent the D2 receptor upregulation in the rats with experimental hemi-parkinsonism.

In general, the effects of acupuncture on the dopamine system appear to be complicated in the literature, and more investigations are needed to draw a clear picture.

5.5 Acetylcholine

ACh is the transmitter of cholinergic neurons in the brain. It is synthesized with choline and acetyl coenzyme A by choline acetyl transferase. The released ACh stimulates the cholinergic receptors and this interaction is quickly terminated by the local choline esterase, which enables ACh hydrolyzation to choline and acetate. The level of ACh is dependent on the intake of choline and the regulation by choline acetyltransferase (ChAT).

5.5.1 Acupuncture and Cholinergic Activity

Cholinergic activity is largely dependent on the regulatory enzymes of ACh. Several early studies have shown that acupuncture could alter the activity of these cholinergic enzymes. Wei et al (1983a) found that under EA analgesia, the activity of acetylcholinesterase (AChE) increased in the hypothalamicus posterior nucleus, lateral hypothalamic area, arcuate nucleus, locus ceruleus, nuclei of median raphe, and spinal cord intermediolateral nucleus of rats, while it decreased in the parasympathetic center, such as hypothalamus preoptic area and dorsal motor nucleus of the vagus nerve. Wu et al (1999) determined the effect of acupuncture on AChE，succinate dehydrogenase, and acid phosphatase of the motor neuron of the anterior horn in the injured rat's spinal cord. They observed that after spinal cord injury, AChE and succinate dehydrogenase decreased, while acid phosphatase increased. Acupuncture increased the level of AChE and succinate dehydrogenase and lowered that of acid phosphatase. They concluded that acupuncture could regulate the enzymology of the motor neuron of the anterior horn of the injured spinal cord, and attenuate or delay the neuronal deterioration and promote their recovery. Tian et al (2004) measured the mRNA expression of ChAT in the rat brain by RT-PCR, and showed that the expression of ChAT mRNA in the brain of the ovariectomized rats could be regulated by acupuncture at the acupoint "Zusanli" (ST-36).

Guan et al (1991) reported that the content of ACh increased in the brain and cerebrospinal fluid, and that the AChE activity increased in the brain, during acupuncture analgesia. AChE inhibitor reinforced the effects of acupuncture, while the inhibitor of ACh synthesis attenuated the effects, which could be reversed by the administration of ACh. There is evidence showing that the turnover rate of ACh in the diencephalons, caudate putamen, and spinal dorsal horn is accelerated by acupuncture. Shi et al (1995) found that EA could facilitate ACh release in the spinal dorsal horn. All these observations demonstrate that acupuncture could enhance the cholinergic activity in the central nervous system.

5.5.2 Role of Acetylcholine in Acupuncture Effects

Cholinesterase inhibitor, neostigmine, and ACh synthesis inhibitor, hemicholine, can pass through the blood-cerebral barrier, and have been used to determine the role of cholinergic system in acupuncture. Guan et al (1990a, 1990b) showed that (1) EA analgesia could be enhanced by subcutaneous injection of neostigmine; (2) EA analgesia could be markedly inhibited by intraperitoneal injection of hemicholine; and (3) the effect of hemicholine could be reversed by ACh in combination with neostigmine, but not by neostigmine alone. These observations strongly demonstrate the important role of ACh in acupuncture. Chen et al (1995) used multi-barreled micropipette and microelectrophoresis for extracellular recordings of thalamic parafascicular neurons in response to noxious stimulation of the plantar area, and found that (1) the lesion of the cortical motor area attenuated the inhibitory effect of EA at the acupoints "Zusanli" (ST-36) and "Huantiao" (GB-30) on nociceptive responses of the neurons; (2) the iontophoretic application of ACh after the lesion of the cortical motor area markedly suppressed the nociceptive responses; and (3) the inhibition induced by iontophoretic ACh was similar to that produced by EA. It seems that EA could promote the cortical motor area to release ACh and thus exert descending modulation of the neuronal responses to nociceptive stress. These observations provide strong evidence that ACh is involved in the effects of acupuncture.

5.5.3 Acupuncture and Cholinergic Receptors

There are two major subtypes of cholinergic receptors, i.e., muscarinic cholinergic receptor (M-ACh receptor) and nicotinic ACh receptor (N-ACh receptor), which function as a ligand-gating ion channel. Several studies suggest that M-ACh receptor could play an important role in acupuncture analgesia. Guan et al (1991) reported that the antagonists of M-ACh receptor could inhibit the effects of acupuncture. Xu et al (1992) showed that the intraperitoneal injection of atropine, an antagonist of M-ACh receptor, could attenuate the analgesic effect of acupuncture.

Mo et al (1994) determined the M-ACh receptor-binding capacity in different brain areas of rats, using receptor radioligand-binding assay after needling at the acupoint “Zusanli” (ST-36). The animals without needling or with needling at the “Taichong” (LR-3) acupoint were used as the control. They found that M-ACh receptor-binding capacity was significantly decreased in the cerebral cortex, hippocampus, striatum, thalamus, and spinal cord, but not in the brainstem when needling at the acupoint “Zusanli” (ST-36) to induce analgesia. However, current information is not yet sufficient to conclude the effect of acupuncture on the expression of cholinergic receptors.

5.6 Amino Acids

Amino acids are mainly divided into excitatory amino acids (such as glutamate, aspartic acid) and inhibitory amino acids (such as GABA, glycine, lactamine, taurine). Many studies suggest that acupuncture may decrease the activity of excitatory amino acids (e.g., reducing their contents in the brain) and increase that of the inhibitory amino acids in the central nervous system, though there are exceptions in some reports.

5.6.1 Excitatory Amino Acids

Zhu et al (1979) reported that acupuncture could significantly increase the contents of glutamate and glutamine in the mouse cortex and thalamus. Other researchers observed that EA could differentially regulate the content of excitatory amino acids in the brain. For example, Wang et al (1997a) showed that EA increased the level of glutamate in the hippocampus and decreased that of the pons. However, most of other studies showed that after acupuncture, the contents of excitatory amino acids decreased. For instance, it was reported that at 15 min after EA, the level of glutamate started to decrease in the cortex, hippocampus, thalamus, midbrain, and medulla oblongata, with a significant change in the thalamus. In the model of acute arthritis, Cao et al (1993) showed that 15 Hz EA could induce a lower level of glutamate in the spinal cord than that in the group subjected to 100 Hz EA. Another study demonstrated that at 20 min after EA in rabbits, both glutamate and aspartic acid showed a downward trend in the brain (Wang and Fan 1995). Therefore, it is very likely that acupuncture could decrease the content of excitatory amino acids in the brain. More recently, Ma et al (2008) reported that EA could produce a significant analgesic effect in rats with neuropathic pain, which is closely related to the reduced release of glutamate and aspartic acid from the dorsal horns of the spinal cord and the decreased content of the excitatory amino acids.

5.6.2 Inhibitory Amino Acids

GABA and glycine are the main inhibitory neurotransmitters in the brain. In an early study, Zhu et al (1979) reported that acupuncture could significantly decrease the GABA levels in mouse cortex and thalamus. However, Wang and Fan (1995) observed that at 20 min after acupuncture in the rabbit, the contents of inhibitory amino acids, such as GABA, glycine, lactamine, and taurine, showed an upward trend. Furthermore, Wang et al (1997b) reported that after acupuncture, GABA increased in the hippocampus, habenular nucleus and hypothalamus, and some regions of the endbrain. The level of glycine was also observed to increase in the lumbosacral areas of the spinal cord, but showed no appreciable change in the cortex and hippocampus. In particular, EA was found to increase the level of GABA by 93.6% in the hypothalamus and by 73.7% in the pons, while the level of glycine was increased by 65.4% and 77.1% in the thoracic and lumbosacral areas of the spinal cord, respectively. Liu et al (1998b) reported that after acupuncture at the acupoint “Yanglingquan” (GB-34), the content of GABA increased in the cerebrospinal fluid. Yan and Li (1999) investigated the GABA content in the brainstem of rats with acute epilepsy induced by intramuscular injection of coriamyrtin. They found that the GABA content was significantly lower in the brainstem of the epileptic rats than that in the naive animals. After one session of acupuncture treatment, the level of GABA was higher than that in the model without acupuncture treatment. Ku and Chang (2001) also showed that GABA was involved in producing the EA effect in the rostral ventrolateral medulla. A recent study by Lee et al (2008) suggested that acupuncture at the specific acupoint HT-7 could normalize the dopamine release in the mesolimbic system and attenuate the withdrawal syndrome through the $GABA_B$ receptor system in the ethanol-withdrawn rats.

5.7 Other Neurotransmitters

Although there are many other neurotransmitters/modulators in the central nervous system, limited information are available regarding their role in acupuncture. Therefore, we will briefly describe some studies on these substances.

5.7.1 Substance P

Substance P exists mostly in the neurons of the habenular nucleus, substantia nigra, basal ganglia, oblongata, and hypothalamus. Its content is also considerably high in the posterior root ganglion. An early study showed that EA could induce the release of substance P, which was observed to vary with the frequency of stimulation (Cui et al. 1990). Li et al (1989) measured the level of substance P in the rat brain and spinal cord using radioimmunoassay, and determined its correlation with EA analgesia. They showed that there was a significant elevation in the levels of substance P in the hippocampus, hypothalamus, and striatum after 30 min of EA, while there was a marked decrease in its level in the spinal cord. Statistical analysis revealed a positive correlation between the EA effect and the content of substance P in the hypothalamus, striatum, and spinal cord.

A study on acupoints suggests that stimulation of acupoints could induce the release of substance P through primary afferent reflex and change the content of substance P in the skin along the channel of Foot-Yangming (Cao and Wang, 1989; Cao et al. 2001). This might be owing to a functional interaction between substance P and endogenous opioid peptides (Cao and Wang, 1989). However, more experiments are needed to verify this phenomenon and indentify its significance.

5.7.2 Prostaglandin

In the rats administered with prostaglandin E2 (PGE2) in the preoptic area, Fang et al (1998) observed that the animals developed rapid and high fevers, which could be attenuated by EA stimulation. Following the intraperitoneal injection of lipopolysaccharide (100 μg/kg), the concentrations of interleukin-6 (IL-6) and PGE2, but not IL-1β, increased in the brain and serum. EA was observed to reduce the level of PGE2 in both the brain and serum in the lipopolysaccharide-injected rats. The results suggest that EA stimulation could produce an antipyretic effect through the inhibition of the action of PGE2.

5.7.3 Cholecystokinin-Octopeptide-8

CCK-8 administered to the periaqueductal gray matter, nucleus amygdala, or nucleus accumbens was found to antagonize EA analgesia (Han et al. 1985, 1986; Han and Wang 1992; Cao et al. 1989; Li and Han 1989; Pu and Han 1993; Pu et al. 1994). Bian et al (1993) observed that the effect of EA subsided after prolonged EA stimulation, suggesting the development of EA tolerance. They found that central (intracerebroventricular) injection of CCK-8 antiserum, aimed at neutralizing the endogenously released CCK-8, resulted in a complete restoration of the EA effect. Furthermore, other reports support the notion that CCK-8 might be an endogenous opiate antagonist (or anti-opiate substance) and may play a role in acupuncture tolerance (Chen et al. 1994; Sun et al. 1995; Zhang et al. 1997).

5.7.4 Somatostatin

Liu et al (1998a) measured the content of somatostatin in 12 nuclei in rat brain after EA at the acupoint "Zusanli" (ST-36) for 30 min. The content of somatostatin increased in the raphe magnus nucleus, caudatus putamen nucleus, and amygdaloid nucleus, while it decreased in the periaqueductal gray matter. However, the content of somatostatin did not change significantly in the following nuclei: suprachiasmatic nucleus, supraoptic nucleus, paraventracular nucleus, arcuatus nucleus, ventro medialis nucleus, dorso medialis nucleus, dorsal raphe nucleus, and locus ceruleus. The results suggest that EA could differentially change the level of somatostatin in the nuclei, in spite of the extensive distribution of somatostatin in the brain. Zhang et al (1999) applied EA at the acupoints Quchi (LI-12), Waiguan (SJ-5), Huantiao (GB-30), and Zusanli (ST-36) in 64 patients with acute ischemic cerebrovascular diseases, and subsequently measured the levels of somatostatin in the plasma and cerebrospinal fluid. They found that after a course of treatment, the level of somatostatin significantly increased in the cerebrospinal fluid and plasma of the patients ($n = 31$) under routine treatments along with EA, who showed better outcome. However, the interpretation of the data has been difficult owing to the lack of strict control.

5.7.5 Orphanin FQ

Orphanin FQ (OFQ), also known as nociceptin, is a non-typical EOP, we therefore discuss it in this chapter. Zhou et al (2001) used the immunohistochemical approach to determine the changes in the central OFQ after EA combined with melatonin treatment. They found that the level of OFQ-like immunoreactivity increased significantly in some pain-modulation-related nuclei, such as ventromedial hypothalamic nucleus, raphe magnus nucleus, dorsal raphe nucleus, and periaqueductal gray matter, after injection of melatonin (60 mg/kg, intraperitoneally). The level was further elevated in the subjects treated with melatonin combined with EA. In-situ hybridization study showed that its precursor protein, prepro-OFQ (ppOFQ), mRNA expression was decreased in the same nuclei after the administration of melatonin. In the group treated with the combination of EA and melatonin, the expression was further decreased. These results suggest that OFQ may play a role in pain modulation in response to acupuncture.

5.7.6 Neurotrophic Factors

Recent studies have shown that acupuncture could regulate the neurotrophic factors in the central nervous system (Xu et al. 2004; Wang et al. 2002; Hu et al. 2006; Ju et al. 2006; Liu et al. 2006; Du 2008). There is evidence showing that EA could increase the expression of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors in the cortex, hippocampus, and other brain regions, and protect the brain from ischemic/hypoxic injury (Xu et al. 2004; Hu et al. 2006; Liu et al. 2006). Interestingly, in the rat model of chronic mild unpredictable stressors depression, acupuncture and moxibustion also increased the BDNF expression in the cortex and hippocampus (Li and Bi 2008). Furthermore, glial cell-derived neurotrophic factor is also presumed to be involved in producing acupuncture effect. An in-situ hybridization study demonstrated that EA at both low and high frequency could upregulate the mRNA of the glial cell-derived neurotrophic factor in the lateral pallidal region. Wang et al (2002) showed that EA might regulate the expression of BDNF and its receptor in the spinal cord, thus producing the therapeutic effect on the spinal cord injury. Yang et al (2005) used immunohistochemistry to determine the effect of EA on BDNF, nerve growth factor, and fibroblast growth factor-2, and observed that EA could promote their expression in the injured spinal cord. EA was also observed to increase the expression of BDNF mRNA in the facial nucleus of rabbits (Ju et al. 2006). Moreover, Tong et al (2007) observed that EA could upregulate the expression of the neurotrophic factors and their receptors in the injured sciatic nerve.

It seems that acupuncture/EA can enhances the activity of neurotrophic factors in the brain in most conditions.

5.7.7 Nitric Oxide

Ma's group observed that the increase in the content of nitric oxide (NO) in the skin acupoints is associated with the enhanced neuronal NO synthase (nNOS) protein level in rats. They concluded that the nonenzymatic reduction of nitrate by bacteria is involved in the chemical generation of NO on the skin acupoints/ meridians, in addition to the neuronal NO ergic system. NO is observed to mediate the noradrenergic function on the skin sympathetic nerve activation, which is believed to contribute to the low-resistance characteristics of the acupoints and meridians, which has been briefly summarized in a recent review (Ma 2008).

5.8 Concluding Remarks

Considerable data demonstrate that manual acupuncture or EA can activate or strengthen the activity of certain central neurotransmitters/modulators, while inhibit or attenuate that of other neurotransmitter systems. These effects alter the release and degradation of the neurotransmitters/modulators involved, thus leading to a major change in their contents in the central nervous system. Generally, acupuncture is observed to enhance the activities of the endogenous opioid peptides (see Chapter 4), serotonin, dopamine, ACh, and inhibitory amino acids such as GABA, glycine, taurine, and lactamine. On the other hand, acupuncture is found to attenuate the activities of noradrenalin and excitatory amino acids including glutamate and aspartic acid. A prolonged period of acupuncture may induce excessive production of CCK-8 and deplete some pro-acupuncture substances, thus causing the so-called acupuncture tolerance. In addition, acupuncture is also observed to regulate the expression and function of the corresponding receptors.

The effects of acupuncture on the central neurotransmitters/modulators depend on the status of the organism and conditions of acupuncture (e.g., stimulation parameters and acupoints), and vary from region to region in the central nervous system. For example, acupuncture decreases the activity of noradrenalin in the brain, while strengthens its release in the spinal cord. Also, some data suggest that acupuncture could increase the release and synthesis of some neurotransmitters and enhance the expression of their receptors, and limit its effect only on the release of other neurotransmitter systems.

Most of the previous results were obtained from the research on acupuncture analgesia. The major changes in the chemical substances in the central nervous system can certainly influence other functions of the body, because all the above-mentioned neurotransmitters and modulators are directly or indirectly involved in the regulation of many functions in the body. For example, an increased activity of serotonergic neurotransmitter may result in the inhibitory regulation of the sympathetic discharges and may downregulate the cardiovascular activity. Furthermore, the change in the dopaminergic activity can affect the behavioral function. Hence, we believe that acupuncture can regulate multiple brain functions through the regulation of neurotransmitters and modulators, which may be the basis for the therapeutic effect of acupuncture on certain neurological disorders.

Many of the studies cited in this chapter were carried out by Chinese scientists in the past 30 years. The abundant data obtained have drawn a compendious picture showing the effects of acupuncture on the central neurotransmitters and modulators. However, this knowledge is far away from the understanding of acupuncture mechanism at the cellular and molecular levels. In addition, the way in which acupuncture alters the expression of their receptors is very poorly understood. Moreover, there exist very limited data on many other neurotransmitters and modulators, which need more attentions in future research. Finally, there are some unexplainable controversies in the existing literature. Some of them may be owing to the different approaches and experimental conditions. However, certain problems may be attributed to the problematic experiments and analysis. We believe that broader and in-depth investigations on acupuncture-induced regulation of neurotransmitters and modulators with advanced techniques may greatly advance our understanding of the mechanism underlying acupuncture therapy for neurological disorders and improve the clinical practice.

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6 Acupuncture-Drug Balanced Anesthesia

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Summary In this chapter, the clinical and experimental studies on acupuncture-drug balanced anesthesia will be reviewed. The history of acupuncture anesthesia in China started in 1958. After two decades of clinical practice and experimental investigation, the combination of acupuncture (usually electro-acupuncture, EA) with drugs has been successfully used to improve anesthesia for surgical operations and pain treatment since the 1980s, and this technique is now known as the acupuncture-drug balanced anesthesia in China. It is more advantageous to use acupuncture combined with selected drugs to produce anesthesia, because acupuncture could regulate the functions of multiple organs of the body in addition to analgesia. Moreover, the underlying mechanism has been elucidated by investigating the potentiation effects of some commonly used drugs on acupuncture analgesia, in various animal models. Substantial evidence has shown that the combination of acupuncture with these drugs promotes the release of endogenous opioid peptides (EOP). In addition, these drugs potentiate EA-induced expression of EOP gene. Furthermore, several lines of evidence show that EA induces an increase in both binding affinity and density of the opioid receptors, while the combined use of acupuncture with drugs can further enhance the EA effect. Currently, clinical and bench studies on acupuncture-drug balanced anesthesia are still in progress to improve the clinical efficacy and to better understand the working mechanisms. We expect that new discoveries through the translational research will bring more benefits to patients.

Keywords *acupuncture, analgesia, anesthesia, balanced anesthesia*

6.1 Introduction: From Acupuncture Analgesia to Acupuncture Anesthesia

Acupuncture treatment is a great conception of ancient physicians in China, and acupuncture analgesia is one of the most influential medical modalities. Since

1949, great progresses have been made in the research of acupuncture analgesia, guided by the principle of integration of Traditional Chinese Medicine (TCM) and Western Medicine (Qian 1986).

Acupuncture anesthesia was developed from acupuncture analgesia. The history of acupuncture anesthesia can be traced back to as early as the 1950s (Zhang 1989). Originally, its discovery was prompted by the notion that the stimulation of acupuncture points could relieve pain of the wound caused by the operation on the tonsil under local anesthesia. Subsequently, some medical doctors tried to use acupuncture in tonsillectomy as an alternative anesthetic approach, in 1958. The first case of operation under acupuncture anesthesia was performed on August 30, 1958. At that time, some doctors of Chinese and Western Medicine in the Shanghai First People's Hospital worked together and learnt from each other. They inserted needles into both the sides of Hegu (LI-4) acupoint to relieve pain, and gained excellent outcomes that were reproducible in different patients. The exciting results rendered them to truly believe that acupuncture could significantly increase the pain threshold and pain-tolerance threshold. Therefore, they applied it to tonsillectomy and again achieved satisfactory results. Besides Shanghai, some medical doctors in other cities, such as Xi-an, Wuhan, and Nanjing, also performed some minor operations, such as tonsillectomy, tooth extraction, thyroidectomy, and appendectomy using acupuncture anesthesia in the same or the subsequent year (Zhang 1989).

In 1960, the Shanghai First Tuberculosis Hospital in China succeeded in using acupuncture anesthesia for pneumonectomy. Subsequently, in the 1960s and 1970s, many doctors performed other major and even difficult operations (such as cardiac surgery, surgery on the anterior cranial fossa, total laryngectomy, subtotal gastrectomy, panhysterectomy, cesarean section, etc.) using acupuncture anesthesia, and obtained satisfactory results (Zhang 1989). However, in the beginning, the acupoints used for an operation were generally as many as dozens. Furthermore, the acupuncture was manipulated manually and the induction time was as long as 60 min, initially. These complexities made the process very inconvenient. However, researchers in the Shanghai First Medical College (the name was changed to Shanghai Medical University in 1985; and Shanghai Medical College of Fudan University since 2000) conducted observations on normal volunteers as well as patients, and found that the number of acupoints could be markedly reduced while maintaining the same analgesic effect, thus making the technique more feasible. Furthermore, after performing some experiments, it was observed that the manipulation of acupuncture could be substituted by an electrical stimulation machine (i.e., electro-acupuncture, EA) as widely known today, and the induction time could be reduced to 20 min, with the analgesic effect remaining the same (Department of Physiology, Shanghai First Medical College 1973). Since the successful use of acupuncture anesthesia in the first case, substantial evidence has been accumulated demonstrating that acupuncture has prominent analgesic effect, and that acupuncture anesthesia is based on a scientific fundament (Cao 2002), showing some benefits in surgical operation. However, acupuncture anesthesia fails to produce complete elimination of pain induced by surgical trauma (only incomplete analgesia), because it induces analgesia via activation of the endogenous pain-modulating system. This limitation has hindered the widespread use of acupuncture anesthesia in clinic.

6.2 From Acupuncture Anesthesia to Acupuncture-Drug Balanced Anesthesia

Since the 1980s, research on acupuncture anesthesia has been extensively conducted in China, although the cases of operation have decreased rapidly. Three national key projects were performed from 1986 to 2000, and it was our great honor that the Shanghai Medical University was appointed as the head of this national collaborative investigation (Wu and Cao 1992; Cao 1997; Wu et al. 2001).

6.2.1 The Advantages of Acupuncture-Drug Balanced Anesthesia

The combination of acupuncture with drugs has been successfully used in anesthesia for surgical operations, such as open-heart surgery with cardiopulmonary bypass, pneumonectomy, craniocerebral operation, thyroidectomy, neolarynx reconstruction, subtotal gastrectomy, cholecystectomy, and renal transplantation. As has been known, in modern anesthesiology, it is more common to use "balanced anesthesia", in which various drugs and/or techniques cooperate with each other to produce better effect. Similarly, acupuncture can also play a cooperative role in balanced anesthesia, because acupuncture produces analgesic as well as regulatory effects on multiple vital organs of the body, which usually cannot be produced by drugs. Thus, acupuncture combined with selected drugs to fulfill the requirement of anesthesia is known as acupuncture-drug balanced anesthesia, which could also be termed as acupuncture-balanced anesthesia (Cao 1997) or acupuncture-assisted anesthesia (Han 1997), which is a type of balanced anesthesia.

The clinical application of acupuncture-drug balanced anesthesia has shown its advantages in surgical operations. Acupuncture could be combined with different types of anesthesia, such as local anesthesia, epidural anesthesia, as well as general anesthesia, and the effect of analgesia has been observed to be much better, with patients usually not feeling the pain during these operations. Furthermore, the postoperative pain could also be reduced, and the doses of analgesic or anesthetic drugs could be markedly reduced during the surgical operations (usually about one-third reduction). Hence, the side-effects has been observed to decrease, with the increase in the rate of the excellent effect of both the operation and anesthesia, increase in the stability of many indices of the physiological condition, accelerated postoperative recovery, and shortened period of postoperative hospitalization.

6.2.2 The Main Cases of Acupuncture-Drug Balanced Anesthesia

Several famous hospitals, institutes and medical universities in Beijing, Shanghai, Chengdu and other cities joined this national cooperation unit and demonstrated that acupuncture-drug balanced anesthesia could lead to better outcome in the patients subjected to several surgical operations.

6.2.2.1 Craniocerebral operation

In the Huashan Hospital affiliated to our university, the clinical application of combined acupuncture-drug anesthesia was observed by employing the technique in the operation of the cerebral functional area (Yan et al. 1998). Satisfactory effects were obtained in all the 80 patients, including 20 cases operated in the language center, and 60 cases in the sensory and motor center. The excellent rate of anesthesia was 100%. After operation, no aggravation in dysphasia of dysfunction was found; however, in 5 cases, the aggravation on myasthenia and dysesthesia was observed, and recovery was within 2 – 4 weeks. Many neurosurgeons presume that the operation with combined acupuncture anesthesia could result in high tumor resection rate and reduce the incidence of disability. Therefore, this method of anesthesia could be regarded as one of the routine anesthesia methods used (Fig. 6.1).

Figure 6.1 Craniocerebral operation performed by Prof. Jiang C (right) in the Huashan Hospital Affiliated to the Shanghai Medical University (now, Shanghai Medical College of Fudan University).

The reinforcing effect of transcutaneous acupoint electric stimulation (TAES) with enflurane anesthesia during craniotomy was studied at the Beijing Tiantan Hospital (Wang et al. 1994). A total of 110 neurosurgical patients were randomly divided into three groups: Anesthesia was maintained with enflurane in Group A ($n = 40$); in Group B, enflurane anesthesia was supplemented by TAES with Han's acupoint nerve stimulator (HANS) at Hegu (LI-4), Yuyao (EX-HN4), and Fengchi

(GB-20) points on the operated side ($n = 40$); and in Group C, enflurane anesthesia was supplemented by TAES and scalp infiltration with 0.5% procaine ($n = 30$). The results demonstrated that the minimum alveolar concentration (MAC) of enflurane in group B and C decreased by 37.8% – 47.0% and 42.1% – 66.1%, respectively, than that in group A. Furthermore, the patients in groups B and C demonstrated more stable hemodynamics during the operation, and recovered faster after the operation, than those in group A. Thus, it can be concluded that TAES with HANS significantly potentiated the anesthetic effect and decreased the side-effects of enflurane during the operation, and the triple combination of TAES, enflurane and scalp infiltration with procaine proved to be a better anesthetic method for craniotomy.

6.2.2.2 Operations of heart, chest and larynx

The protective effect of EA on patients undergoing cardiac surgery was investigated in 40 patients with atria septal defect (ASD) in the Renji Hospital affiliated to Shanghai Second Medical University (Wang et al. 2001). The patients were randomly divided into three groups: Group A (acupuncture anesthesia) comprised 12 cases; Group B (acupuncture along with general anesthesia) comprised 12 cases; and Group C (general anesthesia) comprised 16 cases. The main acupoints were Neiguan (PC-6), Lieque (LU-7), and Yunmen (LU-2), comprising both the sides, with 2 – 3 Hz and 0.5 – 1 mA. Furthermore, some hemodynamic parameters, such as heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), cardiac index (CI), stroke volume (SV), and splanchnic vascular resistance (SVR) were observed in these cases. In addition, several biochemical tests were carried out, such as superoxide dismutase (SOD), malonyldiade-hyde (MDA), creatine posphokinase-isoenzyme (CPKI), using the blood samples from the internal jugular vein. The myocardial samples of the right auricle were taken for detecting the expression of heat shock protein (HSP) 70 mRNA. The results showed that acupuncture could adjust the hemodynamics in patients undergoing cardiac operations, and enhance the ability of oxygen-derived free-radicals clearance and the expression of HSP70 mRNA. Furthermore, acupuncture along with general anesthesia might be a better method for reducing myocardial ischemia-reperfusion injury.

Besides the clinical observation in this hospital, by using different animal models (rabbit and pig), researchers investigated the protective effects of acupuncture on myocardial ischemia-reperfusion injury (Wang et al. 2003; Wang and Sun 2003). The results showed that EA could reduce the release of endogenous epinephrine into the blood, and increase the expression of HSP70 gene in the myocardial tissue.

The study on acupuncture anesthesia for the operation of lung with video-assisted thoracoscope was carried out in 33 patients in the Shanghai Lung Disease Hospital (the former Shanghai First Tuberculosis Hospital) (Zhou H et al. 2001). The results showed that the volume of the compound drug used in this group was 43.5% lesser than that used in the general anesthesia group ($p<0.01$). Furthermore, they found that the blood pressure in the former group was more stable than the latter.

The EA combined with general anesthesia for patients undergoing thoracic operation was observed in 70 cases in the Sichuan Provincial Cancer Hospital (Tang et al. 2001). All the patients were divided into three groups: Group A was given acupuncture along with general anesthesia; Group B was administered with acupoint-skin electrical stimulation along with general anesthesia; and Group C was given general anesthesia. The excellent rates of the operation were 62.5%, 65.22%, and 37.84% for groups A, B, and C, respectively. It was found that the amount of anesthetics used in group A or B was reduced by about 30%. Furthermore, the T-lymphocyte test indicated that acupuncture could upregulate the immune function.

In the Eye-Ear-Nose-Throat Hospital affiliated to our university, following the success of neolarynx reconstruction under combined acupuncture and drug anesthesia (Huang 1995), neoglottis reconstruction was performed under acupuncture anesthesia combined with analgesics (Huang et al. 2001). A total of 30 cases of glottic stenosis received laryngeal reconstruction under general anesthesia. However, after operation, the lumen of the patients' larynxes was not large enough for respiration, and all these patients could not be decannulated. Hence, a new glottic reconstruction under the combination of acupuncture with drugs was performed in these 30 patients. Under the combination of acupuncture with drugs, the patients were in conscious as well as physiological states. The main acupoints employed were Futu (ST-32) and Hegu (LI-4), comprising both the sides, with 100 Hz and suitable intensity. As a result, the reconstructed new glottic easily reached the physiological width. Thus, this new glottic reconstruction under the combination of acupuncture and local anesthesia was performed by increasing the width of the glottic lumen to about 4 – 5 mm, and 28 cases were successfully decannulated with normal respiratory function, while only in 2 cases, the tracheal cannula could not be removed (Fig. 6.2).

Figure 6.2 Neoglottis reconstruction by Prof. Huang H (middle) in the Eye-Ear-Nose-Throat Hospital affiliated to Shanghai Medical University.

6.2.2.3 The abdominal operations

The clinical study on acupuncture combined with epidural administration of anesthetics was reported in a total of 106 cases of cholecystectomy in the Affiliated Hospital of Chengdu University of TCM and Pharmacy (Qin et al. 2001). The patients were divided into Group A with acupuncture along with epidural; Group B with acupoint-skin electrical stimulation along with epidural; and Group C with the routine epidural. The main acupoints were Neiguan (PC-6) and Zusanli (ST-36), comprising both the sides, with 2/15 Hz, 2 – 3 mA. The excellent rates of these groups were 80%, 68.57%, and 25%, respectively, with significant differences among them ($p<0.001$). Furthermore, the surgeons and anesthetists found some advantages in the combination of acupuncture with epidural anesthesia: the patients were quiet; they had no pain or only slight pain; the muscular relaxation was satisfactory; the visceral-pulling reaction was light; the dose of the epidural anesthetic needed was reduced to about 30% – 40%; and the anesthetic-blocked level was rather better.

It was revealed that the acupuncture and acupoint-skin electrical stimulation could reduce or suppress the stress response caused by surgical operation. Furthermore, acupuncture was observed to strengthen the analgesic effect of the anesthetics, reduce the dose of epidural anesthetics, and raise the lymphocyte-mediated immunocompetence.

Besides cholecystectomy, the study on EA combined with low dose of epidural anesthetics for subtotal gastrectomy was also carried out in the same hospital (Qin et al. 1996). It was concluded that EA combined with low doses of epidural anesthetic is a method of anesthesia to be considered for subtotal gastrectomy of benign pathological changes.

A total of 30 cases of herniotomy under acupuncture anesthesia were operated in the Shanghai Dahua Hospital (Chen et al. 1990). A small dose of fentanyl (<3 mg/kg) and droperidol (<0.1 mg/kg) was found to be evidently synergistic with acupuncture. By using the adjuvant drugs and improving the operative technique, the success rate increased up to 93.3%, and the excellent rate reached 66.6%. The fluctuation of blood pressure was lower than that of the control group, and in particular, the approach of acupuncture anesthesia was superior in the cases of senile patients with hypertension.

The combined use of acupuncture with anesthetics in the renal transplantation markedly reduced the consumption amounts of anesthetics, which improved the recovery of the transplanted renal functions and avoided complication in the Shanghai First People's Hospital (Qu et al. 1996). It was found that the anesthetic effect in patients under acupuncture-balanced anesthesia was comparable with that under epidural block. The average amount of anesthetics used in patients under acupuncture-balanced anesthesia was only about half of that used in patients under epidural block. Furthermore, in patients under acupuncture-balanced anesthesia, the blood pressure and heart rate were observed to be stable during the operation, without the need for the hypertensor; however, the blood pressure in patients under epidural block often fluctuated. Also, the start time of urination of the transplanted kidney in patients under acupuncture-balanced anesthesia was significantly reduced when compared with that in patients under epidural block.

Further observation was carried out in 44 patients, who were divided into Group A, administered with routine dose of epidural block; Group B, administered with smaller dose of epidural block; Groups C, administered with routine dose of epidural block along with EA; and Group D, administered with smaller dose of epidural block along with EA (Wang et al. 2002). The main acupoints were Cilao (BL-32), Taixi (KI-3), Sanyinjiao (SP-6), and Zusanli (ST-36), comprising both the sides, with 2 – 4 Hz and suitable intensity. It was found that EA stimulation could evidently decrease the requirement of epidural anesthetics, increase the plasma epinephrine level, stabilize the hemodynamics, and improve early renal functioning of the transplanted kidney under combined anesthesia of EA and epidural administration of small dose of anesthetics.

6.3 Application of Acupuncture Anesthesia in Different Countries or Areas

The success of acupuncture anesthesia in China has already drawn the attention of the academic circles of many countries. Although the surgical operations under acupuncture anesthesia are limited, different kinds of acupuncture treatment have been used during or after surgical operations.

A prospective randomized double-blind controlled test was carried out in Milan, Italy. The anxiety level before and after the cataract surgery was compared in three groups, using the Visual Analog Scale (VAS) (Gioia et al. 2006). The three groups were: Group A = no acupuncture; Group B = true acupuncture, started 20 min before surgery; and Group C = sham acupuncture, started 20 min before surgery. A total of 25 patients scheduled for inpatient phacoemulsification were enrolled in each group. All the surgeries were performed using topical anesthesia. The anxiety in Group B was significantly lower than that in Group A ($p = 0.001$) and Group C ($p = 0.037$). The results showed that acupuncture was effective in reducing anxiety related to cataract surgery under topical anesthesia.

Using a controlled and double-blind study carried out in Japan, the hypothesis that preoperative insertion of intradermal needles at acupoints 2.5 cm from the spinal vertebrae (bladder meridian) may provide satisfactory post-operative analgesia, could be confirmed (Kotani et al. 2001). Before anesthesia, the patients scheduled for elective upper and lower abdominal operations were randomly assigned to one of the two groups: acupuncture ($n = 50$ and $n = 39$ for upper and lower abdominal surgery, respectively) or control ($n = 48$ and $n = 38$ for upper and lower abdominal surgery, respectively). Postoperative analgesia was maintained with epidural morphine and bolus doses of intravenous morphine. Commencing from the recovery room, the intradermal acupuncture produced good pain relief when compared with the control (p<0.05). The consumption of supplemental intravenous morphine was reduced to 50%, and the incidence of postoperative nausea was reduced to 20% – 30% in the acupuncture group (p<0.01). Plasma cortisol and epinephrine concentrations were reduced to about 30% – 50% in this group during recovery as well as on the first postoperative day (p<0.01). The authors suggested that reoperative insertion of intradermal needles could reduce postoperative pain, analgesic requirement, and opioid-related side-effects after both upper and lower abdominal surgery. Acupuncture analgesia is also observed to reduce the activation of the sympathoadrenal system that normally accompanies surgery.

The pain-relieving effects of the implantation of gold beads into dogs with hip dysplasia was investigated with double-blind, placebo-controlled trial in Norway (Jaeger et al. 2006). Seventy-eight dogs were randomly assigned to two groups, 36 in the gold implantation group and 42 in the placebo group. Both groups were treated equally regarding anesthesia, hair clipping and penetration of the skin with the same type of needle. The gold implantation group had small pieces of 24 carat gold inserted through needles at five different acupuncture points and the placebo group had the skin penetrated at five non-acupuncture points so as to avoid any possible effect of stimulating the acupuncture points. After 14 days, three months and six months, the owners assessed the overall effect of the treatments by answering a questionnaire, and the same veterinarian examined and evaluated each dog. There were significantly greater improvements in mobility and greater reductions in the signs of pain in the dogs treated with gold implantation than in the placebo group.

A study of the application of acupuncture analgesia in cranio-maxillofacial surgical procedures was reported in Belarus (Pohodenko 2005). Acupuncture analgesia was applied in 120 patients. In 20 of these, surgery was carried out under general anesthesia in combination with acupuncture analgesia. In 100 patients, acupuncture analgesia was applied in addition to traditional postoperative analgesia. In case of troublesome postoperative pain, it was necessary to carry out additional sessions of acupuncture stimulation. When acupuncture analgesia was used, the pulse rate and blood pressure during surgery generally remained stable, and the serum cortisol was only showed minor elevation. The author suggested that acupuncture analgesia can be a useful adjunct to conventional anesthesia in maxillofacial surgery.

A study was reported in which a simple acupuncture procedure was used in patients under standard intravenous anesthesia in the Chang Gung Memorial Hospital, Taipei, China (Shyr et al. 1990). A total of 64 patients were included and allocated randomly into one of the two groups: control group receiving standard fentanyl-valium-thiopentone anesthesia alone, and the other group receiving an injection of 3 ml of normal saline into the P6 (Neiguan, PC-6) acupuncture point after the anesthesia. About 10 out of the 32 control patients experienced nausea or vomiting, when compared with only 2 out of 32 patients receiving acupoint injection, and the reduction in nausea was significant. Hence, it is recommended that the use of acupuncture as an antiemetic should be explored further.

Another similar study was carried out in Northern Ireland based on the abovementioned test (Dundee and Ghaly 1991). The incidence of postoperative illness was monitored for 6 h in 74 women premedicated with nalbuphine, 10 mg, who were undergoing short gynecologic operations of similar duration under methohexital nitrous oxide-oxygen anesthesia. Each patient received P6 (Neiguan, PC-6) acupuncture for 5 min at the time of administration of premedication. In a random order, the site of the acupuncture was previously infiltrated with normal saline solution in half of the patients, and 1% lidocaine in the remaining patients. Postoperative emetic sequel occurred significantly more often in those who received lidocaine, when compared with the group that received saline solution. This demonstrates that local anesthetic administered at the point of stimulation could block the antiemetic action of PC-6 acupuncture in a manner similar to the block test for analgesia.

Lee and Done (2004) searched database about stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. This systematic review supported the use of PC-6 acupoint stimulation in patients without antiemetic prophylaxis, and compared with antiemetic prophylaxis, PC-6 acupoint stimulation seemed to reduce the risk of nausea but not vomiting.

However, a contrasting conclusion was made in some studies. At the Vienna General Hospital, Austria, the effects of Auricular acupuncture (AA) and Auricular electro-acupuncture (AE) were investigated on pain and analgesic drug consumption in the first 48 h after unilateral mandibular third-molar tooth extraction under local anesthesia, in a prospective, randomized, double-blind, placebo-controlled study in 149 patients (Michalek-Sauberer et al. 2007). During the entire study period, the acupoints were used as the AA points 1 (tooth), 55 (Shen men), and 84 (mouth). Regularly rated pain intensity (five-point verbal rating scale), consumption of 500-mg tablets of acetaminophen, and additional rescue medication with 500 mg of mefenamic acid, were assessed. In this test, neither AE nor AA alone was observed to reduce either pain intensity or analgesic consumption in a molar tooth extraction model of acute pain.

Two-time tests of healthy volunteers were carried out to observe the effects of EA on the anesthetic requirement in the University of Louisville, USA (Chernyak et al. 2005; Morioka et al. 2002). The healthy volunteers were anesthetized with desflurane, and noxious electrical stimuli were administered via 25-gauge needles on both the thighs (70 mA at 100 Hz for 10 s). The results demonstrated that neither Acupoint Group one (Zusanli (ST-36), Yanglingquan (GB-34), and Kunlun (BL-60)) nor Acupoint Group two (Zusanli (ST-36), Sanyinjiao (SP-6), and Liangqiu (ST-34)) could facilitate general anesthesia or decrease the need for anesthetic drugs.

6.4 Clinical and Experimental Research on Combination of Acupuncture with Drugs in Pain Treatment

Besides the application of acupuncture combined with drugs in anesthesia and surgeries mentioned earlier, the technique could also be used in the pain treatment, such as labor pain, back and leg pain, postoperative pain, etc.

It has been reported that the application of acupuncture stimulation with HANS, combined with medicines provides pain relief during labor, as observed in the study carried out in the Beijing Hospital for Gynecology and Obstetrics affiliated to Beijing Capital Medical University (Zhuang et al. 2003). The results showed that the analgesic effective rate was 90.3% (Group of HANS + diazepam) and 78.9% (Group of HANS + tramadol), respectively, which were both higher than that of the Group of HANS (59.8%, $p<0.05$). Furthermore, HANS when combined with some sedative or analgesic drug produced good analgesic effect on labor pain, and no side-effects were found in mothers and babies. Thus, it has been suggested that the combination of HANS and diazepam or tramadol is safe, convenient, and effective for relieving pain during labor.

The study on EA combined with medicines for the treatment of sciatica was carried out in 158 cases in the Beijing Municipal TCM Hospital (Xu et al. 2001). Five groups of patients were treated using different methods: Group A = EA; Group B = EA along with placebo; Group C = EA along with nifedipine (calcium channel blocker); Group D = EA along with beclofen (γ-aminobutyric acid (GABA) receptor agonist); and Group E = EA along with clonidine (α_2 receptor agonist of NA). The results showed that in Group A patients, EA produced specific analgesic effect (28%), improved the symptom, and strengthened locomotion. The drugs, such as clonidine and beclofen, were observed to enhance the therapeutic effect of EA, and the effective rates were 93.93% and 79.41%, respectively ($p<0.001$).

The clinical study on the analgesic effect of acupuncture and acupuncture combined with medicine in postoperative pain of resection of nucleus pulposus of lumber intervertebral disc was carried out in the Institute of Acupuncture and Moxibustion, Chinese Academy of TCM (Mo et al. 2000). When compared with the effect of dolantin, the analgesic effect of EA was initiated later, but remained longer. Hence, the combination of acupuncture with a reduced dose of anesthetics (dolantin) may be advisable. Furthermore, it has been suggested that EA should be applied early after the operation to prevent the occurrence of pain, and a half-dose of dolantin can be used after the acupuncture to achieve better analgesic effect.

In our university (the Shanghai Medical University, now the Shanghai Medical College of Fudan University), the effects of morphine combined with EA were observed in the experimental and clinical studies (Dai et al. 1993; Zhang and Cao 1996). It is well known that epidural morphine is commonly used in the clinic to relieve postoperative pain; however, it is observed to induce immunosuppression, inhibition of the intestinal peristalsis, and respiratory inhibitions. The results obtained from our researches indicate that when morphine is combined with EA, the side-effects induced by morphine are mild (Fig. 6.3).

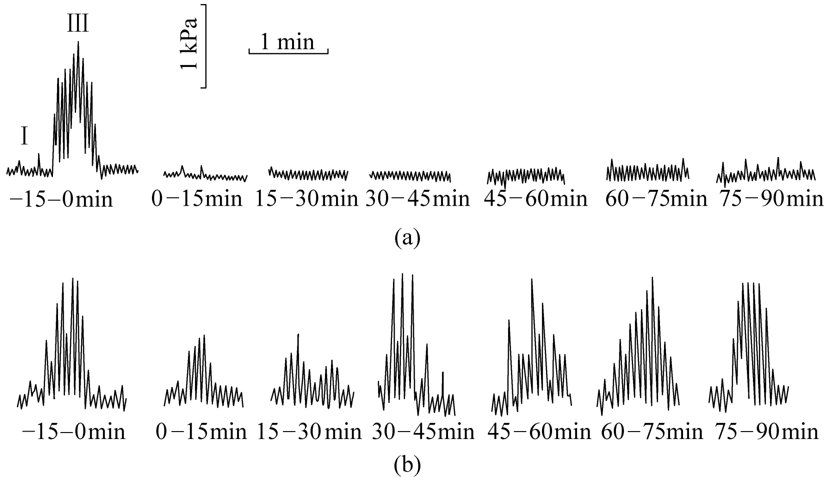

Figure 6.3 EA attenuates the morphine-induced inhibition of the intestinal peristalsis. The experiment was carried out in rabbits: (a) 0 – 90 min after morphine injection; (b) morphine was combined with EA. Note that the morphine induced inhibition of the intestinal peristalsis was significantly reduced.

6.5 Mechanism of the Synergistic Effect of Acupuncture-Drug Combination

By using animal models, some commonly used drugs were screened by our research group (Xu et al. 1989). These drugs were classified into three main categories according to their effect on acupuncture analgesia: drugs with potentiating effect; drugs with reducing effect; and drugs without significant influence. This classification may provide the clinical principles for the medical doctors to select the proper adjuvant according to different conditions.

The drugs with potentiating effect can be divided based on the pharmacological types as: agonists of opioid receptors, such as fentanyl or pethidine; antagonists of dopamine (DA) receptors, such as Droperidol (Fig. 6.4), haloperidol, or rotundine; serotonin (5-HT)-releasing agents, such as fenfluramine; and drugs affecting multiple functions, such as metoclopramide (clinically used as an antiemetic, with actions of anticholinesterase and antidopamine).

Subsequently, the mechanism of some drugs affecting acupuncture analgesia was investigated using multidisciplinary techniques by our experiment research group (Zhu et al. 1997).

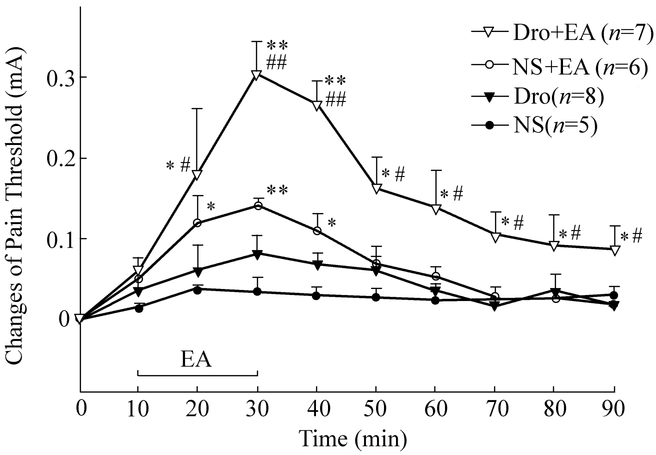

Figure 6.4 Potentiating effects of Droperidol (Dro) on EA analgesia. The rats were divided into four groups. For Dro + EA group, 10 min after the injection of Dro (Droperidol 1.25 mg/kg, i.p.), the EA stimulation was given at Zusanli (ST 36) and Kunlun (BL 60) acupoints for 20 min. For normal saline (NS) + EA group, NS administration was followed by EA treatment. The rats in the Dro or NS group received i.p. injection of Dro or NS, respectively, as the control. The tail flick latency of the rats stimulated by electric currents was tested before, during, and after the EA/Dro treatment. Note that Dro, an antagonist of DA receptors, could potentiate acupuncture analgesia.

Endogenous opioid peptides (EOP) are observed to play important roles in inhibiting pain. It has been known that the EOP release is increased during acupuncture analgesia (He 1987). Our further work showed that EOP release could be promoted by the combination of acupuncture with some drugs, which could potentiate the effect of acupuncture. Second, EA has been observed to induce the increase not only in the affinity, but also in the density of the opioid receptors, and the combined use of acupuncture with drugs has been found to further enhance the effect of EA. This suggests that further activation of the opioid receptors might underlie the mechanisms of the drugs' potentiating effect on acupuncture analgesia (Fig. 6.5). Third, these drugs are also considered to have potentiating roles in the acupuncture-induced activity of EOP gene expression (Fig. 6.6).

Furthermore, Orphanin FQ (also known as nociceptin, OFQ), a recently discovered member of the opioid family, was also observed to be involved in acupuncture analgesia, but showed different effects in the brain or spinal cord. Our group as well as another group in China observed that OFQ played an antagonistic action on acupuncture analgesia in the brain (Zhu et al. 1996; Tian et al. 1997); however, in the spinal cord, the enhancing effect of OFQ on acupuncture analgesia was significant (Tian et al. 1997). In OFQ knockout mice, the analgesic effect induced by EA at 100 Hz was significantly stronger (Wan et al. 2001). Thus, it has been suggested that endogenous OFQ might increase the sensitivity of nociception, and play an antagonistic role in 100 Hz EA analgesia.

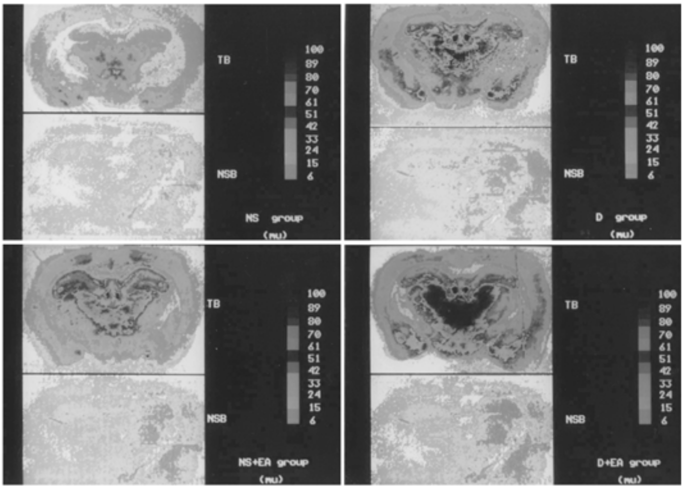

Figure 6.5 Droperidol (Dro) further enhances the EA-induced increase in μ-opioid receptor density. The μ opioid receptor was labeled with 3H ohmefentany (OMF), and the rats were divided into four groups. For Dro + EA group, 10 min after the injection of Dro (1.25 mg/kg, i.p.), EA stimulation was given at Zusanli (ST 36) and Kunlun (BL 60) acupoints lasting for 20 min. For the NS + EA group, normal saline (NS) administration was followed by EA treatment. The rats in the Dro or NS group received i.p. injection of Dro or NS, respectively, as the control. In the autoradiographic images, the red color indicates higher density of the opioid receptors, while the blue indicates lower density. Note that when EA was applied alone (NS +EA), μ like binding sites were significantly increased in the telencephalon (caudate nucleus, accumbens, septum, preoptic area), diencephalon (medial nuclei of thalamus and hypothalamus, reticular nucleus of thalamus, amygdala), and midbrain (periaqueductal gray (PAG), etc.), when compared with the NS group. When Dro was combined with EA (Dro + EA), the increase in μ like binding sites in the abovementioned nuclei was higher than that observed in the EA + NS group. Upper left: NS group; Upper right: Dro group; Lower left: NS + EA group; Lower right: Dro + EA group.

Endomorphine, the endogenous ligand of μ receptor, was discovered in 1997. It was shown that endomorphine-1 mediated 2 Hz, but not 100 Hz EA analgesia in rats (Han et al. 1999). Another result showed that OFQ at the supraspinal level produced hyperalgesia and was antagonistic to endomorphine-1, while at the spinal level, it produced analgesia and was synergic with endomorphine-1 (Wang et al. 1999).

Besides EOP, some monoamine transmitters (e.g., DA, NE, and 5-HT) were also observed to play different roles in acupuncture analgesia. Using techniques of in vivo microdialysis and high-performance liquid chromatography with electrochemical detection (HPLC-ECD), the monoamine contents in the microdialysate from rat brain areas were measured before and after some drugs-enhanced EA analgesia. The results suggest that these drugs potentiate acupuncture analgesia not only via antagonizing the activity of dopaminergic system, but also by coordinating the activities of other monoamines, such as 5-HT in the brain (Li et al. 1999).

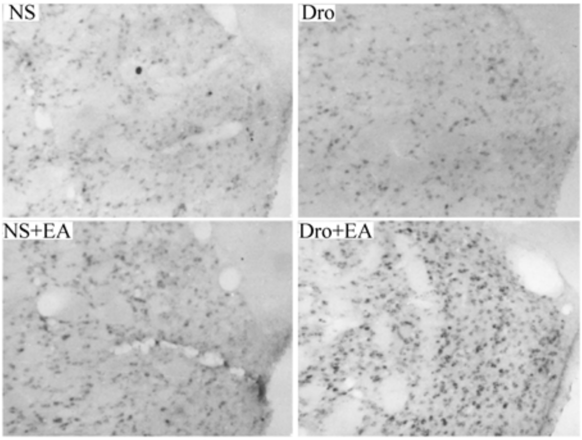

Figure 6.6 Elevation of preproenkephalin (PPE) mRNA expression following Droperidol (Dro)-potentiated EA. In situ hybridization was performed on the brain slices from the rats sacrificed 10 h after Dro (1.25 mg/kg, i.p.) and/or EA (lasting for 20 min) treatment, using the digoxin labeled RNA probes. Note that PPE mRNA positive neurons were extensively distributed in the central nervous system, such as caudate nucleus, accumbens, lateral septum, diagonal band, preoptic area, amygdala, hypothalamus, periaqueductal gray (PAG), etc. The EA enhanced the PPE mRNA expression in the abovementioned regions, and the combination of Dro with EA further promoted the PPE mRNA expression. Upper left: Normal saline (NS) group; Upper right: Dro group; Lower left: NS + EA group; Lower right: Dro + EA group.

On the other hand, the analgesic effects could also be found in some biologically active substances, such as melatonin (Yu et al. 2000). Furthermore, the effects related to the EOP system were also investigated. Melatonin was observed to enhance acupuncture analgesia involved in EOP system, suggesting its potential clinical application as an assisted analgesic in the near future (Zhou et al. 2000, 2001).

6.6 Concluding Remarks

Till date, the clinical researches on acupuncture-drug balanced anesthesia are still being carried out by some Chinese medical surgeons and anesthesiologists. In the Beijing Tiantan Hospital and Shanghai Huashan Hospital of Fudan University, the acupoint stimulation was used to combine the modern awake anesthesia in craniotomy. Furthermore, in the Renji Hospital affiliated to the Shanghai Second Medical University (now affiliated to Shanghai Jiaotong University), the cardiac surgery was performed with acupuncture-drug balanced anesthesia. On December 5, 2005, the British Broadcasting Corporation (BBC) aired a special science program about the acupuncture therapy, in which a cardiac surgery carried out under acupuncture-drug balanced anesthesia in the Renji Hospital was shown

(Fig. 6.7). In April, 2006, the BBC editor came to the hospital again to review this TV program. Currently, in China, several TCM hospitals have started to participate in this clinical research. Surgeons, anesthesiologists and acupuncturists from Shuguang and Yueyang Hospitals affiliated to Shanghai University of TCM have performed different operations, and re-established the acupuncture anesthesia unit.

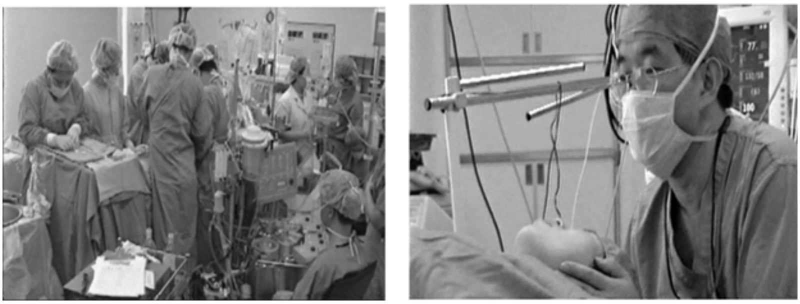

Figure 6.7 Cardiac surgery under acupuncture-drug balanced anesthesia in the Renji Hospital, Shanghai. Left, Doctors performing the operation. Right, Prof. Wang XR, Chairman of the Department of Anesthesiology, taking care of the patient.

In 2007, the research project of acupuncture anesthesia won funds from the National Key Basic Research Program in China. We are confident that the research of acupuncture-drug balanced anesthesia which was initiated in China will continue to make great progresses and improve its application at the bedside, bringing more and more benefits to the patients.

Acknowledgements

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7 Acupuncture Analgesia in Clinical Practice

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Summary As one of the most important complementary and alternative modalities, acupuncture has been used worldwide in pain relief at bedside. Substantial and accumulating clinical evidences show that acupuncture produces analgesic effects in various acute/chronic pain conditions. In this chapter, we will summarize the clinical research of acupuncture-induced analgesic effects on various pain disorders, especially headaches, chronic low back pain, knee osteoarthritis, chronic neck pain, neuropathic pain, motor system injuries, fibromyalgia, cancer pain, dental pain, and phantom limb pain. Furthermore, the clinical designs and acupuncture approaches for pain relief will also be discussed in terms of appropriate use of acupuncture. Finally, we will briefly comment on several problematic issues in acupuncture studies, and present a prospective view in terms of future research to improve the clinical application of acupuncture to make it more beneficial to patients.

Keywords *acupuncture, analgesia, chronic pain, clinical practice*

7.1 Introduction

As a sensory and emotional experience associated with actual tissue damage or described in terms of such damage, pain is a common symptom of most of the diseases in clinic. It is also attributed to the most common cause of mental and physical suffering, as well as disability that seriously impairs the quality of life, especially chronic pathological pain, including inflammatory pain, neuropathic pain, cancer pain, etc. Using non-steroidal anti-inflammatory drugs and opioids, great progress has been made in pain relief in the past years. However, owing to the relative ineffectiveness and side effects of the currently available drugs and other treatments, certain pain conditions cannot be well controlled. In addition, owing to the increasing concerns regarding the side effects of analgesics and non-steroidal anti-inflammatory drugs, side-effect free, non-pharmacological interventions such as acupuncture have been widely used clinically as the alternative or complimentary therapies for treating chronic pain.

Acupuncture as the complementary and alternative medicine (CAM) is now accepted worldwide mainly for the treatment of acute and chronic pain. The clinical efficacy of acupuncture analgesia has been broadly reported in many countries and regions (Fig. 7.1). It is one of the most common alternative treatments with the advantages of simple and convenient application, low cost, and minimal side effects in pain management (Cao 1997; Eshkevari 2003). Although chronic pain is difficult to control when using regular methods, acupuncture has been well documented to treat some chronic pain conditions. Some patients suffering from chronic pain may not experience any relief or experience only partial relief by using analgesics, anesthetics, steroids, and even surgical therapies, which sometimes produce serious side effects or drug addiction. Hence, these sustained pains are often relieved by acupuncture. In the earlier trials, promising results have emerged, for example, demonstrating the efficacy of acupuncture in the postoperative dental pain. However, under other conditions, such as headaches, tennis elbow, fibromyalgia, myofascial pain, osteoarthritis (OA), low back pain, and carpal tunnel syndrome, acupuncture may be useful as an adjunct treatment, acceptable alternative, or included in a comprehensive management program (Birch et al. 2004).

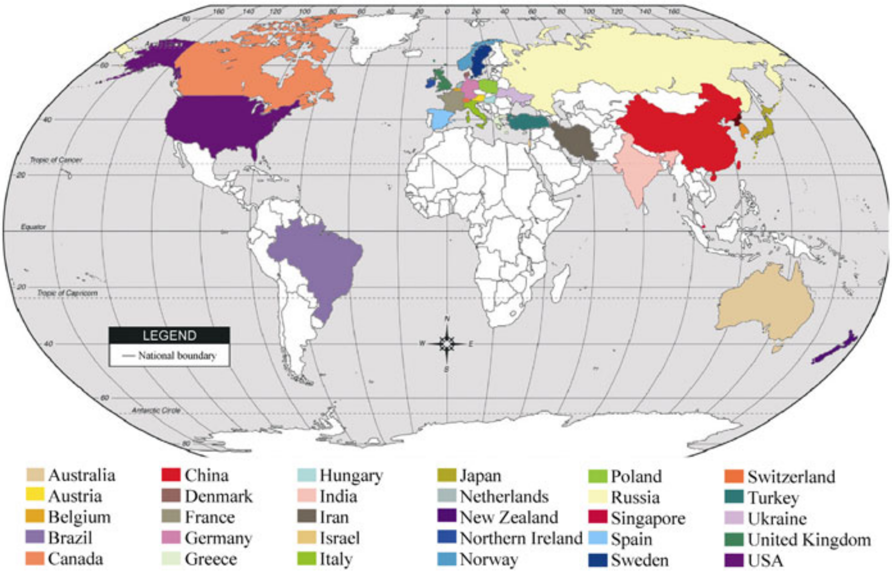

Figure 7.1 Countries where clinical acupuncture is practiced for pain relief. Note that acupuncture analgesia is used in most of the major countries and regions all over the world.

According to the Traditional Chinese Medicine (TCM), acupuncture is necessarily embedded in a complex theoretical framework that provides conceptual and therapeutic directions. The Chinese Medical Theory considers that pain is the result of imbalance of *Yin* and *Yang*, stasis or blockade of meridian *Qi* flow, and the subsequent blood stagnation. Based on this concept, acupuncture is applied to the acupoints (located in parts of the meridian network) and Ashi points (which are also highly important in the treatment of headache) to treat diseases, aiming to restore the balance of *Yin* and *Yang*, the normal flow of *Qi* flow, and blood circulation (Zhao et al. 2005). The acupoints are selected based on a traditional Chinese syndrome diagnosis, the acupuncturists' personal experience, localization of pain, or other symptoms.

Neurobiological researches have supported the hypothesis proposed by the famous Chinese neurophysiologist, Zhang, in the 1970s, who stated that acupuncture analgesia is an integrative effect of the two different signals from acupuncture and pain at different levels in the central nerve system, including the spinal cord, brainstem, and thalamencephalon. During acupuncture analgesia, the specific sites related to pain modulation in the central nervous system were observed to be activated, with the release of various endogenous bioactive substances in the nervous system. These substances that are involved in pain relief include opioids, classical neurotransmitters (such as 5-hydroxytryptamine, acetylcholine), neuropeptides, etc. (Wu and Cao 1999).

7.2 Common Controls for Clinical Acupuncture

Researches on the efficacy of acupuncture have raised a number of difficult methodological issues, particularly with regard to the selection of appropriate controls. The separation of the specific effects of acupuncture from its non-specific effects is extremely difficult, because acupuncture is a physical, invasive, and manual procedure involving considerable time of the practitioner as well as some rituals. However, it is important to quantify the relative effects of these two factors (Hammerschlag 1998). Furthermore, other possible confounding factors might be linked to a patient's preconceived ideas of the efficacy of a particular treatment regime, and this too must be assessed as a part of the non-specific effect (White et al. 2003).

To provide an effective and credible placebo (defined as a physiologically inert procedure), the control must be convincing and should mimic, in all respects, apart from the physiological effect, the real active treatment (Ernst and White 1997; Peck and Coleman 1991). Various control options have been utilized in the context of clinical research of acupuncture, including insertion of acupuncture needles into the non-acupuncture points, several forms of dummy needling, and mock transcutaneous nerve stimulation (TENS). However, till date, none have simultaneously fulfilled all the criteria of being truly inert, easily usable, and effective in mimicking the real pragmatic acupuncture, as shown in Table 7.1. Therefore, in the clinical practice, appropriate control groups should be selected to demonstrate the results of acupuncture.

Table 7.1 Common controls in acupuncture analgesia in clinical practice

Types of Control	Manipulations	Destinations	Disadvantages
Waiting list	Delaying the acupuncture treatment	Compares the difference of the treatment and non treatment	Does not control placebo effects
Placebo acupuncture	Avoiding penetration of the skin with an acupuncture needle (e.g., using specifically designed non insertion needing devices)	Resembles real acupuncture; eliminates the possibility of non specific needing effects	Difficult to maintain patient blinding in long term treatment
Sham transcutaneous nerve stimulation (TENS)	Using TENS device without electrical stimulation	Controls the placebo effects, such as those resulting from patient practitioner relationship	Does not resemble acupuncture; cannot blind patients
Sham acupuncture (Minimal acupuncture)	Needling performed superficially and/or at non acupuncture points	Resembles real acupuncture; tests the specificity of the acupoints; measures the non specific needing effects	Likely to produce non specific physiological needing effects
Positive controls	Conducting routine care, such as drugs, massage, exercise	Compares the effectiveness of acupuncture as complementary or adjunctive care; compares the cost effectiveness, adverse effects, and efficacy	Cannot blind patients

7.3 Types of Acupuncture Approaches

Acupuncture is thought to have existed in China in one form or another since the Xia Dynasty (2000 – 1500 BC) (Helms 1995). It was first recorded in *The Yellow Emperor's Classic of Internal Medicine* (Veith 2002). In the past thousands of years, various acupuncture approaches have been developed during clinical practice. The acupoints used include body acupoints, scalp points, and auricular points, while the therapeutic methods include filiform needing, moxibustion, electroacupuncture (EA), laser acupuncture, trigger-point acupuncture, acupoint injection, Fu's subcutaneous needling (FSN), wrist-ankle needling, etc. (Table 7.2). Different acupuncture approaches are chosen for different diseases. Sometimes, two approaches could be useful, while for some instances, one approach may be better than the other.

Table 7.2 Types of acupuncture approaches in clinical practice

Types of acupuncture	Acupuncture manipulations
Manual acupuncture (hand acupuncture)	After inserting the needle into the acupoint, lifting and thrusting the needle to induce "*De Qi*"
Electroacupuncture (EA)	Applying electrical stimulation to the needle inserted into the acupoint
Laser acupuncture	Applying laser to the acupoint
Trigger point acupuncture	Needling the trigger point
Acupoint injection	Injecting drugs into the acupoint
Fu's subcutaneous needling (FSN)	An innovative needling strategy acting specifically in the subcutaneous layer

7.3.1 Manual Acupuncture

Manual acupuncture is the most common type of acupuncture with a long history in China. Manual application is very important for the acupuncture therapy, and certain acupuncture manipulation, such as rotating the needle, is observed to be necessary to increase the acupuncture therapeutic effect. Often no feeling might be experienced, until the needle reaches the layer where the needle sensation is felt. This sensation might be soreness, numbness, distension, or heaviness, which is called the acupuncture feeling or "*De*-*Qi*". It is a desired result, indicating that the proper point has been punctured. The sensation may become stronger when the needle is lifted or twisted. This is carried out to promote inter-meridian communication, and is observed to increase the therapeutic effect. Twisting causes the acupuncture points to be additionally stimulated, thus, eliminating obstructions in the flow of the *Qi* (He and Qu 1994).

The clinical practice has demonstrated that the therapeutic effects of acupuncture are closely related to achieving the acupuncture feeling or "*De*-*Qi*" as well as the intensity of the acupuncture feeling, except the acupoints. The other important factor that influences the therapeutic effects is the acupuncture manipulation. There are many different types of acupuncture manipulation used in clinic, such as the method of reinforcement and reduction, twisting and twirling, lifting and thrusting, etc., which could produce different stimuli intensity and different effects. Hence, different acupuncture methods are used for different disease conditions. Through manipulation, the location, intensity, and quantity of stimulation of the acupuncture could be adjusted during acupuncture therapy (He and Qu 1994).

7.3.2 Electroacupuncture

The EA treatment has been widely used in China for decades. To attain the acupuncture sense, little electrical current is applied to the acupoints to enhance the acupuncture effects, by using an EA apparatus. The EA treatment could produce two types of stimuli from the acupuncture and electrical current at the same time, and can increase the therapeutic effects on some diseases. The most commonly used EA is the pulse current acupuncture. The effect of EA is conditioned by multiple factors, including wave forms, pulse frequency, intensity, pulse width, and duration of the stimulation. Different stimulating parameters of EA have different influences on acupuncture effects, particularly, analgesic effect. Hence, appropriate EA parameters should be selected according to the condition of the patients.

Pulse frequency

The EA with different frequencies could promote the release of different central neurotransmitters. Han et al (1991) observed that low-frequency stimulation releases enkephalin, while high-frequency stimulation releases dynorphin. Furthermore, the analgesic effect of different frequencies of EA has been observed to be mediated by different central sites. Arcuate nucleus in the hypothalamus is found to be the critical site to mediate low-frequency EA analgesia, while parabrachial nucleus in the pons is observed to be the key site to mediate high-frequency EA analgesia (Wang et al. 1990a, 1990b). In addition, the therapeutic effect of different frequencies is often observed to be different. Thus, different frequencies may induce different neurotransmitters in different sites to produce different effects, and it may be useful to further investigate the effective combination of low and high frequencies to enhance the analgesic effect of EA.

Wave forms

Previously, there were three wave forms commonly used in clinical practice: sharp wave, square wave, and sinusoidal wave (Fig. 7.2). Sharp wave was observed to easily transverse the skin and reach the deep tissues, and assist in exciting the nerves and muscles. It was found to accelerate the nerve-tissue regeneration by improving circulation, accelerating the metabolism, and improving the local tissue nourishment Hence, it was usually used to treat peripheral nerve injury, facial paralysis, post-polio syndrome, muscular atrophy, etc. On the other hand, square wave was observed to produce effects of pain relief, sedation, and hypnosis (He and Qu 1994). Hence, it was widely used to treat acute soft-tissue injury, headache, insomnia, stroke sequel, arthritis, stomach convulsion, terminal neuritis, etc. Furthermore, the sinusoidal wave was observed to regulate the neuromuscular tone.

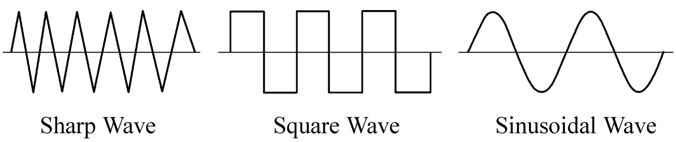

Figure 7.2 The sketch map of the common wave forms used in EA application: sharp wave, square wave, and sinusoidal wave.

However, the EA effects reduced gradually when the regular sharp wave, square wave, and sinusoidal wave, were employed. This was known as the EA tolerance effect. Therefore, to overcome the EA tolerance, the different wave forms were combined together and different frequencies were used. For example, the positive square wave and negative sparse wave were combined together, and the resulting new wave form was widely used for relieving pain. The combination of different frequencies produced dense-disperse wave, continuous wave, and chopping wave (Fig. 7.3). The dense wave demonstrated high frequency, often in the order of 50 – 100 Hz, while the disperse wave was found to have a low frequency of 2 – 10 Hz. The features, effects, applications, and disadvantages of different wave forms in EA treatment are listed in Table 7.3. Based on the characteristics of different wave forms, the dense-disperse wave and continuous wave were observed to be suitable for their use in EA analgesia.

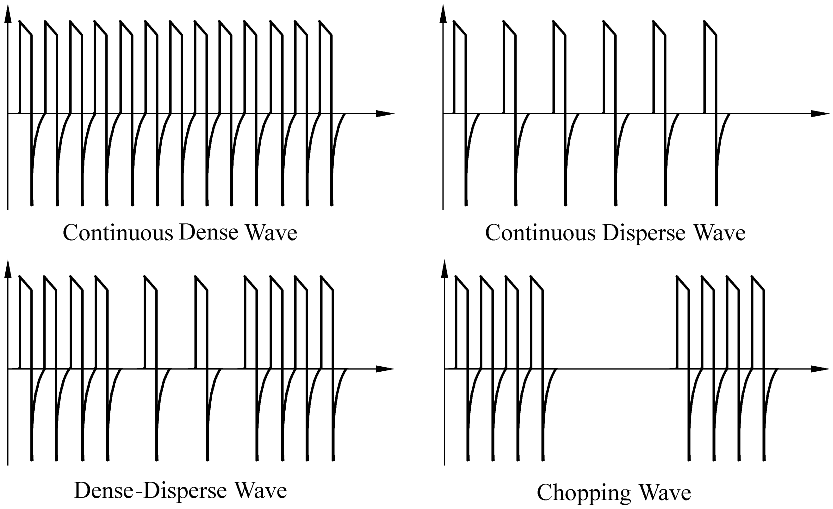

Figure 7.3 The sketch map of the frequency and rhythm commonly used in EA treatment to avoid EA tolerance effect: continuous dense wave, continuous disperse wave, dense-disperse wave, and chopping wave.

Intensity

The high-intensity stimulation may produce severe pain, and may not be tolerated by the patient. Hence, appropriate intensity should be used to increase the pain threshold. As the stimulation of intensity is not directly proportional to the analgesic effect, in EA treatment, the patient should be given enough, but not the highest intensity. Han pointed out that the commonly used intensity is <3 mA (Han 1994).

Duration of stimulation

After the insertion of needles, it usually takes 20 – 40 min to reach the highest pain-threshold level in the human body, and the electrical stimulation has been observed

Table 7.3 The features and applications of different wave forms in EA treatment

Wave forms	Features	Effects	Applications	Disadvantages
Dense wave	High frequency (50 – 100 Hz)	Produces immediate analgesic effect	Used along with surgical incision	Easy to be adapted
Disperse wave	Low frequency (2 – 10 Hz)	Induces muscle construction, improves the circulation of blood, and promotes the recovery of the function of nerves and muscles	Used for treating paralysis of nerves and muscles	
Dense disperse wave	Alternative dense wave and output disperse wave	Produces potent analgesia, maintains the effect, and is less easy to be adapted	Used for producing analgesia or anesthesia	The patient may feel discomfort, and it is difficult to induce potent immediate analgesia
Continuous wave	Combination of single wave	The patients do not feel the discomfort	Used for producing analgesia	
Chopping wave	Chopping combination of disperse wave and dense wave	Increases the excitability of the muscles, and it is difficult to induce adaptation	Used for treating paralysis of nerves and muscles	It does not produce apparent analgesia

to retain the analgesic effect at the highest level. Furthermore, the duration of stimulation in EA analgesia is often 15 – 30 min. In addition, the interval of the treatment of EA in clinical EA analgesia practice is often once every other day or twice a week, and longer or frequent EA stimulation may not necessarily produce a better therapeutic effect.

7.4 Acupuncture Analgesia in Clinical Practice

Acupuncture is now accepted as a complementary analgesic treatment. Although acupuncture has been widely used to treat a variety of pain conditions, there is still limited convincing scientific evidence demonstrating its efficacy. In the following sections, acupuncture analgesia in clinical practice is demonstrated with respect to different kinds of pains.

7.4.1 Headaches

Approximately 4% of the adults experience headaches nearly every day. Migraine and tension-type headaches are the common headache disorders in clinic and result in significant reduction in social activities and work capacity of the suffers (Woolhouse 2005). Medications commonly used to treat headache, such as acetaminophen, aspirin, non-steroidal anti-inflammatory drugs, triptans, narcotics, or barbiturates, can have problematic side effects and paradoxically contribute to the transformation of episodic headaches to chronic daily headache (Coeytaux et al. 2005). Given the limitations of medical therapy, acupuncture as an important promising nonpharmacological treatment for headaches has demonstrated its advantages and has been widely used for the treatment of different types of headache disorders (Table 7.4).

Table 7.4 Acupuncture treatment for different types of headaches

Types of Headache	References
Migraine	Alecrim Andrade et al. 2006; Diener et al. 2006; Linde et al. 2007a; Melchart et al. 2006; Streng et al. 2006; Woolhouse 2005
Episodic or chronic tension type headache	Melchart et al. 2005a, 2005b; Melchart et al. 2006; Soderberg et al. 2006; Woolhouse 2005
Cervicogenic headache	Hu and Xu 2005; Lu and Shan 2006
Cluster headache	Dana 2003; Gwan 1977; Melchart et al. 2006
Vascular induced headache	Melchart et al. 2006
Drug induced headache	Melchart et al. 2006
Myogenic headache	Ahonen et al. 1984; Jensen et al. 1977
Supra orbital headache	Lin 1991; Xia et al. 1987
Facial pain	List and Helkimo 1987; Low 1976; Thayer 2001

An epidemiological study on migraine, episodic or chronic tension-type headache, or several other forms of chronic headache (cluster, vascular, drug-induced headache, and other specific headaches) showed that in 52.6% of the patients, the headache frequency decreased by at least 50% after the acupuncture treatment, when compared with the baseline, and the patients demonstrated clinically relevant improvements after the acupuncture treatment (Melchart et al. 2006). Table 7.4 lists some trials that demonstrated certain effects of acupuncture in migraine and tension-type headache. No significant differences were observed between the acupuncture and metoprolol (a frequently used first-line drug in migraine prophylaxis) groups. Furthermore, the results of the acupuncture group were slightly better than those of the metoprolol group, with respect to migraine attacks and several parameters mentioned in the pain questionnaire (Streng et al. 2006). However, it should be noted that several trials have suggested that acupuncture was not more effective than sham acupuncture in reducing headaches, although both the interventions were more effective than a waiting list control (Table 7.5). In these trials, sham acupuncture was administered by inserting needles superficially into nonacupuncture or acupuncture points. The physiological effects of superficial needling, the distance

Table 7.5 Controlled clinical trials in headache treatment

Conditions	*n*	AT	CT	Primary assessments	Results
Migraine for at least 12 months (Linde et al. 2007a)	145	MA: 12 sessions over 8 weeks	CA: 12 sessions over 8 weeks; WL	Pain questionnaire: pain intensity, pain disability index, affective and sensoric aspects of pain, depression scale, Allgemeine Depressionsskala (ADS), etc.	MA sig > WL in all the relevant outcome measures; CA sig = MA in response rats
Migraine for at least 12 months (Streng et al. 2006)	140	MA: 8 – 15 sessions over 12 weeks	MC: metoprolol, 100 – 200 mg daily for 12 weeks	Pain questionnaire: pain intensity, pain disability index, affective and sensoric aspects of pain, depression scale, ADS, etc.	MA sig = MC in the number of days with migraine, which is proportional to the responders. Improvements owing to MA tended to be slightly better than MC group for migraine attacks and several parameters given in the pain questionnaire.
Migraine for at least 12 months (Alecrim And rade et al. 2006)	28	MA: 16 sessions during 12 weeks	CA: 16 sessions during 12 weeks	Frequency of migraine attacks, average duration of a migraine attack, headache severity	MA sig = CA with regard to any pain parameter
Chronic tension type headache for at least 15 days or 6 months (Soderberg et al. 2006)	90	MA: 10 – 12 sessions during 10 – 12 weeks	PT: 25 sessions over 2.5 – 3 months RT: once a day	Headache intensity (visual analogue scale, VAS), headache free days, and headache free periods	Relaxation group sig > MA with regard to headache free period and the number of headache free days immediately after the last treatment; no other significant group differences were observed between the study group at any time point
Episodic or chronic tension type headache (Melchart et al. 2005b)	270	MA: 12 sessions during 8 weeks	CA: 12 sessions during 8 weeks; WL	Pain questionnaire: pain disability index, scale for assessing emotional aspects of pain, depression scale, ADS, SF 36 (assessment of health related quality of life)	MA sig>WL, MA sig= CA with regard to the main and secondary outcome measures

n, number of trials; AT, Acupuncture Therapy; CT, Control Therapy; MA, Manual Acupuncture; CA, Sham Acupuncture; WL, Waiting List; MC, Medical Care; PT, Physical Training; RT, Relaxation Training; sig, Significantly.

from the classical acupuncture points, as well as a wide range neurophysiological and neurochemical responses, such as the release of neurotransmitters or activation of segmental and heterosegmental antinociceptive system, or particularly, the potent placebo effects, are considered to be involved in headache improvement by sham acupuncture (Melchart et al. 2005b).

7.4.2 Chronic Low Back Pain

Low back pain is one of the most common and expensive musculoskeletal problems in modern society. Acupuncture is widely used on patients with low back pain and is now considered to be effective in treating chronic low back pain. Numerous randomized, controlled trials have been conducted in different countries to assess the effectiveness of acupuncture in treating low back pain (Cherkin et al. 2001; Meng et al. 2003). Table 7.6 lists the common acupoints used for the treatment of low back pain.

Table 7.7 summarizes eight well-designed studies on acupuncture in the treatment of low back pain, and majority of the results have demonstrated its effectiveness. Acupuncture is often used as a complementary method to manage chronic low back pain. Molsberger et al (2002) found that acupuncture can be an important supplement to conservative orthopedic treatment in the management of chronic low back pain. Through a blinded, prospective, randomly controlled study on 52 patients, Yeung et al (2003) reported that the combination of EA and back exercise might be an effective option in the treatment of pain and disability associated with chronic low back pain. Furthermore, meta-analysis of acupuncture for low back pain showed that acupuncture could effectively relieve chronic low back pain. However, no evidence suggested that acupuncture is more effective than other active therapies (Manheimer et al. 2005).

Besides the needle acupuncture and EA, other approaches such as trigger-point acupuncture, electrical heat acupuncture, dry needling, Koryo Hand-Acupuncture, and P-Stim auricular EA have also been used for the treatment of chronic low back pain in elderly patients, and have all been observed to be effective in reducing pain when compared with the control group (Furlan et al. 2005; Itoh et al. 2004; Lim and Yi 2003; Sator-Katzenschlager and Michalek-Sauberer 2007; Tsui and Cheing 2004).

As shown in Table 7.6, the effects of acupuncture have been compared with different controls, and the conclusions have occasionally been different and even contradictory. Some results showed that acupuncture was more effective in improving pain threshold than the treatment without acupuncture. However, the extent of pain was not significantly different between the acupuncture and the minimal acupuncture groups (Tulder et al. 2000). This disparity might be related to various factors. Acupuncture treatment has been associated with clinically relevant improvements in patients suffering from low back pain of varying degrees of duration and/or severity (Weidenhammer et al. 2007). Besides the patients' expectations, the variability in acupuncturists' assessment, diagnosis and treatment patterns, modes of acupuncture, and the number of sessions can also affect the effect of acupuncture treatment (Linde et al. 2007b; Thomas and Lundberg 1994). In addition, the lack of good quality studies can also limit the evaluation of the effectiveness of acupuncture in treating low back pain. Therefore, a worldwide, multicenter, randomized, controlled, prospective, blinded, standard study should be designed and conducted to assess the effectiveness of acupuncture in treating chronic low back pain.

Table 7.6 Acupoints commonly used for the treatment of low back pain

Acupoints	Locations	Meridian	Efficacies and indications
Shenshu (BL 23)	1.5 cun lateral to the lower border of the spinous process of the 2nd lumbar vertebra	Bladder Meridian of Foot Taiyang	Enuresis, nocturnal emission, impotence, irregular menstruation, leukorrhagia, edema, tinnitus, deafness, lumbar pain
Dachangshu (BL 25)	1.5 cun lateral to the lower border of the spinous process of the 4th lumbar vertebra	Bladder Meridian of Foot Taiyang	Abdominal distension, diarrhea, constipation, lumbar pain
Pangguangshu (UB 28)	1.5 cun lateral to the lower border of the spinous process of the 2nd sacral vertebra	Bladder Meridian of Foot Taiyang	Difficulty in urination, enuresis, diarrhea, constipation, stiffness and pain in the lumbar area and back
Yaoyangguang (GV 3)	In the depression on the lower border of the spinous process of the 4th lumbar vertebra	Du Meridian	Irregular menstruation, stiffness and pain in the lumbar area and back, nocturnal emission, pain of the lower limbs
Sanyinjiao (SP 6)	3 cun directly above the tip of the medial malleolus on the posterior border of the medial aspect of the tibia	Spleen Meridian of the Foot Taiyin	Abdominal distension, diarrhea, irregular menstruation, infertility, dystocia, nocturnal emission, impotence, enuresis, hernia, insomnia, muscular atrophy and pain of the lower limbs, beriberi
Weizhong (BL 40)	Midpoint of the transverse crease of the popliteal fossa	Bladder Meridian of the Foot Taiyang	Lumbar pain, muscular atrophy and pain of the lower limbs, abdominal pain, vomiting with diarrhea, difficulty in urination, enuresis
Kunlun (BL 60)	In the depression between the tip of the external malleolus and the Achilles tendon	Bladder Meridian of the Foot Taiyang	Headache, dizziness, stiffness of the neck, epistaxis, epilepsy, dystocia, pain in the lumbosacral area, swelling and pain of the heel
Huantiao (GB 30)	At the junction of the lateral 1/3 and medial 2/3 of the distance between the great trochanter and the hiatus of the sacrum	Gallbladder Meridian of the Foot Shaoyang	Muscular atrophy and pain of the lower limbs, lumbar pain

(Continued)

Acupoints	Locations	Meridian	Efficacies and indications
Yanglinquan (GB 34)	In the depression anterior and inferior to the small head of the fibula	Gallbladder Meridian of the Foot Shaoyang	Pain in the hypochondriac region, vomiting, beriberi, muscular atrophy and pain of the lower limbs, infantile convulsion, jaundice
Shenmen (HT 7)	At the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of m. flexor carpi ulnaris	Heart Meridian of the Hand Yangming	Cardiac pain, dysphoria, palpitation, amnesia, insomnia, mania, epilepsy, pain in the hypochondriac region

Table 7.7 Randomized controlled trials of acupuncture for the treatment of chronic low back pain

Sources	*n*	AT	CT	Number, spacing, and duration of treatments	Results
Carlsson and Sjolund. 2001	50	MA, EA	PA	Once a week for 8 weeks, and 2 further treatments during the follow up 6 months or longer	VAS: AT sig > CT at 1 and 3 months
Cherkin et al. 2001	262	MA, EA	M, SC	Once a week for 10 weeks	SBS: AT sig < M after 1 year
Leibing et al. 2002	131	MA + PT	SA + PT, PT	20 sessions in over 12 weeks (5 times a week in the first 2 weeks, and once a week in the next 10 weeks)	VAS and PDI: MA + PT, SA + PT sig > PT, but MA + PT = SA + PT
Meng et al. 2003	55	EA+UC	UC	Biweekly acupuncture for 5 weeks	RDQ: AT sig > CT at 6 and 9 weeks
Yeung et al. 2003	52	EA+EX	EA	12 sessions	NRS and Aberdeen LBP scale: AT sig > CT at 1 month and 3 month follow up
Tsui and Cheing 2004	42	EA	EH, WL	Twice a week for 4 weeks (a total of 8 sessions)	NRS: AT sig > CT at 4 weeks and 1 month follow up
Sator Katz enschlager et al. 2004	61	AEA	MAA	Once a week for 6 weeks	VAS: AT sig > CT during 6 weeks and at 3 month follow up
Brinkhaus et al. 2006	298	MA	SA, WL	12 sessions over 8 weeks	VAS: MA sig > WL; MA sig = SA at 8 and 26 weeks

AT, Acupuncture Therapy; CT, Control Therapy; MA, Manual Acupuncture; EA, Electroacupuncture; PA, Placebo Acupuncture; UC, Usual Care; PT, Physiotherapy; AEA, Auricular Electroacupuncture; MAA, Manual Auricular Acupuncture; EX, Exercise; M, Massage; SC, Self-care education; RDQ, Roland Disability Questionnaire; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale; PDI, Pain Disability Index; SBS, Symptom Bothersomeness Scale; sig, Significantly.

7.4.3 Knee Osteoarthritis

Acupuncture is widely used to treat chronic pain in OA. Various clinical trials have indicated that acupuncture is beneficial in treating pain that arises from OA (Berman et al. 2004; Vas et al. 2004). Many kinds of acupuncture approaches, including manual acupuncture and EA have been used clinically to treat OA. The selection of acupuncture points in clinic is often based on TCM meridian theory to treat joint pain, known as the "Bi" syndrome, and usually, both the local and the distal points are included. The commonly used acupoints in the clinical practice for treating knee OA are shown in Table 7.8. Bilateral acupuncture is often used in treating OA of the knee, but clinical researches have demonstrated that unilateral acupuncture is as effective as bilateral acupuncture in increasing the function and reducing the pain associated with OA of the knee (Tillu et al. 2001). Therefore, clinically, both unilateral and bilateral acupuncture can be employed.

Table 7.9 summarizes eight large, randomized controlled trials of adjunctive acupuncture for treating OA of the knee. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is commonly used to measure the pain score of OA of the knee (Berman et al. 2004). The results demonstrate that acupuncture can improve the function and pain relief, by acting as an adjunctive therapy for treating OA of the knee, when compared with different control groups with the background of usual care. This suggests the promising use of adjunctive acupuncture in the treatment of OA of the knee. Furthermore, reviews or meta-analysis of the use of acupuncture for the treatment of OA of the knee generally agree with these conclusions (Manheimer et al. 2007).

However, some other trials demonstrated that acupuncture significantly reduced pain owing to OA of the knee, when compared with the non-treatment control, but was not more effective than sham acupuncture in the treatment of OA pain (Scharf et al. 2006; Witt et al. 2005). This contradiction might probably be owing to the different control groups, treatment methods, and the design of the trials, as shown in Table 7.8. However, owing to the heterogenic results, further research is required to confirm these findings and provide more established information.

Table 7.8 Acupoints commonly used for the treatment of OA of the knee

Acupoints	Locations	Meridian	Indications
Yanglingquan (GB 34)	In the depression anterior and inferior to the small head of the fibula	Gallbladder Meridian of Foot Shaoyang	Pain in the hypochondriac region, vomiting, beriberi, muscular atrophy and pain of the lower limbs, infantile convulsion, jaundice
Yinlingquan (SP 9)	In the depression on the lower border of the medial condyle of the tibia	Spleen Meridian of Foot Taiyin	Abdominal distension, diarrhea, edema, jaundice, difficulty in urination, incontinence of urine, pain in the knee

(Continued)

Acupoints	Locations	Meridian	Indications
Zusanli (ST 36)	3 cun below Dubi (ST 35), one finger breath from the anterior crest of the tibia	Stomach Meridian of Foot Yangming	Gastric pain, vomiting, dysphagia, diarrhea, dysentery, constipation, mastitis, appendicitis, pain of the lower limbs, edema, mania, beriberi, emaciation
Dubi (ST 35)	The point in the depression between the patella and the lateral ligament, when the knee is flexed	Stomach Meridian of Foot angming	Pain, numbness and motor impairment of the knee
Xiyan (EX LE5)	The point in the depression of the patella ligament, when the knee is flexed	The Extraordinary Acupoints	Knee pain, weakness of the lower extremities
Kunlun (BL 60)	In the depression between the tip of the external malleolus and the Achilles tendon	Bladder Stomach Meridian of Foot Taiyang	Headache, dizziness, stiffness of the neck, epistaxis, epilepsy, dystocia, pain in the lumbosacral area, swelling and pain of the heel
Xuanzhong (GB 39)	3 cun above the tip of the external malleolus, on the posterior border of the fibula	Gallbladder Meridian of Foot Shaoyang	Wind stroke, hemiplegia, neck pain, abdominal distension, pain in the hypochondriac region, muscular atrophy and pain of the lower limbs, beriberi
Sanyinjiao (SP 6)	3 cun directly above the tip of the medial malleolus, on the posterior border of the medial aspect of the tibia	Spleen Meridian of Foot Taiyin	Abdominal distension, diarrhea, irregular menstruation, leukorrhagia, infertility, dystocia, impotence, enuresis, hernia, insomnia, muscular atrophy and pain of the lower limbs, uterine bleeding, beriberi
Taixi (KI 3)	In the depression between the tip of the medial malleolus and the Achilles tendon	Kidney Meridian of Foot Shaoyin	Irregular menstruation, nocturnal emission, lumber pain, constipation, frequent urination, sore throat, toothache, insomnia
Liangqiu (ST 34)	On the line joining the anterior and superior iliac spine and the lateral border of the patella, 2 cun above the latero superior border of the patella	Stomach Meridian of Foot Yangming	Swelling and pain of the knees, paralysis of the lower limbs, gastric pain, mastitis, hematuria

Table 7.9 Randomized controlled trials of acupuncture for the treatment of OA of the knee

Sources	*n*	AT	CT	Number, spacing, and duration of treatments	Results
Takeda and Wessel 1994	40	MA	SA	2 times per week for 3 weeks	Both AT and CT show better sig; but AT = CT
Berman et al. 1999	73	MA, EA	SC	Biweekly for 8 weeks	AT sig > CT at 4 and 8 weeks
Berman et al. 2004	570	MA, EA	SA, EC	23 acupuncture sessions over 26 weeks	AT sig > CT at 26 weeks
Vas et al. 2004	97	EA	PA	12 weeks	AT sig > CT
Witt et al. 2005	294	MA	SA, WL	12 sessions over 8 weeks (twice per week for the first 4 weeks, once per week for the remaining 4 weeks)	AT sig > CT at 8 weeks AT = CT at 56 weeks
Witt et al. 2006b	1039	MA	SA, WL, SC	15 sessions of acupuncture over 3 months	AT sig > CT at 3 months
Scharf et al. 2006	1007	MA	SA, AD, PT	10 sessions within 6 weeks	Both AT and CT show better sig; but AT = CT at 26 weeks
Yurtkuran et al. 2007	52	LA	PLA	5 days per week for 10 days	Both AT and CT show better sig; but AT = CT

AT, Acupuncture Therapy; CT, Control Therapy; MA, Manual Acupuncture; EA, Electroacupuncture; LA, Laser Acupuncture; PLA, Placebo Laser Acupuncture; WL, Waiting List; PA, Placebo Acupuncture; SC, Standard Care; EC, Education group; PT, Physiotherapy; AD, Anti-inflammatory Drugs; sig, Significantly.

7.4.4 Chronic Neck Pain

Neck pain is one of the three most frequently reported complaints of the musculoskeletal system, and belongs to the “Bi” syndrome in the TCM meridian theory. Acupuncture is being increasingly used to treat many conditions, including chronic neck pain. The acupoints often selected to treat neck pain are shown in Table 7.10.

Trinh et al (2007) systematically reviewed the effects of acupuncture in treating neck disorders by analyzing ten published trials using randomized (RCT) or quasi-randomized (quasi-RCT) assignment on the intervention groups from the beginning of the study till February 2006. They found moderate evidence showing that acupuncture relieved pain better than some sham treatments, which was measured at the end of the treatment; those who received acupuncture reported less pain during short-term follow-up than those on a waiting list; and acupuncture was more effective than inactive treatments in relieving pain post-treatment, which was observed during the short-term follow-up.

Table 7.11 summarizes five controlled clinical trials for the treatment of chronic neck pain. As listed in the table, the evidence on the effectiveness of acupuncture in the treatment of chronic neck pain remains inconclusive, indicating the need for further well-designed, large-scale research. The inconsistent results may also be owing to the small sample, different intervention approaches, controls, and measures. Acupuncture is also used as a complementary treatment for chronic neck pain, and is often combined with usual cares, such as massage, physiotherapy, and anti-inflammatory drugs (David et al. 1998; Irnich et al. 2001; Witt et al. 2006a). Some other acupuncture approaches, such as manual acupuncture to tender points, dry needling, etc., have also been also used to treat chronic neck pain.

Table 7.10 Acupoints commonly used for the treatment of chronic neck pain

Acupoints	Locations	Meridian	Indications
Fengchi (GB 20)	In the depression between m. sternocleidomastoideus and m. trapezius, at the same level of Fengfu (DU 16)	Gallbladder Meridian of Foot Shaoyang	Headache, dizziness, redness, swelling and pain of the eyes, running nose, epistaxis, tinnitus, stiffness and neck pain, common cold, epilepsy, wind stroke, febrile diseases, malaria, goiter
Jianjing (GB 21)	Midway between Dazhui (DU 14) and the acromion	Gallbladder Meridian of Foot Shaoyang	Stiffness and pain of the head and neck, pain of the shoulder and back, paralysis of the upper limbs, dystocia, mastitis, agalactorrhea, scrofula
Yanglingquan (GB 34)	In the depression anterior and inferior to the small head of the fibula	Gallbladder Meridian of Foot Shaoyang	Pain in the hypochondriac region, vomiting, muscular atrophy and pain of the lower limbs, infantile convulsion, beriberi, jaundice
Taichong (LR 3)	On the dorsum of the foot, in the depression anterior to the junction of the 1st and 2nd metatarsal bones	Liver Meridian of Foot Jueyin	Headache, dizziness, vertigo, hiccup, vomiting, epilepsy, irregular menstruation, pain in the hypochondriac region, muscular atrophy and pain of the lower limbs
Hegu (LI 4)	On the dorsum of the hand, between the 1st and 2nd metacarpal cones, approximately to the midpoint of the 2nd metacarpal bone	Large Intestine Meridian of Hand Yangming	Headache, redness, swelling and pain of the eyes, epistaxis, toothache, trismus, deviation of mouth and eye, deafness, mumps, sore throat, febrible diseases with anhydrosis, hyperhydrosis, abdominal pain, constipation, amenorrhea, dystocia

(Continued)

Acupoints	Locations	Meridian	Indications
Dazhui (DU 14)	Below the spinous process of the 7th cervical vertebra	Du Meridian	Febrile diseases, malaria, cough, asthma, steaming bone, night sweats, epilepsy, headache, stiffness of the neck, urticaria
Houxi (SI 3)	The point on the ulnar side of the little finger, distal to the 5th metacarpophalangeal joint, at the junction of the red and white skin, when a loose fist is made	Small Intestine Meridian of Hand Taiyang	Stiffness and pain of the head and neck, deafness, redness of the eyes, lumbar and back pain, acontracture and pain of the finger, elbow, and arm
Shenmai (BL 62)	In the depression on the inferior border of the external malleolus	Spleen Meridian of Foot Taiyin	Headache, vertigo, mania, epilepsy, soreness and pain in the lumbar area and legs, redness and pain of the eyes, insomnia

Table 7.11 Randomized controlled trials of acupuncture for the treatment of chronic neck pain

Sources	*n*	AT	CT	Number, spacing, and duration of treatments	Results
David et al. 1998	70	MA	PT	Once a week for 6 weeks	VAS and NPQ: MA and PT sig better, but MA = PT at 6 weeks and 6 months
Irnich et al. 2001	177	MA	M, SLA	5 treatments over 3 weeks	VAS: MA sig > M, but MA = SLA at 4 weeks
White et al. 2004	135	MA	TENS P	8 treatments over 4 weeks	VAS: MA and TENS P sig better, but MA = TENS P at 8 weeks, 6 and 12 months
Vas et al. 2006	123	MA	TENS P	5 sessions over 3 weeks	VAS: AT sig > CT at 4 weeks
Witt et al. 2006a	14 161	MA+ RC	RC	15 sessions over 3 months	NPAD: VAS: AT sig > CT at 3 and 6 months

AT, Acupuncture Therapy; CT, Control Therapy; MA, Manual Acupuncture; TENS-P, Transcutaneous Nerve Stimulation-Placebo; RC, Routine Care alone; PT, Physiotherapy; M, Massage; VAS, Visual Analogue Scale; NPAD, Neck Pain and Disability Scale; NPQ, Neck Pain Questionnaire; sig, Significantly.

7.4.5 Neuropathic Pain

Neuropathic pain, or pain associated with disease or injury to the peripheral or central nervous system, is a common symptom of a heterogeneous group of conditions. The traditional approach classifies neuropathic pain according to the underlying cause (e.g., painful diabetic neuropathy, trigeminal neuralgia, postherpetic neuralgia, or spinal cord injury (SCI)), as well as the presumed location of the nerve injury (peripheral or central) (Chong and Bajwa 2003).

Currently, no consensus on the optimal management of neuropathic pain exists and the practices vary greatly worldwide. Acupuncture is a valuable method of complementary medicine with broad application in neuralgia. The commonly used acupuncture points and approaches for neuropathic pain are listed in Table 7.12.

Table 7.12 Commonly used acupoints and acupuncture approaches for treating different kinds of neuropathic pain

Conditions	Acupoints	Acupuncture approaches
Diabetic neuropathic pain	Sanjian (LI 3), Yinlingquan (SP 9), Sanyinjiao (SP 6), Zusanli (ST 36)	MA, AI, EA
Trigeminal neuralgia	Fengchi (GB 20), Wangu (GB 12) Tianzhu (BL 10), Shangxing (GV 23), Yintang (EX HN3)	MA, EA, AI, SA, AA, HA
Spinal cord injury (SCI) induced neuropathic pain	Houxi (SI 3), Shenmai (BL 62), Yanglingquan (GB 34), Huantiao (GB 30)	MA, EA, AA
Sciatica	Huantiao (GB 30), Weizhong (BL 40), Kunlun (BL 60), Yanglingquan (GB 34), Xuanzhong (GB 39), Zusanli (ST 36), Shenshu (BL 23), Dachangshu (BL 25)	MA, EA, AI, AA, HA
Postherpetic neuralgia (PHN)	Yanglingquan (GB 34), Zusanli (ST 36), Hegu (LI 4), Jiaji (EX B2)	MA, FSN, EA

MA, Manual Acupuncture; EA, Electroacupuncture; AEA, Auricular Electroacupuncture; AI, Acupoint Injection; SA, Scalp Acupuncture; HA, Heated Acupuncture; FSN: Fu's subcutaneous needling.

Brunelli and Gorson (2004) carried out a prospective study to determine the prevalence and patterns of use of CAM therapies on 180 consecutive outpatients with peripheral neuropathy. Among them, 30% chose acupuncture therapy, 27% thought their neuropathy symptoms improved with these approaches, while the most common reason for using CAM was inadequate pain control (32%). Rapson et al (2003) reported that EA treatment could improve the below-level central neuropathic pain induced by SCI (24% of 36%, 67%). This finding suggests that acupuncture may be an effective treatment option for patients with below-level central neuropathic pain induced by SCI. Abuaisha et al (1998) reported that 34 of 44 (77%) patients with chronic, painful, peripheral diabetic neuropathy showed significant improvement in their primary and/or secondary symptoms ($p<0.01$) after six courses of classical acupuncture analgesia over a period of 10 weeks. Among them, only seven (21%) noted that their symptoms cleared completely. These patients were followed up for a period of 18 – 52 weeks, and 67% were able to stop or reduce their medications significantly. These data suggest that acupuncture is a safe and effective therapy for the long-term management of painful diabetic neuropathy.

All these data show that acupuncture is effective in treating various neuropathies. However, this effect is limited, and neither the pain could be fully relieved nor all the treatments demonstrated satisfactory results (Nayak et al. 2001). Till date, large-scale, randomized controlled trials for neuropathy are relatively rare, and the standard inclusion criteria, acupuncture approach, course of treatment, and efficacy are yet to be established.

7.4.6 Motor System Injuries

Motor system injuries, including tennis elbow, carpal tunnel syndrome, acute lumbar sprain, and periarthritis of the shoulder, are diseases with pain as their main symptom. Acupuncture has long been used to treat motor system injuries in China and Western countries, though it is more popular and common in China. In Table 7.13, the acupuncture treatment for the common motor system injuries is presented.

Table 7.13 Acupuncture for common motor system injuries

Conditions	Definitions	Acupoints used	Treating courses
Tennis elbow	A common condition causing pain in the elbow and forearm and lack of strength and function of the elbow and wrist	Yanglingquan (GB 34), Tiaokou (ST 38), Tianzong (SI 11)	6 treatments within 2 weeks
Carpal tunnel syndrome (CTS)	A common entrapment neuropathy of the median nerve characterized by paresthesias and pain in the first through fourth digits	Shaohai (HT 3), Quze (PC 3), Wangu (SI 4), Yangxi (LI 5), Shousanli (LI 10), Chize (LU 5)	Once daily for 3 – 4 weeks
Acute lumbar sprain	A common condition causing pain in the lumbar as well as local soft tissue inflammation and edema	Tianzhu (BL 10), Fuyang (UB 59), Zhibian (UB 54), Houxi (SI 3), Weizhong (BL 40)	Once daily for 6 days
Periarthritis of the shoulder	A disease characterized by progressive pain and movement restriction in the peripheral tissues of the unilateral shoulder joint	Yanglingquan (GB 34), Jianyu (LI 15), Jianliao (SJ 14), Jianzhen (SI 9), Binao (LI 14), Tiaokou (ST 38)	Once daily for 2 weeks

Green et al (2002) reviewed a series of studies on acupuncture for the treatment of lateral elbow pain, and concluded that there is insufficient evidence to either support or refute the use of acupuncture (either needle or laser) for the treatment of lateral elbow pain, and observed that needle acupuncture produces short-term benefit with respect to pain (<24 hours following treatment). Furthermore, there are limited reports on acupuncture for the treatment of acute lumbar sprain and periarthritis of the shoulder in the Western countries. However, in China, a large number of uncontrolled trials demonstrated that acupuncture can be very effective in treating acute lumbar sprain as well as periarthritis of the shoulder, with an efficacy rate reaching up to 85% – 100% (Chen 2006; Chen et al. 2006; Cui 1992; Hu 1993; Wang et al. 1990b). This difference may probably be owing to the different treating methods and statistic processes.

As most of the earlier studies had employed low-quality methodologies, there is a need for further high-quality randomized controlled trials. In addition, future studies should also employ larger sample size and a valid acupuncture treatment to reach a convincing conclusion.

7.4.7 Fibromyalgia

Fibromyalgia is a condition of unknown cause, which is characterized by chronic, diffuse pain and tenderness to palpation at specific musculoskeletal sites. It is the second most common rheumatologic condition after OA (Assefi et al. 2005), and approximately 2% of the general population is affected by fibromyalgia with the highest prevalence in women aged from 40 to 60 years (Mayhew and Ernst 2007). The CAM is commonly used for treating fibromyalgia patients. One survey found that 91% of the patients suffering from fibromyalgia had used CAM, with acupuncture being the most commonly used form of CAM (Mayhew and Ernst 2007).

Mayhew and Ernst searched seven electronic databases for relevant RCTs, and analyzed five RCTs using acupuncture treatment (Table 7.14). The results showed that three RCTs were positive, but mostly produced short-term effects, while two yielded negative effects. Interestingly, all the three positive trials used EA treatment, whereas the two negative ones used only manual acupuncture. However, there was no significant difference between the quality of the negative and positive RCTs (Mayhew and Ernst 2007). Another study on 21 participants showed significant improvement of fibromyalgia symptoms after 8 weeks of acupuncture treatment (Singh et al. 2006). However, whether acupuncture is effective in treating fibromyalgia is still a topic under debate, and the existing evidences are mixed. Therefore, further systematic and rigorous studies should be carried out to establish the effectiveness of acupuncture in the treatment of fibromyalgia.

7.4.8 Cancer Pain

Cancer pain is a common clinical pathological pain syndrome, which greatly decreases the cancer patients' quality of life. Approximately 30% – 50% of all the cancer patients may experience moderate to severe pain, and 75% – 95% of the patients with advanced or metastatic cancer may experience substantial, life-altering cancer-induced pain (Mantyh et al. 2002; Mercadante 2001). It has been reported

Table 7.14 Controlled clinical trials of acupuncture for the treatment of fibromyalgia

Conditions	*n*	AT	CT	Primary assessments	Results
Fibromyalgia patients' ACR criteria 3 (Martin et al. 2006)	50	EA: 25 sessions during 1.5 – 3 weeks	CA: 25 sessions during 1.5 – 3 weeks	Fibromyalgia Impact Questionaire (FIQ), Multidisciplinary Pain Inventory (MPI)	EA sig > CA in FIQ mean score
Fibromyalgia patients' ACR criteria 3 (Vas et al. 2005)	100	MA: 24 sessions over 12 weeks	CA: 24 sessions over 12 weeks	Visual Analogue Scale (VAS) for pain, fatigue, sleep and overall well being; SF 36 for physical and mental functioning	MA sig = CA in main outcome measurements
Fibromyalgia patients' ACR criteria 1 (Guo and Jia 2005)	66	EA: 40 sessions over 4 months	MT: 40 sessions over 4 months	VAS scale	EA sig > MT in pain
ACR criteria 1 (Sprott 1998)	30	MA: 6 sessions over 3 weeks	CA: 6 sessions over 3 weeks; WL	Dolorimetry of tender and control points, VAS, pain score sheet, follow up questionnaire	MA sig > CA in the number of tender points; MA sig = CA in other outcome
Fibromyalgia patients' ACR criteria 3 (Deluze et al. 1993)	70	EA: 6 sessions over 3 weeks	CA: 6 sessions over 3 weeks	Pain threshold, number of analgesic used, regional pain score, pain recorded on VAS, sleep quality, morning stiffness, patient's and evaluating physician's appreciation	EA sig > CA in the main parameter

AT, Acupuncture Therapy; CT, Control Therapy; MA, Manual Acupuncture; CA, Sham Acupuncture; WL, Waiting List; MT, Medical Therapy; sig, Significantly; ACR, American College of Rheumatology: 1990 classification criteria.

that 45% of the cancer patients experience inadequate and undermanaged pain control owing to the relative ineffectiveness and side effects of the current treatments, though great progress has been made in relieving cancer pain, according to the guidelines of the World Health Organization's "analgesic ladder" (de Wit et al. 2001; Meuser et al. 2001). However, it is still difficult for the clinicians to provide absolute relief from pain, because analgesic drugs do not always procure complete relief.

Acupuncture is one of the most important complementary medical treatment used in cancer patients not only to relieve them from pain, but also for treating nausea and vomiting (Alimi et al. 2003; Dang and Yang 1998; Samuels 2002). In an observational study on 20 patients, the average pain intensity was observed to get reduced significantly following auricular acupuncture treatment. Furthermore, the patients who experienced pain diminution also felt better, and some even felt well enough to interrupt their analgesic treatment (Alimi et al. 2000). However, in the last 30 years, there has seldom been any large, randomized and controlled clinical trial to determine the effectiveness of acupuncture in treating cancer pain (Vickers and Cassileth 2001). Though the uncontrolled trials have shown promising results, the value of acupuncture in reducing cancer pain still remains to be sufficiently evaluated. Alimi et al (2003) reported a randomized controlled trial on 90 patients experiencing chronic pain, with two placebo groups and blind evaluation of the results. They observed that the pain intensity decreased by 36% in 2 months from the baseline in the group receiving acupuncture, while those in the placebo exhibited only a 2% decrease, thus, demonstrating the clear benefit of auricular acupuncture in cancer patients who were in pain.

In these earlier studies, the cancer sites were breast, stomach, head, neck, etc. (Alimi et al. 2003; Dang and Yang 1998). The auricular acupuncture has been commonly used as a complementary treatment for reducing cancer pain, when the analgesic drugs do not produce sufficient effects (Alimi et al. 2003). Though the benefits of acupuncture in treating cancer patients are undoubtedly clear, many acupuncturists do not prefer to treat cancer patients for the fear of "dispersing" the tumor, as according to the TCM, acupuncture is considered to "disperse" the stagnation of energy that is thought to cause the tumor form. However, according to Samules' opinion, there is no reason to fear about the "dispersal" of tumor if distant points are used, instead of inserting the acupuncture needles in the vicinity of the tumor. Furthermore, the immunomodulatory effects of acupuncture, both via the release of pituitary β-endorphin and adrenorticotrophin hormones (ACTH), as well as by alleviating the patient's stress through relief of the symptoms, are considered to be anti-carcinogenic (Samuels 2002).

7.4.9 Dental Pain

Acupuncture is often advocated as an effective treatment for dental pain. Kitade and Ohyabu (2000) evaluated the analgesic effects of acupuncture on postoperative pain by comparing the patients who underwent routine tooth extraction alone with those who underwent tooth extraction in combination with acupuncture. The acupoints of Hegu (LI-4) on both the sides, and Xiaguan (ST-7) and Jiache (ST-6) on the affected side were selected, and low-frequency EA was carried out. When acupuncture was used in combination with tooth extraction, 3 of the 22 patients did not develop postoperative pain. In patients who underwent difficult wisdom-teeth extraction, acupuncture used in combination with local anesthesia was observed to decrease the postoperative pain. In addition, a series of studies were conducted to evaluate the efficacy of Chinese acupuncture in reducing postoperative oral surgery pain (Lao et al. 1995, 1999). The results of randomized, double-blinded, placebo-controlled trial on 39 healthy subjects showed that acupuncture is superior to the placebo in preventing postoperative dental pain. Besides, a systematic review was reported to assess the effectiveness of acupuncture in dental pain (Ernst and Pittler 1998). Sixteen controlled trials were included and the Jadad score was used to evaluate the methodological quality. The result demonstrated that acupuncture is effective in producing dental analgesia. However, optimal acupuncture technique and its relative efficacy when compared with the conservative methods of analgesia should be further investigated.

7.4.10 Phantom Limb Pain

Studies on acupuncture for treating phantom limb pain are comparatively limited, with most of them being case reports (Bradbrook 2004; Monga and Jaksic 1981; Xing 1998). In an earlier study, three amputees with acute or chronic phantom limb pain and phantom limb sensation were treated with western medical acupuncture, by needling the asymptomatic intact limb. Two of the three subjects reported complete relief from phantom limb pain, indicating that acupuncture was successful in treating phantom limb pain (Bradbrook 2004). However, the result is preliminary, as the sample is too small. Larger cohort studies should be carried out to provide more evidence on the efficacy of acupuncture in the treatment of phantom limb pain.

7.5 Side Effects

Acupuncture treatment is relatively safe, especially when provided by properly trained acupuncturists. The adverse effects of acupuncture are relatively lower than many drugs or other therapeutic procedures used for the same conditions for which acupuncture is used (Birch et al. 2004). However, a number of adverse effects, including systemic reactions and local reactions, have been reported. The systemic reaction includes tiredness, drowsiness, aggravation of preexisting symptom, itching in the punctured regions, dizziness or vertigo, feeling of faintness or nausea during treatment, headache, and chest pain, while local reaction includes bleeding on withdrawal of the needle, pain on the punctured region during or after needling, petechia or ecchymosis, subcutaneous hematoma, etc. (Birch et al. 2004; Yamashita et al. 2000). These adverse effects are often transitorily associated with acupuncture treatment.

Though acupuncture treatment is generally safe in most situations and the side effects are commonly minimum, some severe side effects have been reported. The most serious side effects include transmission of disease such as hepatitis or HIV, punctured organs such as pneumothorax, heart and pericardium, brain and spinal cord, and miscellaneous events such as seizure or convulsive syncope (Kung et al. 2005; Peuker 2004; Su et al. 2007; White 2004).

In general, acupuncture is a relatively safe therapy. Although minor side effects have been observed, they are well-tolerated by patients. Furthermore, the serious side effects are rare and can be avoided if acupuncture is performed by well-trained acupuncturists. However, general precautions are still necessary to avoid possible side effects.

7.6 Concluding Remarks

Acupuncture has been used in the treatment of many kinds of acute and chronic pain conditions for pain relief in many countries. This review has summarized the analgesic effects of acupuncture on several pain conditions. We have found good and promising evidence on the efficacy of acupuncture in treating most of the pain conditions described in this chapter. The endogenous pain modulating system is observed to be activated during the process of acupuncture analgesia, which might be the major mechanism underlying this process.

Generally, a well-trained acupuncturist is recommended for administering acupuncture treatment to avoid unnecessary side effects, and proper acupuncture approaches are suggested to yield better analgesic effect. Furthermore, acupuncture combined with drugs is considered to be a good technique to enhance the analgesic effect, which has been well confirmed by our previous studies.

However, we did observe some inconsistent results from different clinical trials, which might be owing to the methodological differences among the acupuncturists. For example, the intervention time, criteria for efficacy evaluation, time of observation of the therapeutic effect, statistical method, and control group are often different in various trials. Therefore, it is necessary to properly design the clinical trial, including the selection of proper control and the use of uniform acupuncture manipulation, to achieve convincing results.

With the increasing evidence from numerous studies on the analgesic effect of acupuncture in the treatment of different kinds of acute and chronic pain, we believe that more and more people would be benefited from the use of acupuncture in pain relief, with the advantages of low costs, simple manipulation, and minimal adverse effects.

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8 Neurochemical Basis of Electroacupuncture Analgesia on Acute and Chronic Pain

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Summary Electroacupuncture (EA) stimulation has immediate or cumulative (therapeutic) effects on acute pain and chronic pain in various experimental models. This chapter summarizes the mechanistic exploration of EA analgesia. The analgesic effect of EA on acute and chronic pain involves multi-synaptic pathways and various neurotransmitters/neuromodulators including endogenous opioid peptides, glutamate, glial cell derived neurotrophic factor, serotonin and their receptors. EA analgesia is also related to the regulation of glial activity and inhibition of inflammatory cytokines in the spinal cord.

Keywords *acute pain, chronic pain, endogenous opioid peptides, neurotransmitters, inflammatory cytokines*

8.1 Introduction

Electroacupuncture (EA), an acupuncture therapy, has been used for several decades in the treatment of acute and chronic pain. Clinical observations and laboratory research have established the overwhelming recognition that acupoint stimulation can produce analgesic effect on various types of acute or chronic pain. Since 1970s, mechanistic research of EA analgesia (EAA) has made remarkable progress in exploring the neural pathway of acupuncture signals (also see Chapter 3), neurotransmitter release and expression of particular receptors and genes in the spinal cord and supraspinal structures. A large body of literature has revealed that the essence of acupuncture analgesia is mainly the activation of the endogenous antinociceptive system to modulate pain transmission and pain response, resulting in the diminution of pain perception and aversive reactions. The neural process involves the integration of different neurotransmitter and modulator systems at various levels of the central nervous system. In the early 1970's, an elegant study from Han's group found for the first time that when the cerebrospinal fluid of donor rabbits given acupuncture was infused into the cerebral ventricles of recipient rabbits, the pain threshold of the recipients was increased, strongly suggesting the involvement of central chemical mediators in acupuncture analgesia (Research Group of Acupuncture Anesthesia, Peking Medical College 1974). Since then, many lines of evidence found in clinical and animal studies has demonstrated that acupuncture analgesia is mediated by various neurotransmitters and modulators. However, compared to the extensive and advanced studies on the mechanism underlying EAA on acute (physiological) pain models, studies on the therapeutic analgesic effect of EA on chronic pain, which involves different mechanisms from those of physiological pain, are relatively delayed in spite of the fact that EA is mainly applied on pathological and chronic pain at the bedside. Recently, increasing evidence has shown that various neurotransmitters and modulators are involved in EA analgesia on chronic pain.

8.2 EA analgesia on Acute and Chronic Pain

There are two categories of pain: acute and chronic. Chronic pain includes inflammatory pain (e.g., Rheumatoid arthritis and Osteoarthritis), neuropathic pain (e.g., Sciatica) and cancer pain, respectively. The chronic pain is characterized by hyperalgesia, allodynia and spontaneous pain. The underlying mechanism thought to account for these phenomena include peripheral sensitization (the hyperexcitability in primary nociceptors) and central sensitization (the increase in neuronal activity of spinal dorsal horn neurons).

Unlike acute pain, which is a protective response of the body, chronic pain persists and serves no useful purpose, and severely affects the quality of life. Both laboratory research and clinical practice demonstrate that pain is relieved immediately after needling of the acupuncture points in many cases, particularly cases of pain caused by a certain injury. Most importantly, repeated acupuncture has been confirmed to have cumulative (therapeutic) effect in chronic pathological pain.

Compared to the large body of previous studies on immediate analgesia effect of acupuncture, it is more clinically significant to assess the cumulative (therapeutic) effect of acupuncture, since clinically acupuncture is chronically applied for chronic pain. Consistent to the clinical study, animal experiment has shown that consecutive EA produces cumulative (therapeutic) effect on chronic pain including neuropathic pain, inflammatory pain and cancer pain (Luo 1996).

8.2.1 Neuropathic Pain

Neuropathic pain refers to pain as a result of damage (due to injury or disease) to the nervous system. Patients with neuropathic pain often suffer from spontaneous pain, allodynia (pain response to normally innocuous stimuli) and hyperalgesia (aggravated pain evoked by noxious stimuli) (Wang and Wang 2003). Acupuncture has long been used to relieve neuropathic pain. Clinical trials have shown that acupuncture has significant analgesic effects on peripheral neuropathy-induced chronic pain including facial nerve neuropathy, sciatic nerve neuropathy, herpetic trigeminal ganglionic neuropathy, diabetic neuropathy, HIV related neuropathy, etc.

Most neuropathic pain models were made to simulate human neuropathic conditions by inducing or injuries to the spinal cord or peripheral nerves (Fig. 8.1), most of which are based on procedures at or near sciatic nerves including transection, loose or tight ligation, cryoneurolysis, crush, peripheral inflammation and tumor invasion.

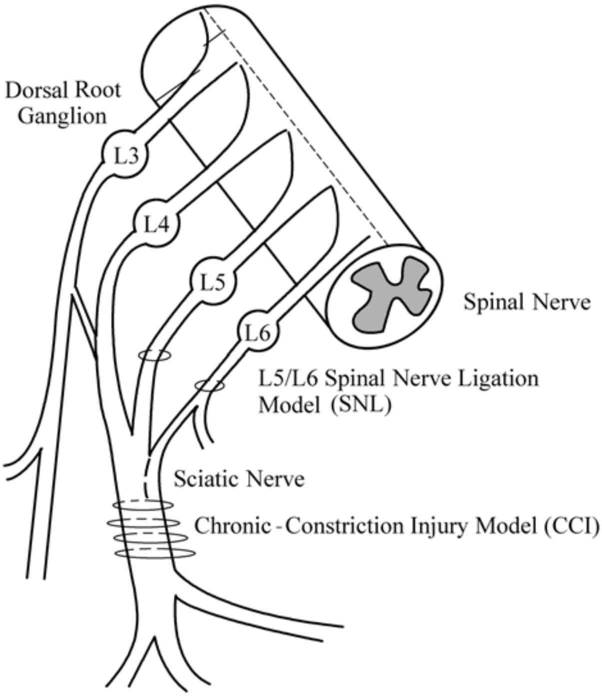

Figure 8.1 Schematic diagram showing the two peripheral neuropathic pain models induced by chronic constriction injury to the unilateral sciatic nerve (CCI model) or ligation of L5 and L6 spinal nerves.

Chronic-constriction injury (CCI) of the sciatic nerve causes mechanical and heat hyperalgesia and mechanical allodynia in the plantar surface of the hind paw of rats (Bennett and Xie 1988). Single EA treatment has immediate analgesic effect (Dai et al. 2001) while cumulative EA have been proved to have potent anti-hyperalgesic effect on neuropathic pain induced by CCI of the sciatic nerve in rats (Dong et al. 2006b). Scientists from South Korea tested the effects of EA on the mechanical allodynia induced by S3 and S4 spinal nerves resection in rats.

They found that low frequency EA stimulation delivered to Houxi (SI-3, 2 Hz, 0.3 ms, 0.07 mA) or Zusanli (ST-36, 2 Hz, 0.3 ms, 0.2 – 0.3 mA) for 30 min relieved significantly the signs of mechanical as well as cold allodynia of rats. (Hwang et al. 2002; Kim et al. 2004; Kim et al. 2005). EA treatment has antinociceptive effects on both pain behavior and neuronal activation (marked as the c-Fos expression) of the spinal dorsal horn neurons in CCI rats. Kim and Chung reported in 1992 another experimental mononeuropathy simulating human causalgia. In the L5/L6 spinal nerve ligation model (SNL), L5 and L6 spinal nerves are unilaterally and tightly ligated at a location distal to the dorsal root ganglia. Allodynia and hyperalgesia develop quickly after ligation and last for at least 4 months. By using the SNL model, it has been reported that EA at low frequency of 2 Hz had greater and more prolonged analgesic effects on mechanical allodynia and thermal hyperalgesia than that EA at high frequency of 100 Hz in rats with neuropathic pain (Xing et al. 2007).

8.2.2 Inflammatory Pain

Chronic inflammatory pain is one of the most common pathologic pain in clinic. Inflammatory pain arises as a debilitating consequence of injury to the peripheral tissue, which is characterized by combination of spontaneous burning pain, hyperalgesia and allodynia. By using intraplantar Complete Freund's Adjuvant (CFA)-induced chronic inflammatory pain model in rats (Fig. 8.2), Huang et al. examined whether EA has the effect on the thermal and mechanical hyperalgesia. They observed that (1) single session of 100 Hz EA (0.5 – 1.0 – 1.5 mA, 10 min for each intensity) at both ST-36 and Sanyinjiao (SP-6) acupoints significantly increased the mechanical withdrawal threshold determined by von Frey filaments, but not with thermal withdrawal latency that is determined by hot plate (52 ± 0.2℃); (2) 100 Hz EA applied twice a week for 4 weeks showed a significant decrease in the mechanical hyperalgesia at the third and fourth week. These results demonstrated that single or repetitive EA could reduce mechanical hyperalgesia (Huang et al. 2004a). On the same inflammatory pain model, Lao et al. demonstrated that EA treatment at Huantiao (GB-30) could also reduce CFA-induced thermal hyperalgesia (Lao et al. 2001; Zhang et al. 2005a, b, c). Their further study showed a parameter-dependent and point-specific anti-hyperalgesic effect of EA stimulation. They found that 10 Hz and 100 Hz EA frequencies at a current intensity of 3 mA produced the greatest anti-hyperalgesia, when compared to other parameters. A sufficient but tolerable intensity of 3 mA was more effective than lower intensities (1 – 2 mA). The studies on the Acupoint-specific effect demonstrated that GB-30 produced significant EA anti-hyperalgesia, while Waiguan (TE-5) and sham points, an abdominal point and a point at the opposite aspect of GB-30, did not. They provide important information for designing further clinical acupuncture research on persistent inflammatory pain (Lao et al. 2004); Zhang et al. evaluated the potential synergism of EA and a sub-effective dosage of indomethacin in a rat model of inflammatory pain induced by CFA. EA treatments were given at acupoint GB30 immediately and 2 h post-CFA injection. Both low- and high-frequency EA combined with low dose indomethacin enhanced antihyperalgesia compared to each component alone. Their study demonstrated for the first time that EA combined with indomethacin synergistically inhibits hyperalgesia and suggest an improved treatment strategy for inflammatory pain (Zhang et al. 2004b). In the rat model of collagen or CFA induced arthritis the analgesic effects of both acute and chronic EA have also been proved (Baek et al. 2005; Sun et al. 2006).

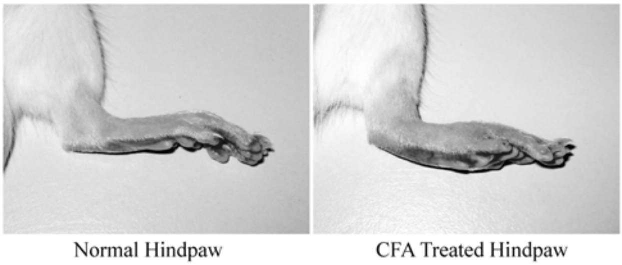

Figure 8.2 Peripheral inflammatory pain model induced by injecting CFA into the hand paw of rats.

There are significant immediate and cumulative effects of EA on chronic visceral pain induced by colorectal distention stimuli in rats using an irritable bowel syndrome model (a chronic visceral hypersensitivity model). Cui et al (2005) demonstrated that EA could significantly depress both abnormally increased abdominal withdrawal reflex (AWR) scores and the magnitude of electromyograms recorded from the rectus abdominis in response to colorectal distention stimulation. Repeated EA treatment for two weeks showed the therapeutic effects of EA on visceral pain.

8.2.3 Cancer Pain

Pain is a common symptom in cancer patients, affecting 30% – 50% of patients undergoing active treatment for a solid tumor and 70% – 90% of those with advanced diseases. Whereas improving diagnosis and treatment methods are increasing the survival rate and life expectancy of cancer patients, cancer pain is increasingly becoming a bigger problem affecting the quality of life. Current treatment is largely based on empirical clinical experience with incomplete success. Cancer-related pain may be caused by tumor infiltration or compression of nerve, plexus, or roots, immunoreactive and pronociceptive substances released from tumors, or by treatment (chemotherapy, radiation, or surgery). The lack of suitable experimental animal models for cancer pain has been the major stumbling block in the investigation of the mechanisms underlying cancer pain. Bone cancer pain is one of the most common cancer-related pain of which the cancer can be primary or metastatic from breast, prostate, ovary and lung tumors. Deep pain with a burning and stabbing sensation is often described by bone cancer patients.

So far a few reports are available for the analgesia effect of acupuncture on cancer pain. We examined the immediate and therapeutic anti-hyperalgesic effect of EA on a mouse model of cutaneous cancer pain. B16-BL6 melanoma cells were inoculated into the plantar region of unilateral hind paw of C57BL/6 mice and the thermal hyperalgesia was measured by using radiant heat test and hot plate test. Single EA on day 8 after inoculation showed significant analgesic effect immediately after the treatment, while single EA treatment on day 20 showed no significant analgesic effect; Repeated EA treatments (started from day 8, once every other day) showed therapeutic analgesic effect, while it showed no therapeutic effect when started from day 16, a relatively late stage of this cancer pain model (Fig. 8.3). These results demonstrated that EA had anti-hyperalgesic effect on early stage of cutaneous cancer pain but not on late stage indicating a tight correlation of EA anti-hyperalgesic effects with the time window of cancer pain (Mao-Ying et al. 2006). Recently, Zhang et al (2007) observed an alleviating effect of EA on cancer induced hyperalgesia on a prostate cancer induced bone cancer pain model of rats.

8.3 Neurochemical Mechanism Underlying EA Analgesia on Acute Pain

Large body of literature has revealed that the essence of acupuncture analgesia is mainly the activation of the endogenous antinociceptive system to modulate pain transmission and pain response, resulting in the attenuation of pain perception and aversive reactions. The neural process involves the integration of different neurotransmitter and modulator systems at various levels of the central nervous system.

8.3.1 Endogenous Opioid Peptides

With the discovery of Endogenous Opioid Peptides (EOPs) including enkephalin in 1975, β-endorphin in 1976 and dynorphin in 1979, the studies on the roles of EOPs in acupuncture analgesia developed rapidly and have been the most important advance in the study of acupuncture analgesia in the past decades (Cao 2002; Han 2003).

Years later, two new EOPs, the nociceptin/orphanin FQ (N/OFQ) and endomorphins were identified in 1995 and 1997 respectively. The endomorphin was considered as the pure μ opioid receptor endogenous agonist and dynorphin the relatively pure κ opioid agonist, the enkephalin and β-endorphin were mixed μ and δ opioid receptor agonists (Han 2004).

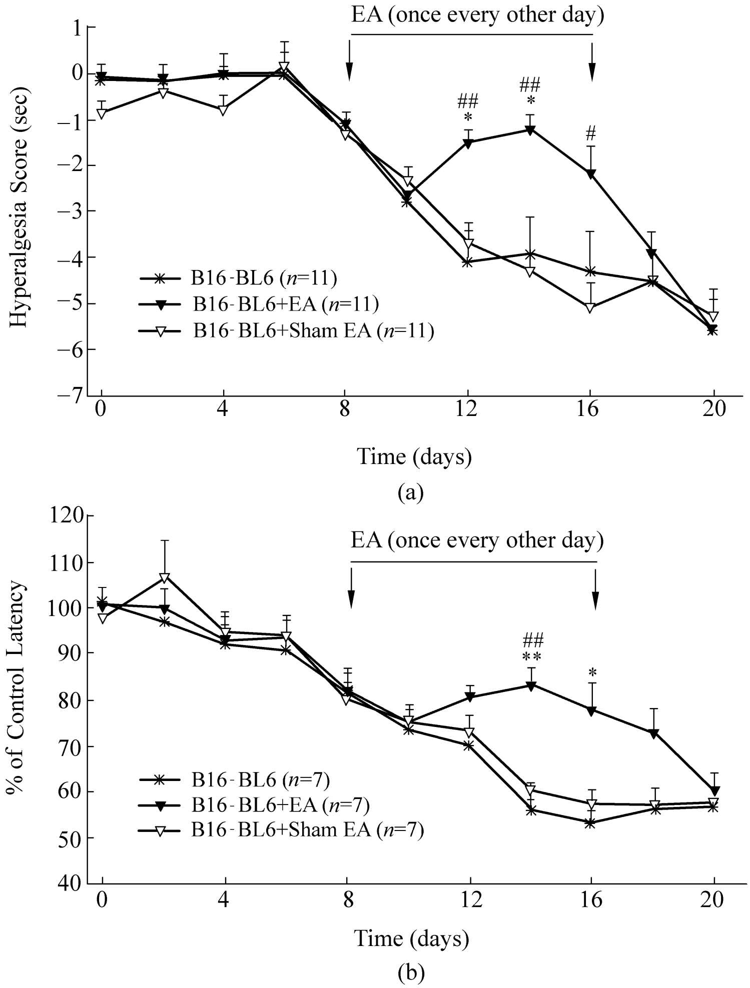

Figure 8.3 Therapeutic effect of repeated EA on thermal hyperalgesia of mice inoculated with B16-BL6 melanoma cells. Hyperalgesia was tested by radiant heat (a) and hot plate (b), respectively. Sham EA is a control treatment without electrical current on the needles. Hyperalgesia score was calculated as the difference of the bila teral paw withdrawal latency (ipsilateral contralateral) to radiant heat stimulation (a). The percentage of control latency was calculated as 100% times response latency of experimental mice/response latency of normal mice (b). To avoid the disturbing effect of immediate EA analgesia on the observation of the therapeutic effect of repeated EA, EA and sham EA (as a control) were administered after the pain tests. Arrowheads indicate the beginning (day 8) and ending (day 16) of the EA treatments, which were given once every other day, each treatment lasted for 30 min. Data are expressed as means ± SEM. $*p<0.05$, $**p<0.01$ vs. B16 BL6 group; $\#p<0.05$, $\#\#p<0.01$ vs. sham EA group. (Mao Ying et al. 2006). Note that repeated EA treatments (started from day 8, once every other day) showed therapeutic analgesic effect, while it showed no therapeutic effect when started from day 16, a relatively late stage of this cancer pain model.

These opioid peptides are significantly implicated in antinociceptive processes. They were found to be expressed in the regions involved in nociception and pain. Opioid receptors are differentially distributed in the neuronal nociceptive system including periaqueductal grey, locus coeruleus, substantia nigra, ventral tegmental area, raphe nuclei, nucleus tractus soli tarii and the spinal cord which are closely involved in the transmission of nociceptive stimuli and the modulation of nociception (Przewlocki and Przewlocki 2001).

As early as in 1970s, it was reported that EAA in cats and in humans can be reversed by naloxone, a specific opioid receptor antagonist, strongly suggesting the involvement of EOPs in acupuncture analgesia (Pomeranz and Chiu 1976; Mayer et al. 1977). Our department (Zhang et al. 1978) also observed that naloxone 0.4 mg/kg i.v. injection markedly antagonized the analgesic effect of EA in rabbits. Microinjection of opioid receptor antagonist (naloxone) or antiserum against EOPs into selected brain regions (for example, the periaqueductal gray, PAG) of animals attenuated the EAA (He et al. 1985, 1991; Zhou et al. 1995; Ulett et al. 1998). Huang et al. established a monkey model on which acupuncture significantly prolonged the latency of the operant lever-pressing response to noxious stimulus, with naloxone effective in blocking analgesia (Chinese Academy of Sciences Institute of Physiology 1978; Huang et al. 1981).

Multiple research approaches have shown that acupuncture activates endogenous opioid mechanisms. Measurement of the EOP levels in the cerebrospinal fluid is a potential approach to evaluate their release. Clinical studies of our department showed that EA elevated the content of β-endorphin-like immunoreactive substances in ventricular cerebrospinal fluid of patients with brain tumor (Acupuncture Anesthesia Research Coordinating group 1978) and in the lumbar CSF of patients with chronic pain (Sjolund et al. 1977). There was a linear correlation between the percentage increase of β-endorphin-like immunoreactive substances and the pain threshold or pain tolerance threshold. By using push-pull perfusion techniques, it was found that there was a marked increase of endorphins in the perfusate of periaqueductal grey (PAG) after acupuncture in rabbits, and the release of endorphins was correlated with the analgesic effect of acupuncture (Zhang et al. 1979, 1981; Chen and Pan 1984).

Notably, the effect of electroacupuncture on the release of EOPs is dependent on the frequency of EA stimulation. Using microinjection of antiserum to MEK, LEK, β-endorphin or dynorphin A and dynorphin B, it was found that low frequency and high frequency EAA could be blocked by MEK antiserum and dynorphin A antiserum respectively, indicating that endogenously released MEK was responsible for mediating low while dynorphin A was responsible for high frequency EA effects. Their further studies by using different subtypes of specific opioid receptor antagonists confirmed that the analgesia induced by 2 Hz EA (low frequency) was mediated by the μ receptor and that of 100 Hz EA (high frequency) by κ opioid receptors (Chen and Han 1992). Han et al (2003) observed that EA of 2 Hz showed significantly lower analgesic effect in mice lacking β-endorphin (knock out) compared to that in wild type mice, whereas 100 Hz EA stimulation produced analgesia in both β-endorphin knock out mice and wild type mice. These results provided genetic support for the hypothesis that the analgesic effect induced by EA of different frequencies was mediated by different kinds of opioid peptides. EA of 2 Hz accelerates the release of enkephalin, β-endorphin and endomorphin, while that of 100 Hz selectively increases the release of dynorphin. A combination of the two frequencies produces a simultaneous release of all four opioid peptides, resulting in a maximal therapeutic effect (Han 2004).

From the results of localization studies by injecting naloxone into discrete brain areas and assessing its effect on acupuncture analgesia in rabbits, it was concluded that the preoptic area, septal area, nucleus accumbens, amygdala, habenula, caudate nucleus and periaqueductal grey are the strategic sites for endogenous opioids to exert their analgesic effect (He et al. 1987). These brain areas are also of extreme importance for morphine analgesia (Zhou et al. 1981; Sato et al. 1991). For example, as a critical region in the descending pain inhibitory system for morphine- and brain stimulation-induced analgesia, PAG also plays critical role in acupuncture analgesia. In addition to lesion, blockade of opioid receptors in the PAG by naloxone or antibody against μ- or δ-receptors also attenuated EAA. By using multimicropipettes for extracellular recording and iontophoresis of drugs, it was found that opiates produced a naloxone reversible inhibition on the spontaneous discharge of certain neurons. Such neurons were distributed mostly in the ventral part of the PAG. Similar to iontophoretic opiates, EA had an inhibitory effect on PAG neurons and the inhibition could be reversed by iontophoretic naloxone. It was postulated that acupuncture signals activate the brain EOPs to modulate the transmission of pain signals in the PAG, i.e., to block the conveyance of nociceptive impulses at situ and at other relay stations through inhibitory systems (He and Dong 1983).

Proteolytic cleavage of the precursor protein preproenkephalin, preprodynorphin and proopiomelanocortin yields enkephalin, dynorphin and β-endorphin respectively. β-endorphin is mainly concentrated in cell bodies of the hypothalamic arcuate nucleus. These neurons provide an intense innervation of the PAG (Yaksh 1999). The immediate early gene, c-Fos encodes a nuclear phosphoprotein, Fos which has been proposed to be a third messenger to regulate the expression of specific target genes. Digoxin-labeled antisense RNA probes were used for in situ hybridization to detect the mRNA encoding proopiomelanocortin in the rat brain. Fos protein and proopiomelanocortin (POMC) mRNA were found to be coexisting in the hypothalamic arcuate nucleus (Arc) detected by in situ hybridization and immunocytochemistry, suggesting the activation of β-endorphinergic neurons in the Arc by EA (Zhang et al. 1996).

EA at different frequencies can affect the transcription of genes encoding different opioid peptides. EA induced an increase of preproenkephalin mRNA in rostromedial reticular formation (gigantocellular, paragigantocellular and lateral reticular nucleus); whereas in supraoptic nucleus, suprachiasmatic nucleus, arcuate nucleus, paraventricular hypothalamic nucleus, ventromedial nucleus and the nucleus of lateral lemniscus, 2 Hz EA induced a higher PPE mRNA expression than 100 Hz EA. 100 Hz EA markedly increased the preprodynorphin mRNA levels in supraoptic nucleus, paraventricular hypothalamic nucleus, ventromedial nucleus and parabrachial nucleus, while 2 Hz was without effect. Since de novo peptide synthesis is regarded as a natural outcome following accelerated peptide release, the present results substantiate the observation that EA of different frequencies exert different acceleratory effects on the release and synthesis of different opioid peptides in the central nervous system (Guo et al. 1997).

The newly discovered opioid peptide such as nociceptin/orphanin FQ (N/OFQ) and endomorphins have also been indicated to be involved in EAA during the past ten years. N/OFQ is a heptadecapeptide which is structurally similar to the EOPs especially dynorphin A. N/OFQ has higher affinity with opioid receptor-like1 receptor (ORL1)-an opioid receptor identified in 1994 (Meunier et al. 1995; Reinscheid et al. 1995). Morphological studies have established that N/OFQ-containing neurons and fibers as well as ORL-1 receptor are widely distributed along all parts of pain circuitry, including the ascending and descending pain pathways, such as PAG, the rostal ventromedial medulla (RVM), locus coeruleus and the dorsal horn of the spinal cord (Harrison and Grandy 2000; Neal et al. 1999). On acute pain models, Administration of N/OFQ (i.c.v.) produced a dose-dependent antagonism of the analgesia induced by EA in the rats, whereas antisense oligonucleotides (i.c.v) to N/OFQ mRNA or anti-OFQ antibody (OFQ-Ab, i.c.v) potentiated EA-induced analgesia, suggesting that endogenous N/OFQ in the brain exerts a tonic antagonistic effect on EA-induced analgesia via activating N/OFQ receptor. However, intrathecal administration of N/OFQ enhanced EA-induced analgesia rather than antagonism (Zhu et al. 1996; Tian et al. 1997). These findings are consistent with the experimental results obtained in rats where morphine, endomorphin-1 or fentanyl induced analgesia were antagonized by i.c.v. N/OFQ and potentiated by i.t. N/OFQ (Wang et al. 1999a, 1999c). Interestingly, given that rats were classified as either high responders (HR) or low responders (LR) based on the analgesic effects of EA, LRs could be converted into HRs by the intracerebroventricular (i.c.v.) microinjection of OFQ-Ab, while HRs could be changed into LRs by the intrathecal (i.t.) injection of OFQ-Ab (Tian et al. 1998).

Endomorphins (EM1 and EM2), the endogenous μ-opioid receptor agonist, are also involved in electroacupuncture (EA)-induced analgesia. Intracerebroventricular (i.c.v.) injection of antiserum against EM1 or EM2 dose-dependently antagonized 2 Hz EAA in C57BL/6J mice, indicating that endogenously released EM1 and EM2 and the cerebral μ-receptors are involved in mediating 2 Hz EAA in mice (Huang et al. 2000; Han et al. 1999; Hao et al. 2000).

8.3.2 CCK-8

Cholecytokinin octapeptide (CCK-8) is widely distributed in various brain areas and the spinal cord and exerts many physiological functions, in which CCK-8 as the most potent neuropeptide is involved in processing an anti-opioid activity. It hinders opioid analgesia and facilitates opioid tolerance. The serial studies of Han and the others revealed that CCK-8 acts as an anti-opioid factor in the acupuncture analgesia. Intracerebroventricular or intrathecal injection of CCK-8 at the dose range of 0.25 – 4.0 ng, dose-dependently antagonized the effect of morphine analgesia and EAA in the rat. CCK-8 antiserum was capable of reversing the tolerance to EAA and changing the non-responders of EAA into responders. CCK-B antagonist administered into the PAG of rats significantly potentiated EA-induced anti-nociception (Chen et al. 1998). The mRNA expression of CCK-A and CCK-B receptors in the hypothalamus was significantly higher in non-responders to electroacupuncture analgesia in rats, suggesting that the level of CCK receptor mRNA expression has an important relationship with the individual variations to high frequency EA analgesia in rats (Ko et al. 2006). These results suggest that blocking the effect of CCK-8 may be a powerful way of augmenting the effect of morphine analgesia and EAA (Han et al. 1985; 1986).

Radioimmunoassay revealed that EA stimulation, especially at 100 and 15 Hz, produced a marked increase in the CCK-8 immunoreactivity in the perfusate of the rat spinal cord. The increased release of CCK-8 following EA may limit the effect of opioid peptides (Zhou et al. 1993; Han 1995).

Further observation showed that rats with weak EA-induced analgesia, low responders, had a remarkable increase in CCK release by high-frequency EA, whereas rats with strong EAA, high responders, had little increase in CCK release. Particularly, following i.c.v. microinjection of antisense oligonucleotides to CCK mRNA, a responder rat could be changed into a non-responder by inducing over-expression of CCK in the brain (Tang et al. 1997; Zhang et al. 1997). Further studies demonstrated that subcutaneous injection of the CCK-B receptor antagonist L365,260 produced a dose-dependent potentiation of the analgesia induced by 100 Hz EA. In addition, L365,260 significantly reversed chronic tolerance to 100 Hz EA in mice. These results suggest that the CCK-B receptor might play a role in the tonic inhibition of 100 Hz EAA and in the mediation of chronic tolerance to 100 Hz EA in mice. The results opened a way for further investigation of the function of CCK-8 in pain modulation using inbred strains of mice (Huang et al. 2007). Moreover, the level of CCK receptor mRNA expression in the hypothalamus, rather than CCK mRNA, has an important relationship with the individual variations to high frequency EAA in rats (Ko et al. 2006).

8.3.3 Glutamate

Excitatory amino acids, such as glutamate and aspartate, are richly contained in nociceptive primary afferent fiber terminals. Glutamate receptors, N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid/kainate (AMPA/KA) receptors as well as the metabotropic receptors are distributed densely in the superficial dorsal horn of the spinal cord where primary nociceptive afferents terminate. A large body of evidence showed that glutamate and its receptors play a pivotal role in spinal transmission of nociceptive information and central sensitization. Although neither intrathecal injection of NMDA antagonist D-AP-5 or AMPA/KA antagonist NBQX disodium alone had any effect on analgesia, spinal application of D-AP-5 and NBQX disodium significantly prevented analgesia induced by 2 Hz EA suggesting the involvement of ionotropic glutamate receptors in EAA (Choi et al. 2005b).

The effect of glutamate on cortical somatosensory area Ⅱ (S Ⅱ) producing descending modulation of intralaminar nuclei (ILN) via the motor cortex (MCtx) in acupuncture analgesia was also investigated. The glutamate antagonist glutamate diethylester or saline was topically applied at MCtx in 17 cats. Single unit activities of ILN neurons were extracellularly recorded. The nociceptive responses of ILN neurons were attenuated by stimulating S Ⅱ after topical administration of saline at MCtx. However, the inhibitory effect of stimulating S Ⅱ in the same neurons was reduced after application of glutamic acid diethyl ester, a glutamate receptor antagonist. There was a significant difference at 0' – 1' after the stimulation between the two groups. The inhibitory effect of EA on nociceptive responses was reduced after topical application of diethylester, while marked inhibition was shown at 0' – 10' after cessation of EA in the saline control group. The results, together with the finding that the majority of S Ⅱ neurons could be activated by EA, showed that glutamate released from S Ⅱ to MCtx might be involved in corticofugal modulation of ILN from S Ⅱ via MCtx in acupuncture analgesia (Zheng et al. 1994).

8.3.4 GABA

EA treatment resulted in strong expression of c-Fos immunoreactivity in the ventrolateral to lateral subdivision throughout the PAG. It was of particular interest in the experiment of the acupoint that strong expression of gamma aminobutylic acid (GABA) frequently showed similar pattern of distribution to that of c-Fos in the PAG. This overlapped pattern of distribution, demonstrated in the present study, suggesting that the PAG neurons activated by EA might play an important role in the descending pain control system involving the GABA since the PAG has special reference to the dorsal horn of the spinal cord and function of pain control (Fusumada et al. 2007).

8.3.5 Serotonin (5-HT)

Compelling evidence has testified that both serotonergic descending and ascending pathways originated from the nucleus raphe magnus are implicated in mediating acupuncture analgesia. The analgesic effect of acupuncture can be enhanced or attenuated by the increment or the decrement of the 5-HT level in the CNS. After the formation of selective chemical lesion of serotoninergic fibers with 5, 6-DHT, blockade of 5-HT biosynthesis by pCPA or antagonism of 5-HT receptors by cyproheptadine or methysergide, acupuncture analgesia was obviously attenuated in the different animals tested. In contrast, following the administration of 5-HT precursor such as 5-HTP or tryptophan, blockade of 5-HT degradation by monoamine oxidase inhibitor pargyline or reduction of 5-HT uptake by clomipramine, acupuncture analgesia was potentiated. The finding that EA increased in the central content of 5-HT and its metabolic products particularly in the nucleus raphe magnus and the spinal cord further imply the involvement of 5-HT in acupuncture analgesia (Han et al. 1979).

8.3.6 Noradrenaline

The role of noradrenalin (NA) in acupuncture analgesia is complicated and paradoxical. NA seems to exert the different action in the spinal and supraspinal level. By using double labeling immunohistochemistry between c-Fos-like immunoreactive neurons and dopamine-β-hydroxylase/tyrosine hydroxylase-positive neurons, it was found that EA increased the number of c-Fos-like immunoreactive neurons in catecholaminergic neurons, such as the dorsal raphe, hypothalamic arcuate nucleus, locus coeruleus, A5 noradrenaline cells, and A7 noradrenaline cells (Kwon et al. 2000). When the catecholaminergic terminals were destructed by microinjection of 6-hydroxydopamine into the preoptic area the acupuncture analgesia was significantly enhanced suggesting that the reduction of catecholamine content in the preoptic area may enhance acupuncture analgesia (Li et al. 1990). By means of increase or decrease of activity of NA system with lesion of the locus coeruleus, degeneration of NA, extragenous administration of agonist or antagonist of NA receptor in the brain and spinal cord, studies indicated that NA might produce inhibition of EAA in supraspinal structures but potentiation in the spinal cord. Acupuncture analgesia is closely related to the activation of α2 adrenergic receptors in the spinal dorsal horn.

We measured the central and peripheral sympathetic activities both physiologically and biochemically in either human subjects or conscious rabbits. EA reduced NA levels in perfusates of certain brain areas as well as in blood circulation, accompanied with a rise of pain threshold, and changes of certain physiological indices (palm temperature, fingerplethysmogram and pain tolerance threshold) which are related with functions of sympathetic nervous system. These results suggest that the NA neurons of NA ascending dorsal fasciculus have antagonizing effects on acupuncture analgesia, acupuncture inhibits sympathetic activities and in hence plays a favorable role in acupuncture analgesia (Cao et al. 1983).

8.3.7 Dopamine

Several studies have shown that dopamine (DA) is involved in EAA. Our study showed that chlorpromazine (CPZ) (0.1 or 0.5 mg/kg, iv) attenuated EAA with elevations of DOPAC and HVA concentration in CSF. There was a positive correlation between the increases of DOPAC and HVA contents in CSF and the attenuation effect of CPZ on EAA. These results suggested that activation of dopamine system attenuate EAA (Dai and Xu 1991). We found that, L-tetrahydropalmatine (l-THP), a DA receptor antagonist can potentiate EAA in both laboratory research and clinical practice. SK&F-38393 and quinpirole, selective agonists of D1 or D2 receptors respectively were injected into nucleus accumbens of rats to investigate the roles of D1 and D2 receptors in the potentiation of EAA induced by l-THP. The injection of D1 agonist SK&F-38393 (5 μg SK&F-38393) attenuated EAA as well, while the injection of D2 agonist Qui (10 or 20 μg) had no effect on EAA and the potentiation of EAA induced by *l*-THP. By using dot blot technique, we observed that noxious electric stimulation was found to elevate the tyrosine hydroxylase (TH) mRNA level in substantia nigra and hypothalamus, while EA attenuated the effect of noxious stimulation on TH mRNA. These results indicate that D1 but not D2 receptor in nucleas accumbens plays an important role in EAA. EA might regulate the biosynthesis of DA by altering the TH gene transcription (Wang et al. 1999b).

Gao et al (1998) investigated the role of D1 and D2 dopamine receptors in spinal dorsal horn in EAA. They found that intrathecal administration of D2 receptor agonist LY171555 or D1/D2 receptor agonist apomorphine had a potentiating effect on EAA. In contrast, D1 receptor agonist SKF38393 had no effect. Intrathecal D2 receptor antagonist sulpiride attenuated the effect of EA, suggesting that D2 receptor is involved in EAA.

8.4 Neurochemical Basis of EA Analgesia on Chronic Pain

The using of modern scientific methodology demonstrated that a variety of neural and neurochemical mechanisms are involved in the acupuncture analgesia, particular emphasis on the endogenous opioid system. However, there are distinct differences between acute and chronic pain. In contrast to the transient pain studied using uninjured animal models, persistent chronic pain is associated with long lasting alterations of the nervous system including the hypersensitivity of peripheral nociceptive receptors and the increases of the hyperexcitability of the central nervous system (e.g. spinal dorsal horn neurons) in relation to the transmission and modulation of noxious messages. Moreover, chronic pain is more clinically relevant, as acupuncture treatment is often used to relieve ongoing chronic pain, it is worthwhile to investigate the mechanisms underlying the anti-hyperalgesic and antiallodynic effects of EA under pathophysiological conditions.

8.4.1 EOPs

The effects of opioids in animal models of inflammatory pain and neuropathic pain have been studied in great detail. Inflammation in the periphery influences the central sites and changes the opioid action. Inflammation increased while peripheral neuropathy decreased spinal potency of various opioid receptor agonists. In general, the antinociceptive potency of opioids is greater against various noxious stimuli in animals with peripheral inflammation than in control animals. In contrast, the antinociceptive potency of opioids is attenuated against various noxious stimuli in animals with peripheral neuropathy (Przewlocki and Przewlocki 2001).

Our study showed that the serum levels of opioid peptides in patients with chronic pain were lower than those in healthy pain-free subjects (Liu et al. 1984). EA raised the level of opioid peptides towards normal in patients expressing good acupuncture effects but not in those with poor effects Moreover, the antiallodynic effect on neuropathic pain of EA can be blocked by pretreatment with naloxone indicating that EAA on chronic pain can also be mediated by endogenous opioid systems (Huang et al. 2004a). Further study on rat neuropathic pain model demonstrated intrathecal h-FNA or naltrinodole significantly blocked 2 Hz EA effects suggesting the involvement of μ and δ opioid receptors in the spinal cord (Kim et al. 2004). Pretreatment with Derm-sap, a selective toxin for neurons that contain μ opioid receptors, specifically decreases μ opioid receptors and blocks EA anti-hyperalgesia, indicating that spinal μ opioid receptor-containing neurons are involved in the processes by which EA produces anti-hyperalgesia in inflammatory pain (Zhang et al. 2004a, 2005b).

It has also been reported that EAA in uninjured animals is mediated by μ and δ opioid receptors at 2 – 15 Hz and by κ opioid receptor at 100 Hz. Zhang et al (2004b) demonstrated that the mechanisms of EA anti-hyperalgesia was different under conditions of persistent pain since they found that both 10 and 100 Hz EA-produced anti-hyperalgesia were blocked spinally by μ and δ but not κ receptor antagonists in a rat model of inflammatory pain induced by subcutaneous injection of CFA into the hind paws of rats.

Several studies have demonstrated profound alterations in the spinal dynorphin system when there is peripheral inflammation or chronic arthritis. Endogenous dynorphin biosynthesis also increases under various conditions associated with neuropathic pain following damage to the spinal cord and injury of peripheral nerves. EA inhibited the up-regulation of preprodynorphin mRNA and dynorphin compared to sham control. Intrathecal injection of antiserum against dynorphin A (1 – 17) also significantly inhibited the cancer-induced hyperalgesia. These results suggest that EA alleviates bone cancer pain at least in part by suppressing dynorphin expression, and they support the clinical use of EA in the treatment of cancer pain (Zhang et al. 2008).

Intraplantar but not intraperitoneal injection of naloxone methiodide, a peripherally acting opioid receptor antagonist, eliminated the analgesic effect of EA treatment on CFA induced inflammatory pain. Intraplantar injection of an antibody against-endorphin and a corticotropin-releasing factor antagonist also produced a reduction in paw withdrawl latency in rats receiving EA, suggesting that peripheral opioids are also released by EA at the inflammatory site (Zhang et al. 2005a, b, c).

Both N/OFQ immunoreactivity and preproorphanin FQ (ppOFQ) mRNA expression could be observed in the brain regions involved in pain modulation, for instance, nucleus of raphe magnus (NRM), dorsal raphe nucleus (DRN), and ventrolateral periaqueductal gray (vlPAG). In the sciatic nerve CCI model, Ma et al (2004) investigated the changes of ppOFQ mRNA and N/OFQ immunoreactivity in NRM after EA by in situ hybridization and immunohistochemistry methods. Their study showed that expression of ppOFQ mRNA decreased and N/OFQ immunoreactivity increased after EA treatment in the neuropathic pain rats. These results indicated that EA modulated N/OFQ synthesis and N/OFQ peptide level in NRM of the neuropathic pain rats. The involvement of N/OFQ in EA-produced anti-hyperalgesia was also investigated in rats with peripheral inflammation induced by injecting CFA into one hind paw of rats. Intrathecal (i.t.) administration of N/OFQ (15 nmol) or EA at acupoints GB-30 and GB34 significantly attenuated hyperalgesia. The anti-nociceptive effect of N/OFQ or EA was significantly blocked by intrathecal injection of [Nphe 1]nociceptin(1 – 13)NH_2, a selective antagonist of the N/OFQ peptide receptor (NOP receptor), indicating the NOP-receptor-mediated mechanism. Additionally, the combination of N/OFQ injection with EA treatment could enhance anti-hyperalgesia compared to that produced by each component alone. These findings strongly suggested the involvement of the spinal N/OFQ-NOP system in EAA on peripheral inflammatory pain (Fu et al. 2006; Fig. 8.4).

8.4.2 Other Neuropeptides

Neurokinin-1 (NK-1)/substance P receptors play an important role in nociception and hyperalgesia at the spinal cord level. Persistent hind paw inflammation was shown to induce a significant increase of NK-1 receptor expression in the spinal dorsal horn and that this effect was significantly suppressed by EA. This suggests that EA-induced suppression of hyperalgesia is involved, at least partly, in the suppression of the spinal NK-1 receptors induced by sustained peripheral nociceptive input (Zhang et al. 2005a).

Attempts were also made to evaluate whether substance P (SP), cholecystokinin octopeptide (CCK-8), and met-enkephalin (MEK) are involved in the mechanism of the cumulative effect of repeated EA on experimental arthritis using neuropharmacological (receptor antagonists) and neurochemical (radioimmunoassay, RIA) approach. In arthritic rats there was also a change in the releasing rate of spinal SP, CCK-8, and MEK as compared to control rats. These plastic changes occurred under chronic pain condition and can be modulated by repeated acupoint stimulation which may explain the mechanisms of the cumulative effect of acupuncture on chronic pain (Luo 1996).

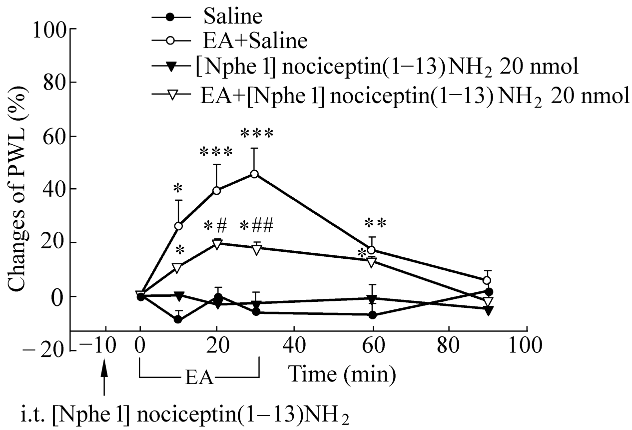

Figure 8.4 Effect of intrathecal injection of [Nphe 1]nociceptin(1 – 13)NH_2 on EA-induced increases in PWL to thermal stimulation in inflammatory rats. Rats received i.t. injection of 20 nmol of [Nphe1]nociceptin(1 – 13)NH_2 followed 10 min later by EA treatment ($n = 8$). Changes of PWL were presented as means ± SEM. Control (saline) and experimental ([Nphe1] nociceptin(1 – 13)NH_2, EA + saline and EA + [Nphe1]nociceptin (1 – 13)NH_2) groups were compared at the time points of 10, 20, 30, 60, and 90 min after EA treatment. As compared with EA + saline group, EA induced increases of PWLs were partly reversed by 20 nmol of [Nphe1]noci ceptin(1 – 13)NH_2. *$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. control (saline) group; #$p<0.05$, ##$p<0.01$, ###$p<0.001$ vs. EA + saline group (Fu et al. 2006).

8.4.3 Glutamate

Excitatory amino acids and the receptors are implicated in many actions in the central nervous system, and one of the more relevant is its role in excitotoxicity. Apart from this, it also has a role as pro-nociceptive agent. Excitatory amino acids, such as glutamate and aspartate, are richly contained in nociceptive primary afferent fiber terminals and NMDA, AMPA/KA and metabotropic receptors are distributed densely in the superficial dorsal horn of the spinal cord, where primary nociceptive afferents terminate. It is well-documented that glutamate and its receptor play a pivotal role in spinal transmission of nociceptive information and central sensitization. Increasing evidence suggests the involvement of NMDA and AMPA/KA receptors in acupuncture analgesia. In the spinal nerve ligation model, immunohistochemistry revealed that neuropathic pain induced increase of NMDA receptor subtype NR1 immunoreactivity in the spinal superficial laminae could be reversed by low-frequency EA in the rat. A combination of ketamine, a NMDA receptor antagonist, with EA produced more potent anti-allodynic effect than that induced by EA alone. EA and NMDA or AMPA/KA receptor antagonists have a synergetic anti-nociceptive action against inflammatory pain (Zhang et al. 2002; Zhang et al. 2005c). In the c-Fos expression study, when a combination of EA with AP5 or DNQX was used, the level of c-Fos expression in the spinal cord induced by carrageenan was significantly lower than EA or i.t. injection of AP5 or DNQX alone (Zhang et al. 2002; Fig. 8.5).

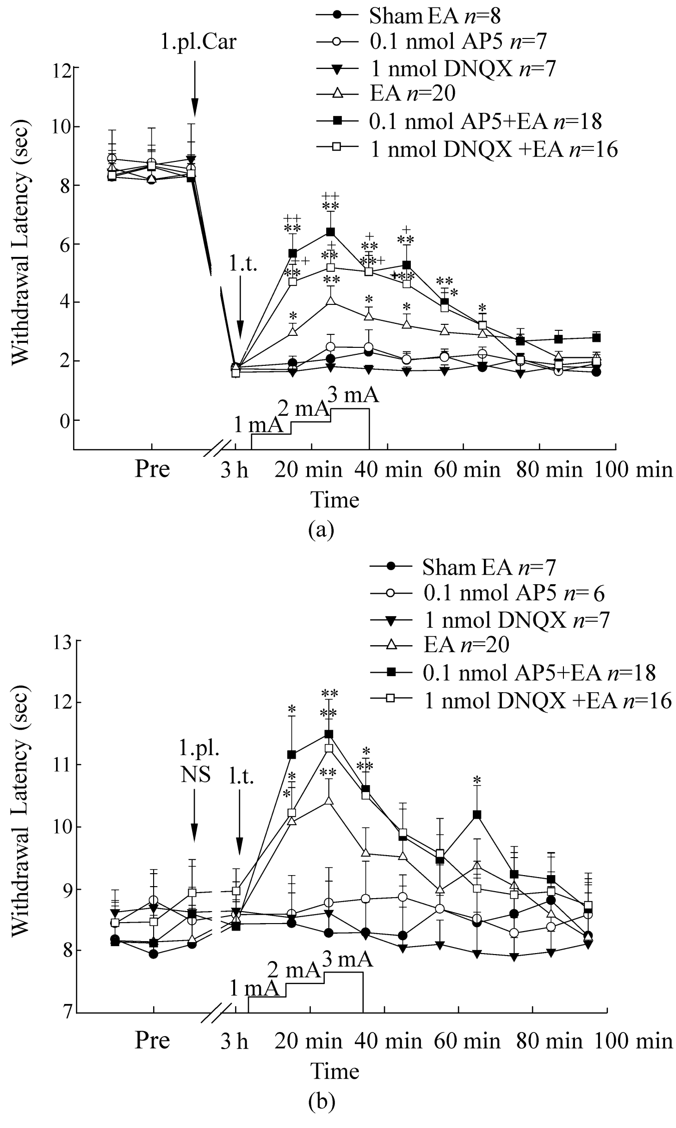

Figure 8.5 Effects of i.t. injection of 0.1 nmol AP5 and 1 nmol DNQX on EA-induced analgesia in carrageenan-injected rats (a) and normal saline (NS)-injected rats (b). *p<0.05 and **p<0.01 indicate significant differences from sham EA; +p<0.05 and ++p<0.01 indicate significant differences from EA (Zhang et al. 2002). Note that both 0.1 nmol AP5 and 1 nmol DNQX enhanced the anti hyperalgesic effect of EA in carrageenan injected rats.

On a CFA model, repeated bilateral EA stimulation at 2, 15 and 120 Hz was applied at those acupoints corresponding to Zusanli (ST-36) and Sanyinjiao (SP-6). 30 days after the CFA injection, the number of c-Fos-like immunostained cells was decreased significantly in the superficial laminae of the dorsal horn by 2Hz EA, but CGRP expression also showed a marked decrease in the same region using the other types of EA stimulation. NMDA receptor subunit NR-1 and NR-2A expression was attenuated in all regions of the dorsal horn by all types of EA indicating that EA treatment can attenuate inflammatory edema and mechanical thresholds in CFA-injected rats through modulating the expression of ionotropic glutamate receptors, and especially N-methyl-D-aspartate receptors, in the dorsal horn of the spinal cord (Choi et al. 2005a).

NMDA receptor of the central terminals of the dorsal root ganglion (DRG) appears to play an important role in the development of central sensitization related to persistent inflammatory pain. The increase of the expression of NMDA receptor in DRG can be blunted by chronic EA treatment on the ipsilateral GB 30 and Yanglingquan (GB-34) once a day from the first day post-injection of CFA in rats, suggesting that EA affects the progress of experimental inflammatory pain by modulating the expression of NMDA receptors in primary sensory neurons, in particular, IB4-positive small neurons (Wang et al. 2006).

However, how EA at different frequencies produces distinct analgesic effects on neuropathic pain is unclear. Neuronal plastic changes in spinal cord might contribute to the development and maintenance of neuropathic pain. Xing et al (2007) investigated the changes of spinal synaptic plasticity in the development of neuropathic pain and its modulation by EA in rats with neuropathic pain. Field potentials of spinal dorsal horn neurons were recorded extracellularly in sham-operated rats and in rats with SNL. We found for the first time that the threshold for inducing long-term potentiation (LTP) of C-fiber-evoked potentials in dorsal horn was significantly lower in SNL rats than that in sham-operated rats. The threshold for evoking the C-fiber-evoked field potentials was also significantly lower, and the amplitude of the field potentials was higher in SNL rats as compared with those in the control rats. EA at low frequency of 2 Hz applied on acupoints ST 36 and SP 6, which was effective in treatment of neuropathic pain, induced long-term depression (LTD) of the C-fiber-evoked potentials in SNL rats. This effect could be blocked by NMDA receptor antagonist MK-801 and by opioid receptor antagonist naloxone. In contrast, EA at high frequency of 100 Hz, which was not effective in treatment of neuropathic pain, induced LTP in SNL rats but LTD in sham-operated rats. Unlike the 2 Hz EA-induced LTD in SNL rats, the 100 Hz EA-induced LTD in sham-operated rats was dependent on the endogenous GABAergic and serotonergic inhibitory system. Results from our present study suggest that (1) hyperexcitability in the spinal nociceptive synaptic transmission may occur after nerve injury, which may contribute to the development of neuropathic pain; (2) EA at low or high frequency has a different effect on modulating spinal synaptic plasticities in rats with neuropathic pain. The different modulation on spinal LTD or LTP by low- or high-frequency EA may be a potential mechanism of different analgesic effects of EA on neuropathic pain. LTD of synaptic strength in the spinal dorsal horn in SNL rats may contribute to the long-lasting analgesic effects of EA at 2 Hz (Xing et al. 2007).

Ketamine, another NMDA receptor antagonist, can enhance the anti-allodynic effects induced by 2 Hz EA in a rat model of neuropathic pain following SNL. The anti-allodynic effect of EA combined with ketamine could be reversed by i.p. injection of naloxone (2.0 mg/kg), suggesting that ketamine potentiate the anti-allodynic effect of EA in rats with spinal nerve ligation, and endogenous opioid system is likely to be involved in this process (Huang et al. 2004b).

8.4.4 Serotonin

In the rat model of collagen-induced arthritis (CIA), Baek et al investigated the analgesic effect and its cholinergic and serotonergic mechanism of EA in the CIA rat model. To induce CIA, male Sprague-Dawley rats were immunized with bovine type II collagen emulsified in Freund's incomplete adjuvant, followed by a booster injection 14 days later. The analgesic effect was evaluated by tail flick latency (TFL). After induction of arthritis, the inflammatory pain threshold decreased as time passed and there was no big change of the pain threshold after 3 weeks. Three weeks after the first immunization, low frequency EA stimulation (2 Hz, 0.07 mA, 0.3 ms) delivered to ST-36 for 30 min showed the analgesic effect. Also, the analgesic effect of EA was blocked by pretreatment with atropine (muscarinic cholinergic receptor antagonist, 1 mg/kg i.p.), spiroxatrine (5-HT_{1A} receptor antagonist, 1 mg/kg i.p.), and ondansetron (5-HT_3 receptor antagonist, 0.5 mg/kg i.p.), but not by pretreatment with ketanserin (5-HT_2 receptor antagonist, 1 mg/kg i.p.). These results suggest that low frequency EA can relieve inflammatory pain in CIA and the analgesic effect of EA can be mediated by muscarinic cholinergic receptor, 5-HT_{1A} and 5-HT_3 receptors, but not by 5-HT_2 receptor (Baek et al. 2005).

Intracerebroventricular administration of 5-HT exhibited an analgesic effect, which partially mimicked the analgesic actions of EA. The anti-nociception of EA at different frequencies was attenuated after reduced biosynthesis of serotonin by the administration of the tryptophan hydroxylase inhibitor, P-chlorophenylalanine. The 5-HT_{1A} and 5-HT_3 receptor antagonists, pindobind-5-HT_{1A} and LY-278584, respectively, blocked EAA, but the anti-nociceptive effect of 100 Hz EA was potentiated by the 5-HT_2 receptor antagonist, ketanserin. These observations suggest that 5-HT_{1A} and 5-HT_3 receptors partially mediate the analgesic effects of EA, but that the 5-HT_2 receptor is conversely involved in the nociceptive response

(Chang et al. 2004).

Yonehara studied the effect of NAN-190 ($5\text{-}HT_{1A}$ antagonist), ketanserin ($5\text{-}HT_2$ antagonist) and ICS 205-930 ($5\text{-}HT_3$ antagonist) on tooth pulp stimulation (TPS)-induced 5-HT release and substance P (SP) release in the superficial layers of the trigeminal nucleus caudalis (SpVc-Ⅰ, Ⅱ) in the presence or absence of EA. TPS slightly increased 5-HT release and significantly increased SP release. In combination with EA, TPS-induced 5-HT release was remarkably enhanced, whereas SP release was significantly suppressed. Pretreatment with NAN-190 (3.5 mg/kg, i.v.) significantly enhanced the increase in TPS-induced 5-HT release in the presence of EA. On the other hand, the increase of 5-HT release induced following TPS in the presence of EA was inhibited by pretreatment with ketanserin (2.5 mg/kg, i.v.) and ICS 205 – 930 (1 mg/kg, i.v.). When NAN-190 was pre-treated in the animals combined TPS and EA, the amount of SP release was significantly reduced compared with the absence of this drug. On the other hand, pretreatment with ketanserin and ICS 205 – 930 reversed the inhibitory effect of EA on the TPS-generated SP release, especially ICS 205 – 930, which remarkably enhanced TPS-induced SP release compared with the absence of this drug. On the basis of the obtained results, we concluded that NAN-190 and ICS 205 – 930 act on EA-induced analgesia positively and suppressively, respectively, by regulation of TPS-generated SP release through activation of their subtype receptors. On the other hand, ketanserin does not affect TPS-induced 5-HT release and SP release in the presence of EA (Yonehara 2001).

8.4.5 EAA and Neuroinflammation

Central neuroinflammation and neuroimmune activation may mediate central sensitization and the development of allodynia and hyperalgesia. In the spinal cord, immune-like glia (microglia and astrocytes) are attractive candidates as mediators of central sensitization. Robust glial activation has been observed on the lumbar spinal cord in various rodent models of chronic pain, including spinal nerve injury, peripheral inflammation (Raghavendra et al. 2004), nerve injury (Colburn et al. 1999; Milligan et al. 2003; Scholz et al. 2007) and bone cancer (Honore et al. 2000; Zhang et al. 2005). Following inflammation or injury, microglia and astrocytes become less ramified and begin to proliferate. Upon activation, microglia and astrocytes release a variety of algesic substances that enhance pain transmission, such as proinflammatory cytokines, ATP, nitric oxide (NO), prostaglandins (PGs) and excitatory amino acids. Blocking the activation of spinal cord glia with fluorocitrate (a glial metabolic inhibitor), propentofylline (a glial modulator) or minocycline (a microglia inhibitor) can block diverse exaggerated pain. Taken together, these data lead to the postulate that glial activation is necessary for induction of exaggerated pain (Watkins et al. 2001; Watkins and Maier 1999, 2003).

Whether EA might alter spinal chemistry by modulating glial function, thereby producing a higher efficient antinociceptive under pathological pain conditions, is an interesting question to be answered. Studies showed that intrathecal injection of fluorocitrate, a glial metabolic inhibitor significantly potentiated EAA in a rat model of monoarthritis induced by intra-articular injection of CFA (Sun et al. 2006). Repeated EA stimulation of ipsilateral Huantiao (GB-30) and Yanglingquan (GB-34) acupoints significantly suppressed CFA-induced nociceptive behavioral hypersensitivity and spinal microglial activation. Combination of EA with minocycline significantly enhanced the inhibitory effects of EA on allodynia and hyperalgesia. For the first time, these data provide direct evidence for the involvement of spinal microglial functional state in anti-nociception of EA (Sun et al. 2008).

Cytokines especially proinflammatory cytokines (mainly including IL-1, IL-6 and TNFα) have been strongly implicated in the generation of pathological pain states at both peripheral and central nervous system sites (Dinarello 1999). A massive upregulation of IL-1 (more than 10,000-fold) occurs in the inflamed paw soon after CFA administration and lasts for several days. IL-1 is also increased 50 and 20-fold in the CSF 2 and 4 h after inflammation, respectively, which precedes the peak upregulation of Cox-2 mRNA. The type-Ⅰ IL-1b receptor is strongly expressed in the spinal cord, especially in laminae Ⅰ± Ⅲ of the dorsal horn, where Cox-2 is induced upon inflammation. A large intravenous dose of IL-1β (1 mg) upregulated spinal Cox-2 mRNA only fourfold, which is much less than peripheral inflammation (16 fold). A much greater effect (20- and 30-fold) was produced by intrathecal injection of lower IL-1β doses (5 and 50 ng, respectively). Intraspinal administration of an interleukin-converting enzyme or Cox-2 inhibitor decreases inflammation-induced central PGE2 levels and mechanical hyperalgesia, indicating that the major inducer of central Cox-2 upregulation is IL-1β in the CNS and thus, preventing central prostanoid production by inhibiting the IL-1β mediated induction of Cox-2 in neurons or by inhibiting central Cox-2 activity reduces centrally generated inflammatory pain hypersensitivity. Interestingly, Ji et al (2003) found that following carrageenan inflammation, the expression of IL-1RI mRNA in rat periaqueductal gray was significantly increased and EA could significantly inhibit the expression of IL-1RI mRNA. In rats inoculated with cancer cells into bone cavity, repeated EA stimulation inhibited the upregulation of IL-1β and its mRNA compared to the sham control indicating that EA alleviates bone cancer pain, at least in part by suppressing IL-1β expression (Zhang et al. 2007).

8.4.6 Neural Growth Factors and Neurotrophins

Neuroplasticity of the spinal cord following EA has been demonstrated although little is known about the possible underlying mechanism. Wang et al evaluated the effect of EA on expression of neurotrophins in the lamina II of the spinal cord, in cats subjected to dorsal rhizotomy. Cats received bilateral removal of L1-L5 and L7-S2 dorsal root ganglia (DRG, L6 DRG spared) and unilateral EA. They were sacrificed 7 days after surgery, and the L6 spinal segment removed and processed by immunohistochemistry and in situ hybridization histochemistry, to demonstrate the expression of neurotrophins. Significantly elevated numbers of Nerve Growth Factor (NGF) and neurotrophin-3 (NT-3) positive neurons, Brain-Derived Neurotrophic Factor (BDNF) immunoreactive varicosities and NT-3 positive neurons and glial cells were observed in lamina II on the acupunctured side, compared to the non-acupunctured, contralateral side. Greater number of neurons expressing NGF mRNA was also observed on the acupunctured side. No signal for mRNA to BDNF and NT-3 was detected. The above findings demonstrate that EA can increase the expression of endogenous NGF at both the mRNA and protein level, and BDNF and NT-3 at the protein level. It is postulated that EA may promote the plasticity of the spinal cord by inducing increased expression of neurotrophins (Wang et al. 2007).

Glial cell line-Derived Neurotrophic Factor (GDNF) was discovered as a potent neurotrophic factor for midbrain dopaminergic neurons by Lin et al (1993) and was shown to be a member of transforming growth factor- β (TGF-β) super-family. The biological action of GDNF is mediated by a two-component receptor complex consisting of a glycosylphosphatidylinositol-linked cell surface molecule, the GDNF family receptor GFRα-1 (originally named GDNFR-α), which acts as a ligand-binding domain and the receptor protein tyrosine kinase Ret, which acts as the signal transducing domain. GDNF is thought to bind preferentially to GFRα-1 and GDNF fails to exert its biological effect in the absence of GFRα-1. Besides its potent survival promoting effects on diverse groups of neurons, GDNF has been proved by previous studies to play an important role in modulation of nociceptive signals especially during neuropathic pain state (Bennett et al. 1998; Boucher et al. 2000; Hao et al. 2003; Wang et al. 2003; Dong et al. 2006a).

By using immunohistochemistry, Western blot, and RT-PCR analysis techniques, Dong et al. observed the effects of EA on the expression of GDNF and GFRα-1, the high-affinity receptor of GDNF in neuropathic pain rats. The results showed that both protein and mRNA levels of GDNF and GFRα-1 in the DRG, as well as GDNF protein in the spinal dorsal horn, were significantly increased after chronic constriction injury of the rats' sciatic nerve and could be further enhanced by EA treatment. These results demonstrated that EA could activate endogenous GDNF and GFRα-1 system of neuropathic pain rats and this might underlie the effectiveness of EA in the treatment of neuropathic pain (Dong et al. 2005). Their further study showed that intrathecal injection of antisense oligodeoxynucleotide (ODN) specifically against GFRα-1 significantly attenuated EAA on neuropathic pain in rats (Dong et al. 2006b) (Fig. 8.6).

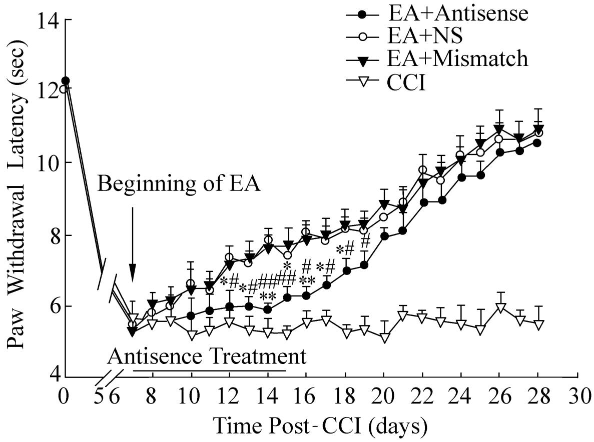

Figure 8.6 Effects of antisense ODN against GFR-1 on EA analgesia. Antisense ODN was delivered at a dose of 30 g per injection (once a day) for 8 days since the seventh day after CCI surgery. EA was administered once every other day from the seventh day after surgery until the end of the experiment. Values are mean ± S.E.M. (CCI group $n = 6$; the other three groups $n = 12$) *$p<0.05$, **$p<0.01$ vs. EA + NS group. #$p<0.05$, ##$p<0.01$ vs. EA + mismatch group (Dong et al. 2006b). Note that intrathecal injection of antisense oligodeoxynucleotide (ODN) specifically against GFRα 1 significantly attenuated EAA on neuropathic pain in rats.

8.5 Concluding Remarks

A large body of evidence demonstrates that the analgesic effect of EA on acute and chronic pain involves multiple neurotransmitter/neuromodulator systems such as EOPs, glutamate, glial cell line-derived neurotrophic factor, serotonin and their receptors. However, the mechanism underlying the cumulative effect of EA on chronic pain is poorly understood at present. Further investigation into the modulatory effect of EA on peripheral and central sensitization is essential in future acupuncture research.

On the other hand, given the complexity of chronic pain and acupuncture analgesia, many cellular factors and genes are possibly involved in the pathogenesis of chronic pain and the mechanism by which acupuncture exerts analgesic effect. The further use of genomic and proteomic approaches to study the acupuncture mechanism in different chronic pain models will identify key targets for it. To identify genes that might serve as either markers or explain these distinct biological functions, an attracting study by using cDNA microarray analysis was carried out to compare the expression of 8,400 genes among three sample groups. Sixty-eight genes were differentially expressed more than 2-fold in the neuropathic rat model when compared to the normal, and restored to the normal expression level after the repeated EA treatment. These genes including those coding opioid receptor sigma are involved in a number of biological processes, including the signal transduction, gene expression, and nociceptive pathways (Ko et al. 2002). The protein expression profile of the hypothalamus in both neuropathic pain and EA treatment models was analyzed using two-dimensional electrophoresis-based proteomics. Thirty-six proteins were found to be differentially expressed in the neuropathic pain model compared with normal rats and that restored to normal expression levels after EA treatment, most of which are involved in a number of biological processes, including inflammation, enzyme metabolism and signal transduction (Sung et al. 2004). Potential applications of these include the identification and characterization of signaling pathways involved in EA treatment and further exploration of the role of selected identified genes/proteins in the animal model.

Acknowledgements

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9 Acupuncture Therapy for Stroke

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Summary In this chapter, we shall review the clinic application of acupuncture treatment on stroke, and the mechanistic research on animal models of ischemic brain infarction. Acupuncture has been employed to treat patients with stroke in China as well as other oriental countries. Clinical data suggest that patients show better outcome and require less nursing and rehabilitation therapy after acupuncture treatment, although more studies with better control are needed to clarify the efficacy and optimal conditions of acupuncture for the treatment of ischemic brain injury. In contrast to clinical research, considerable experimental results have been obtained from bench work regarding the effect of acupuncture/electro-acupuncture on ischemic injury and the underlying mechanism. The data from our work and those from other researches suggest that acupuncture/electro-acupuncture greatly attenuate the ischemic infarction and neurological defects. Furthermore, we have recently defined the optimal conditions for maximal protection against ischemic injury in the experimental model of stroke. Appropriate stimulation of acupoints may increase the blood flow, upregulate the inherent neuroprotector activity, stabilize the ionic homeostasis, and balance the intracellular survival and death signals in the ischemic brain region. As there is no promising therapy for ischemia injury till date, acupuncture may be a useful option for the treatment of stroke. More research on acupuncture therapy for stroke may significantly improve the clinical outcome after ischemic injury and reduce the devastating effects on the individuals and their families.

Keywords *cerebral blood flow, hypoxia, middle cerebral artery occlusion, reperfusion, stroke*

9.1 Introduction

Stroke, a type of cerebrovascular accident (CVA), is the result of the lack or insufficient blood supply to the brain resulting from blood-vessel diseases. There are basically two primary types of stroke: occlusive and hemorrhagic. An occlusive stroke is typically caused by embolic, atherosclerotic, or thrombotic occlusion of the cerebral vessels. This is the most common type of stroke at the bedside, comprising approximately 88% of all the patients with stroke. Blood-flow restriction induced by vascular occlusion produces neurological deficits and loss of neurological functions controlled by the affected area. On the other hand, epidural, subdural, and subarachnoid bleeding can cause hemorrhagic stroke. This type of stroke also results from insufficient blood supply to specific brain region. Temporary ischemia may have little or no pathological evidence of tissue damage with no appreciable clinical symptoms, but prolonged ischemia may induce death of the neurons and ultimately, tissue infarction. When brain injury occurs owing to lack of blood flow, the specific neurological functions controlled by the affected brain region are damaged or even lost, and the resulting neurological disabilities are dependent on the ischemic region and severity of infarction (Kandel et al. 2000).

Both the types of stroke may occur at any age owing to various reasons, and several risk factors have been identified to increase stroke occurrence. One of the most critical risk factors is high blood pressure. Nicotine and carbon monoxide in tobacco smoke greatly increase the stroke risk by reducing the amount of blood oxygen and damaging the walls of the blood vessels, thus, increasing the possibility of clot formation. Furthermore, carotid or other artery diseases may also raise the risks of stroke.

Among the most frequent and serious neurological disorders, stroke is the third killer disease, ranking behind heart diseases and cancers, and is a leading cause of severe, long-term disability in the world. Each year, approximately more than 2 million people die of stroke (in Asia), and more than 1.2 million people may experience a new or recurrent stroke (in China). Survivors of stroke often are beset by serious long-term disabilities, including paralysis and disruption of higher cognitive functions, such as speech and memory. Among the survivors of ischemic stroke, one-sided paralysis, inability to walk without some assistance, aphasia (trouble in speaking or understanding the speech of others), and dependent activities of daily living (grooming, eating, bating, etc.) are the most frequently observed disabilities within 6 months after the onset of stroke. Some of the patients may even have mental disorders such as depressive symptoms. Individuals with such disabilities often require extensive long-term care by health care professionals and family. In 2008, the estimated direct and indirect cost of stroke was about $65.5 billion in the US.

When the neurons are affected owing to ischemia or hypoxia, the ischemic cascade chain-reaction sets off (Fig. 9.1). Following limited oxygen and nutrients supplementation, harmful cellular and molecular events, including excitotoxicity, inflammation, and programmed cell death occur and spread from the ischemic core to the penumbra area. Although damages to the neurons in the ischemic core are usually severe and mostly result in their death after the ischemia onset, the penumbra neurons can still be saved and functionally recovered by employing rapid interventional treatment. The "time window" for the interventional treatment is usually about 6 h, and during the period of acute ischemia, reestablishment of the blood flow and administration of neuroprotective agents can result in better recovery of the patients. However, beyond this window, treatments may have little efficacy and may even potentially cause further damage.

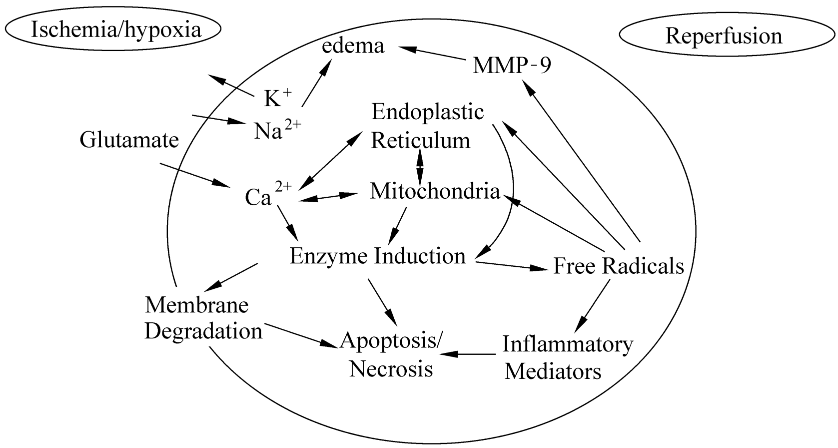

Figure 9.1 Injury cascade that leads to cell death after ischemia/reperfusion.

Based on the ischemic cascade, therapeutic strategies have been designed to minimize the potentially devastating effects of stroke. Currently, the best available strategy is the restoration of blood supply with drugs within the 6-h "time window". The use of aspirin and thrombolytic agents including urokinase, streptokinase, and recombinant tissue plasminogen activator (rt-PA), are recommended in patients who had a stroke attack, within 6 h after the onset of stroke. Although excessive accumulation of extracellular excitatory amino acids and overload of intracellular calcium have been identified as one of the cellular and molecular mechanisms underlying ischemic injury, the antagonists of excitatory amino acids (e.g., MK-801 and dextrorphan) and calcium channels, such as nimodipine, are observed to have little clinical efficacy (Ahmed et al. 2000) in spite of their significant protection in animal models (Roda et al. 1995). The antagonist of sodium channel, lubeluzole, has been observed to inhibit the glutamate release and the activity of nitric oxide synthase (NOS) in post-synapse. It has been reported that lubeluzole is currently in the third phase of clinical trial. Other possible neuroprotective agents include free-radical scavengers such as tirilazad, anti-inflammation drugs such as IL-1 receptor antibody, etc. However, comprehensive and sophisticated research on all these agents is still required to evaluate their efficacy and side effects in patients. With regard to patients with chronic stroke, increasing attention has been paid to enhance their ability to promote self-repair and survival of the injured cells, and neurotrophic and growth factors have been observed to be the potential candidates for this strategy. In animal studies, brain-derived neurotrophic factor (BDNF) and basic fibroblast growth factor (bFGF), when administered exogenously, were observed to produce neuroprotection against ischemia (Schabitz et al. 2000; Jiang et al. 1996; Sugimori et al. 2001). Currently, bFGF is considered as a possible agent to treat stroke. Another strategy is focused on the application of neural stem cells (NSC). Numerous studies on different cerebral ischemia models have demonstrated the regeneration of NSC in the subventricular zone (SVZ) and subgranular zone (SGZ) of dentate, as well as the specific movement of the newborn cells from these regions to the injury areas after ischemia. These studies form the basis for the development of a new method for the treatment of stroke. However, there is a long way to go, because all these therapeutic potentials are at the initial stage toward the actual practice at the bedside.

Clearly, no clinical modality has demonstrated promising efficacy in terms of stroke treatment, and there exists a long gap between the current treatments and our expectation. Hence, new strategies should be developed to establish better prevention measure or therapy against this serious disease.

9.2 Clinical Practice of Acupuncture on Stroke

Acupuncture is one of the main medical modalities in traditional Chinese medicine (TCM). The ancient Chinese Medicine believes in balance. Imbalance, for whatever reasons, is considered to cause disorders or diseases. Based on the theory of TCM, stroke is considered to be in the category of "*Yin* and *Yang*" imbalance and/or "*Qi* and *Blood*" imbalance, and acupuncture treatment is believed to restore the healthy balance by stimulating specific acupoints along the meridians.

The practice of acupuncture therapy for stroke has been reported several years ago in the Chinese history. According to the ancient literature, *Huang Di Nei Jing* (The Yellow Emperor's Inner Classic, a product of various unknown authors in the Warring States Period, 475 – 221 BC), the clinical practice of acupuncture on stroke can be traced back more than 3000 years ago. As recorded in *Huang Di Nei Jing Ling Shu Jing* (Miraculous Pivot), hemiplegia with no aphasia and consciousness could be treated by needling at some acupoints to rebalance the "insufficient" or "excessive", while syncope with trismus could be treated by puncturing at the meridian of *Shaoyin*. Another ancient literature, *Zhen Jiu Jia Yi*

Jing ("A Classic of Acupuncture and Moxibustion", written in the period of East Han Dynasty, approximately AD 259), states that hemiplegia with dark urine could be treated by puncturing mainly at Zhaohai (KI-6) with supplemental needling at *Yin Heel Vessel* (Yin HV) and the meridian of *Shaoyin*, whereas awry mouth and eyes as well as trismus could be treated by needling at acupoints Renzhong (GV-26) and Waiguan (TE-5), respectively. Since then, the acupuncture theory and therapy methods have been developed and advanced. Currently, acupuncture is widely used for the treatment of stroke in China and other oriental countries such as Japan and Korea, and is recommended by the World Health Organization (WHO) as one of the alternative and complementary strategies against stroke. The National Institute of Health Consensus Development Conference on Acupuncture concluded that "acupuncture might serve as a useful adjunct or alternative treatment for stroke rehabilitation" (NIH Consensus Development Panel on Acupuncture 1982).

9.2.1 Clinical Acupuncture and Commonly Used Acupoints in Stroke Treatment

In the acupuncture treatment, there are several ways to deliver stimulation at acupoints. The traditional way is to insert fine needles at acupoints and manipulate them manually. Alternatively, the acupoints can be stimulated by electrodes conducting the electrical currents through the needles (electroacupuncture (EA)). Currently, in the hospitals of China, acupoints are also stimulated by drug injection into the acupoints or thread imbedding at the acupoints. Furthermore, some people even use magnetic beads stimulation at the acupoints (Fan et al. 2001).

Stroke is described using two symptoms based on TCM theory. Symptom 1 (apoplexy involving meridians and collaterals) is a mild form of apoplexy with paralysis of face and limbs, and dysphasia with no impairment of consciousness. On the other hand, Symptom 2 (apoplexy involving *zang*-organs and *fu*-organs) is a serious form of apoplexy with sudden loss of consciousness, aphasia, paralysis of lips with salivation, hemiplegia, distortion of the face, and dysphasia. According to *Huang Di Nei Jing*, different stroke symptoms should be treated with different acupoints. The commonly used acupoints for treating Symptom 1 are mainly from the meridians of *Yangming*, *Taiyang*, *Shaoyang,* and *Du channel* (*Governor Vessel)*, comprising the acupoints Baihui (GV-20), Fengfu (GV-16), Tianchuang (SI-16), Xiaguan (ST-7), Dicang (ST-4), Jiache (ST-6), Jianyu (LI-15), Quchi (LI-11), Hegu (LI-4), Huantiao (GB-30), Zusanli (ST-36), and Yanglingquan (SP-9). On the other hand, the acupoints used for treating Symptom 2 are mainly from the meridians of *Du channel* and *Ren Channel* (*Conception Vessel*), comprising the acupoints Renzhong (GV-26) and Guanyuan (CV-4). Apart from these acupoints, acupuncturists may sometimes add several specific supplementary acupoints during the treatment based on the individual and the disease. For example, Jianliao

(TE-14) and Houxi (SI-3) acupoints might be selected for patients with upper limbs disability, whereas Futu (ST-32) and Xuanzhong (GB-39) acupoints might be used for patients with lower limbs disability. On the other hand, for those with difficulties in speaking, Lianquan (CV-23) or Yamen (GV-15) acupoint could be employed (Wang 2002).

Several different approaches have been used to treat stroke: scalp acupuncture, eye acupuncture, and ear acupuncture are each advocated through numerous clinical trials in China. Traditional Chinese literature considers that the brain is the seat of mentality. Usually, head acupoints, such as Baihui (GV-20), Fengfu (GV-16), and Shenting (GV-24) are first selected for the treatment of hemiplegia or aphasis. In the 1970s, acupuncturists in China developed the method of scalp acupuncture, using the filiform needles to puncture the corresponding functional areas, such as contralateral motor area, sensory area, foot motor sensory area, or speech areas along the skin. Currently, scalp acupuncture is widely used for the treatment of stroke sequel, and some acupuncturists consider that it could induce better recovery than ear acupuncture or body acupuncture therapy (Lu 1991). Ear acupuncture therapy is often applied in combination with other acupuncture therapies, such as scalp acupuncture and body acupuncture. Some commonly used acupoints for stroke therapy in Chinese hospitals are listed in Table 9.1.

Table 9.1 Commonly used acupoints in stroke treatment

Meridians and Collaterals	Acupoints
Lung Meridian of Hand Taiyin (LU)	Shaoshang (LU 11), Yuji (LU 10), Taiyuan (LU 9), Lieque (LU 7), Chize (LU 5)
Large Intestine Meridian of Hand Yangming (LI)	Shangyang (LI 1), Sanjian (LI 3), Hegu (LI 4), Yangxi (LI 5), Shousanli (LI 10), Quchi (LI 11), Binao (LI 14), Futu (LI 18), Yingxiang (LI 20)
Stomach Meridian of Foot Yangming (ST)	Sibai (ST 2), Juliao (ST 3), Daying (ST 5), Jiache (ST 6), Dicang (ST 4), Renying (ST 9), Shuitu (ST 10), Quepen (ST 12), Biguan (ST 31), Futu (ST 32), Tiaokou (ST 38), Fenglong (ST 40), Jiexi (ST 41), Neiting (ST 44), Zusanli (ST 36)
Spleen Meridian of Foot Taiyin (SP)	Yinbai (SP 1), Taibai (SP 3), Gongsun (SP 4), Sanyinjiao (SP 6), Yinlingquan (SP 9), Xuehai (SP 10)
Heart Meridian of Hand Shaoyin (HT)	Jiquan (HT 1), Shaohai (HT 3), Tongli (HT 5), Shenmen (HT 7), Shaochong (HT 9)
Small Intestine Meridian of Hand Taiyang (SI)	Shaoze (SI 1), Houxi (SI 3), Wangu (SI 4), Jianzhen (SI 9)
Bladder Meridian of Foot Taiyang (BL)	Cuanzhu (BL 2), Wuchu (BL 5), Chengguang (BL 6), Tongtian (BL 7), Tianzhu (BL 10), Dazhu (BL 11), Xinshu (BL 15), Geshu (BL 17), Ganshu (BL 18), Pishu (BL 20), Shenshu (BL 23), Dachangshu (BL 25), Ciliao (BL 32), Chengfu (BL 36), Weizhong (BL 40), Chengshan (BL 57), Feiyang (BL 58), Kunlun (BL 60), Shenmai (BL 62), Zhiyin (BL 67)

(Continued)

Meridians and Collaterals	Acupoints
Kidney Meridian of Foot Shaoyin (KI)	Yongquan (KI 1), Taixi (KI 3), Zhaohai (KI 6)
Pericardium Meridian of Hand Jueyin (PC)	Quze (PC 3), Jianshi (PC 5), Neiguan (PC 6), Daling (PC 7), Laogong (PC 8), Zhongchong (PC 9)
Triple Energizer Meridian of Hand Shaoyang (TE)	Guanchong (TE 1), Yemen (TE 2), Zhongzhu (TE 3), Yangchi (TE 4), Waiguan (TE 5), Zhigou (TE 6), Huizong (TE 7), Jianliao (TE 14), Yifeng (TE 17), Sizhukong (TE 23)
Gallbladder Meridian of Foot Shaoyang (GB)	Tinghui (GB 2), Yangbai (GB 14), Fengchi (GB 20), Qubing (GB 7), Huantiao (GB 30), Fengshi (GB 31), Yanglingquan (GB 34), Yangjiao (GB 35), Yangfu (GB 38), Xuanzhong (GB 39), Qiuxu (GB 40)
Liver Meridian of Foot Jueyin (LR)	Dadun (LR 1), Xingjian (LR 2), Taichong (LR 3), Xiguan (LR 7), Ququan (LR 8)
Du Channel (Governor Vessel, GV)	Yaoshu (GV 2), Yaoyangguan (GV 3), Mingmen (GV 4), Shenzhu (GV 12), Dazhui (GV 14, Yamen (GV 15), Fengfu (GV 16), Shangxing (GV 23), Renzhong (GV 26), Baihui (GV 20)
Ren Channel (Conception Vessel, CV)	Zhongji (CV 3), Guanyuan (CV 4), Qihai (CV 6), Shenque (CV 8), Tanzhong (CV 17), Tiantu (CV 22), Lianquan (CV 23), Chengjiang (CV 24)
Extra points	Yintang (EX HN 3), Shixuan (EX HN 11), Jinjin (EX HN 12), Yuye (EX HN 13), Jiaji (EX B 2)
Scalp acupoints	Contralateral motor area, sensory area, foot motor sensory area, or speech areas

Cited and modified from the work of Fan et al (2001).

9.2.2 Efficacy of Acupuncture on Stroke

Acupuncture is a relatively safe and convenient therapy with minimal discomfort. However, does acupuncture really benefit patients with stroke? Although scientific studies on acupuncture therapy have been performed since the last 50 years, there has been no satisfactory report on this issue so far. However, several clinic studies, especially those published in China, Japan, and Korea, have proved the efficacy of acupuncture. Some of these trials (but not all) suggest that acupuncture has a positive effect on recovery after stroke. These studies demonstrated that after acupuncture therapy, the patients showed better recovery and less infarction, with the beneficial effects on motor function, reduction of spasticity, and improvement in post-stroke depression (Fan et al. 2001; Johansson et al. 1993; Naeser et al. 1994; Hu et al. 1993; Wong et al. 1999; Bao 2003; Moon et al. 2003; Liu et al. 2008). In China, lots of clinical reports on acupuncture therapy for the treatment stroke have been published in Chinese journals during the last decade (Si et al. 1998; Xiang et al. 2001). Despite the different acupoints and acupuncture therapies, most of these reports show that acupuncture is beneficial. Furthermore, some acupuncturists (Shi 2000) achieved better efficacy than others, as documented in a large database. In some reports (Liu et al. 1999; Li 1996), the efficacy was also evaluated using some generally accepted index, such as Barthel's Index (measures of disability/activities of daily living ADL) and Stroke Impairment Assessment Set (SIAS), thus, making the results more convincing. However, most of these reports are similar to simple case summaries, with no strict patient-selection criteria. In addition, these reports lack either convincible control or universally accepted criterion for the evaluation of efficacy. Hence, their results could not be appreciated by the general medical community.

In some studies published in English, stroke patients under acupuncture treatment showed less ankle spasticity and better gait-cycle parameters (Chen et al. 1990; Moon et al. 2003). Naeser et al (1992) compared the real acupuncture with sham acupuncture, and observed that real acupuncture is more beneficial to patients whose lesion area covers less than half of the involved motor pathway, than the sham acupuncture. Wong et al (1999) compared the electrical stimulation at acupoints with standard rehabilitation treatment. Their results showed that patients treated with EA had shorter durations of hospital stay and better recovery of neurological and functional outcomes. In a 10-week EA-treated and 12-month follow-up trial, Johansson et al (1993) evaluated the motor function, balance ability, and ADL (Barthel's Index) of patients with stroke before and after acupuncture treatment. Their results demonstrated that patients under acupuncture along with standard treatment showed faster recovery, not only in the balance and mobility, but also in the quality of life, than those under standard medication only.

However, there have also been contradictory reports demonstrating no beneficial of EA on the functional outcome or quality of life (Gosman-Hedstrom et al. 1998; Johansson et al. 2001; Sze et al. 2002a, 2002b; Hopwood et al. 2008). For example, in a clinical trial (Gosman-Hedstrom et al. 1998) that evaluated the efficacy of acupuncture on patients with acute stroke, the patients were provided with either EA, superficial sham acupuncture, or no acupuncture treatment. Furthermore, no significant differences were observed between the groups in both the neurological scores and the daily living index scores after a 1-year follow-up. Johansson et al (2001) compared the efficacy of EA with that of high-intensity, low-frequency transcutaneous electrical nerve stimulation (TENS) and low-intensity (subliminal) high-frequency electrostimulation, in a double-blinded trial on 150 stroke patients. They selected patients with 5 – 10 days of stroke attack and delivered the treatments 30 min twice a week during the following 10-week period. At 3-month and 1-year follow-ups, they observed no statistically significant differences between the groups in either the measures of the functional outcome or the quality of life. In another trial (Sze et al. 2002a) designed to examine whether traditional acupuncture produced more benefits than standard rehabilitation medication in patients with moderate or severe functional impairment, the researchers found no statistically significant differences in the motor recovery, functional disability, cognitive disability, and neurological impairment between the intervention group receiving acupuncture treatment along with traditional care and the control group with traditional care alone.

Several reviews have covered these inconsistent results from different studies (Naeser, 1997; Park et al. 2001; Sze et al. 2002b). Shortly after acupuncture became one of the complementary therapies in the West, Naeser (1997) reviewed ten studies on the effect of acupuncture on paralysis resulting from stroke, and presumed that despite the different designs and qualities of these studies, acupuncture in addition to the standard treatment is always better than the standard treatment alone, thus, indicating that acupuncture is to some extent more beneficial than placebo in stroke therapy. Park et al (2001) carried out a systematic review on nine randomized controlled trials selected from four independent computerized literature searches (MEDLINE, Cochrane Controlled Trials Register, EMbase, and CISCOM databases). Of the nine trials, six showed positive results and three demonstrated negative results, and only two studies obtained a Jadad score of >3. Owing to the lack of sufficient sample size, subject blinding, and sham-acupuncture control, the reviewers concluded that there is no compelling evidence to show that acupuncture is effective in stroke rehabilitation. Furthermore, regardless of their conclusion, their search in the Chinese literature was not exhaustive, and several randomized controlled trials were not covered. In addition, another larger meta-analysis was conducted by Sze et al (2002b), who analyzed 14 randomized controlled trials that compared the acupuncture treatment with no acupuncture treatment within 6 months after stroke. The total sample comprised 1213 patients within the trials selected from the databases including MEDLINE, CINAHL, EMBASE, Cochrane Library, and Chinese medical literature databases. Their data analysis also failed to provide strong support on the efficacy of acupuncture on motor recovery; however, a small positive effect on disability was observed. The reviewers believed that this positive effect of acupuncture “may be due to a true placebo effect and varied study quality”.

These reviews of the currently available randomized controlled trials indicate that the evidence to support the application of acupuncture in stroke rehabilitation is not sufficient, and this may be owing to several reasons. The first and most important reason is that the sample size of patients in these reviews is not large enough. As most of the trials have been published in Chinese language literature, they could not be accessed by the Western reviewers unless they are published in the English journals. In addition, most of the studies have been poorly designed, with insufficient control group or blinding. Several studies even failed to follow strict inclusion criteria, and as a result, the patients included varied with a wide array of severity of residual deficits and a large range of intervals since the onset of stroke. Hence, reviewers would certainly abandon these articles, because they do not necessarily meet the research criteria for contemporary medicine. Second, appropriate acupuncture condition (e.g., acupoint selection, stimulation intensity and frequency, intervention time point of acupuncture therapy, etc.) may play a critical role in acupuncture efficacy. Indeed, our recent studies demonstrated that EA-induced protection from ischemic injury is acupoint-specific and largely dependent on the stimulation parameters (Zhou et al. 2007b, 2007c). As earlier clinical studies employed various approaches with different acupoints, controversies in the literature are inevitable. Third, different statistical techniques might result in different opinions. In a clinic trial, Johansson et al (2001) concluded that acupuncture had no effect on the functional improvement in stroke. However, when Shiflett et al (2001) reinspected the data using an admittedly subjective criterion of clinical importance, they observed that the data indicated the possible benefit of acupuncture in restoring the function of subacute stroke patients, and assumed that the negative results may be owing to the less-than-optimal choice of statistical techniques. However, it appears that the scientific support for acupuncture therapy in stroke is still limited, and the effectiveness of acupuncture therapy in stroke must be proved with more strict and scientific research design and analysis. A multiple-center study with strict control and careful consideration of therapeutic criteria is critical for the clinical research on EA application for stroke.

9.2.3 Various Factors That Affect the Efficacy of Acupuncture

In TCM, there are no standard procedures of acupuncture treatment for patients with stroke. Acupuncture/EA therapy is used in different ways by different acupuncturists, with major differences in the acupoint selection, stimulation intensity and frequency, intervention time point, etc. Recently, some studies investigated the factors that could affect the efficacy of acupuncture.

Intervention time point of acupuncture

When is the best time for the stroke patients to receive acupuncture therapy? Most (but not all) of the acupuncturists in China believe that if the acupuncture is administered earlier, then the efficacy of the treatment for ischemic stroke would be better (Chen et al. 1990; Fan et al. 2001). It has been observed that acupuncture delivered during the early period of stroke may produce better outcome than that administered during the period of sequel, which has also been documented by our studies on experimental stroke (see later section).

Interval and frequency of acupuncture

Generally, acupuncture therapy is administered to the patients once a day, according to the TCM practice. However, other treatment intervals, for example, once every other day, once a week, or twice a week, are also popular in some oriental countries. Till date，very few studies have focused on the relationships between the different intervals or frequencies of acupuncture delivery and their efficacy (Bao et al. 1992; Xing et al. 1994). These studies have indicated that insufficient acupuncture stimulation might produce weaker efficacy than that with more stimulation.

Acupuncture combined with other therapies

In stroke treatment, traditional Chinese doctors commonly administer acupuncture therapy along with Chinese herb medicine or standard clinic drugs. In fact, most of the trials discussed earlier in this chapter belong to this type of treatment. Other combinations include exercise, massage at acupoints, cupping therapy, ear acupuncture, *qigong,* and psychology therapy. These combination therapies are observed to be superior to acupuncture alone.

Individual condition of patients

The outcome of acupuncture therapy is more or less dependent on the individual patients. With different age, lesion site, and degree of injury, even the identical acupuncture approach may produce different outcomes. It has been reported that acupuncture is more effective in patients with slight or moderate stroke than those with severe stroke (Fan et al. 2001).

Taken together, most clinical data indicate that acupuncture might be a potentially useful therapeutic treatment for stroke, although more scientific studies are needed to substantiate this notion. On the other hand, there is no doubt that acupuncture treatment is, to some extent, more convenient and inexpensive than standard strategies/medications. Hence, further investigation on the clinical efficacy and optimal conditions for acupuncture therapy might produce a significant impact on the clinical therapy for stroke. Owing to the difficulty and limitations in human research, experimental studies on efficacy, optimal condition, and the underlying mechanisms of acupuncture therapy for stroke are invaluable.

9.3 Experimental Study of Acupuncture-Induced Protection from Stroke

As acupuncture is considered to exert protection against stroke at the bedside, there should be some neurological bases underlying this process. Although the "black box" between acupuncture and neurological outcomes are not yet fully understood, recent works have drawn a sketch map of the mechanisms underlying acupuncture-induced brain protection from stroke.

9.3.1 Animal Models

Acupuncture induces a complex and integrative effect on the brain. However, we could barely understand its mechanisms through the ancient Chinese literature, as the record is much more like a philosophic theory owing to the lack of contemporary medical knowledge in the ancient system of TCM. Today, it is still extremely difficult, if not impossible, to explore the cellular and molecular mechanisms in stroke patients, because of the ethical issues and complexity of the clinical research. Hence, researchers could standardize the various factors, including acupuncture duration, manual or electrical stimulation, frequency and intensity parameters if using EA, and applying window, only in the animal models. More importantly, multiple experimental approaches can be adopted and repeated to dissect out a single delicate mechanism in the central nervous system.

Rat, mice, and gerbils are the most commonly used animals in the stroke models. However, some researchers also use monkey, dog, cat, and rabbit to establish the stroke models (Harrington et al. 1972; Cechetto 1993; Carmichael 2005). Currently, the most frequently used animal models are the focal brain ischemia and global brain ischemia models (Carmichael 2005). These two models can further be subdivided into transient and permanent ischemia according to whether reperfusion is allowed or not.

The model of middle cerebral artery occlusion (MCAO) can represent the clinical brain ischemia. In our work, a modified Longa Method (Longa et al. 1989) was used to produce regional ischemia in the territory of Middle Cerebral Artery (MCA), including frontal and parietal cortex (Fig. 9.2). In brief, ischemia is induced by a nylon suture insertion from the internal carotid artery to the beginning of the MCA. The advantage of this method is that reperfusion is achieved by slowly withdrawing the suture out of the cerebral artery. Another MCAO model has been developed by occluding the middle cerebral artery directly by clips, and reperfusion is produced by taking away the clip. This model has a higher stability of infarction degree than nylon suture insertion method. However, it has the disadvantage of major injury owing to an open-skull operation, which may affect the outcome of the research.

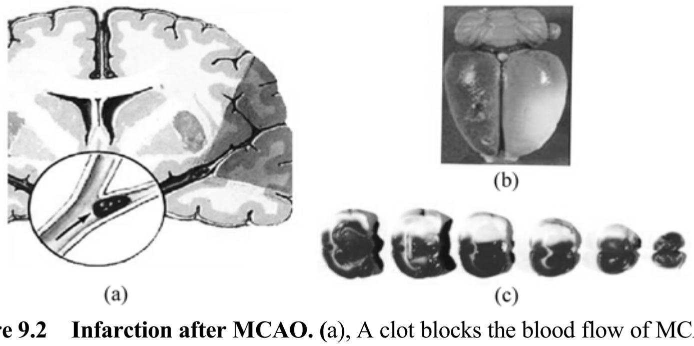

Figure 9.2 Infarction after MCAO. (a), A clot blocks the blood flow of MCA and induces infarction, which is represented by grey color. (b) and (c), Triphenyltetrazolium chloride (TTC) staining after transient MCAO and reperfusion. Infarction is represented by pale white color. (b) shows the whole brain tissue. (c) shows the coronal brain section.

In another type of model, permanent ischemia is induced by occluding the MCA permanently. A photochemical reaction is used to induce reproducible thrombosis leading to cerebral infarction (Waston et al. 1985). After intravenous injection of the photosensitizing dye, Rose Bengal, the skull is opened and the parietal cortex is illuminated by green light (560 nm) for 20 min. Thus, the ischemic lesion can be formed by thrombosis of the small blood vessels. Though relatively simple in terms of operation, the stability of this model is low, because the infarct volume greatly depends on the degree of coagulation of the dye. Gerbil is an ideal animal model. Direct occlusion of the bilateral common carotid arteries of the gerbil can induce global ischemia, and reperfusion can be achieved by loosening the aneurysm clips. Usually, 4-artery occlusion is employed in rats to achieve global ischemia, and the degree of infarct can be regulated in the global ischemia model by modulating the ischemic duration.

9.3.2 Anti-Ischemic Effect of Acupuncture in Animals

In China, studies on acupuncture mechanisms commenced from the mid-1970s. Researches were focused on the mechanisms of acupuncture analgesia, and obtained strong evidence on the fact that acupuncture could be explained on a physiological rather than metaphysical basis. Only at the end of the 1980s, research reports about the effect of acupuncture on stroke appeared in some Chinese journals. Since then, it has attracted more and more attention from both clinicians and scientists.

The administration of acupuncture on the stroke model is schematically shown in Fig. 9.3. Our studies demonstrated that EA at the head acupoints (*Du channel* acupoints) greatly reduced the ischemic infarction and decreased the brain swelling, when compared with ischemia alone or sham acupuncture-treated ischemia (Fig. 9.4). Crystal violet staining revealed that the ipsilateral neurons in the acupuncture-treated animals have almost normal shape and relatively lower level of cell loss (Ouyang et al. 1999). Similar results were also observed in the studies on MCAO monkey models (Gao et al. 2002). On this sub-human primate model, a characteristic deficit extremely similar to that of the patients with stroke was observed at 3 and 23 h post-reperfusion. The EA was applied at Renzhong (GV-26) and Baihui (GV-20) for 30 min right after the onset of ischemia. After the acupuncture treatment, a notably improved neurological deficit score and decreased infarction volume were observed at 23 h after reperfusion (Fig. 9.5).

Besides the application of acupuncture in acute stroke, some researchers also reported an acupuncture effect on the chronic ischemic models (Chen et al. 2000). During reperfusion, they administered “GV” meridian acupuncture daily (once a day) in the MCAO rats. Seven days after reperfusion, the infarct volume was observed to be much smaller than that of the rats exposed to acupuncture for only once during reperfusion. This implies that repeatedly delivered acupuncture induces

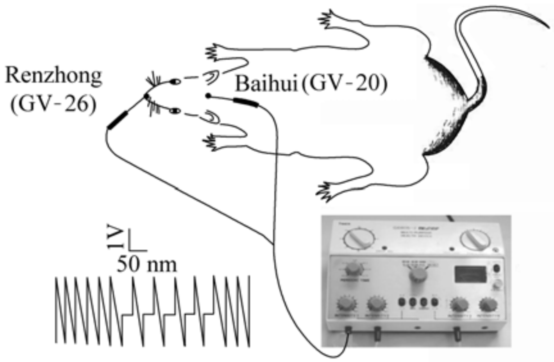

Figure 9.3 Schematic diagram of the EA delivery to the rat model with MCAO. Two needles were inserted into the *Du channel* acupoints: GV 20 and GV 26, according to the anatomic structure analogous to that of the humans. The wave form of the electric stimulation given was sparse dense, illustrated at the left bottom of the figure.

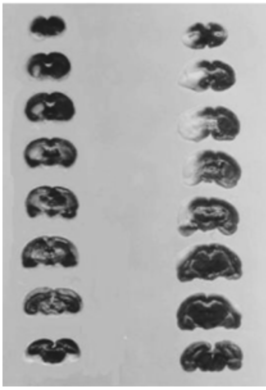

Figure 9.4 The decrease in the ischemic infarction volume after EA treatment. The rat brains were cut into a series of 2 mm thick slices and stained using TTC. Left column, EA plus ischemia (MCAO). Right column, ischemia alone.

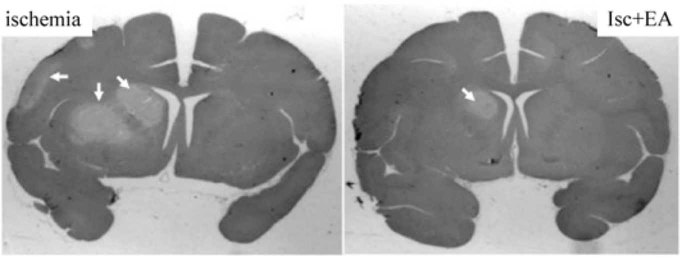

Figure 9.5 EA-induced protection against cerebral ischemia in the monkey MCAO model. TTC staining showed typical infarction in the striatum and parietal cortex in the ischemic group (left, arrow). The infarction volume was restricted in the striatum and cortex after EA (right, Isc + EA).

a better protective effect, which is consistent with the clinical data (Xing et al. 1994). Moreover, our preliminary studies as well as other studies showed a better anti-ischemic efficacy in MCAO rats when acupuncture or EA was delivered before the onset of ischemia, than those delivered after the onset. This finding is very interesting, as it suggests a possible preventive effect of acupuncture on stroke. Although not many researchers have paid attention to this issue, we believe that it is essential to clarify the relationship between acupuncture conditions and acupuncture effects. The conditions should include the specificity of different acupoints, frequency, intensity and duration of stimulation, and times of repeated delivery, as these are necessarily needed in clinical practice. Recently, our group carried out some preliminary studies to address these issues. For example, we chose four pairs of acupoints: Baihui (GV-20) and Renzhong (GV-26), Neiguan (PC-6) and Quchi (LI-11), Yanglingquan (GB-34) and Sanyinjiao (SP-6), and two non-acupoints in the buttocks. These groups are observed to exhibit differences in terms of changes in the cerebral blood flow (CBF), infarction volume, and cell loss, with Baihui (GV-20) and Renzhong (GV-26) providing the best protection.

9.3.3 Effect of Acupuncture on the Functional Recovery of the Ischemic Brain

Functional studies have demonstrated that electrical activity is recovered much faster after ischemia in the rats with EA, than those without EA (Fig. 9.6). Electroencephalogram (EEG) and somatosensory evoked potentials (SEP) are the two most commonly used indicators that reflect the electrofunctional status of brain. Ying et al (1994a) detected changes in the EEG in a gerbil global ischemia model. Owing to the ischemia-induced insufficiency of energy, the amplitude of the brain electricity was seriously suppressed at 10 min post-ischemia. Even at 120 min post-reperfusion, the total power of EEG only recovered up to 27.39 ± 11.31% of the pre-ischemia level, and was maintained till the end of detection (2 h after reperfusion). After the treatment with EA delivered to Fengfu (GV-16) and Jinsuo (GV-8), the brain electricity recovered faster than that in the ischemia group. At 120 min post-reperfusion, the total power recovered reached up to 71.45 ± 16.34% of the pre-ischemia level, and at 240 min post-reperfusion, it reached up to 75.27 ± 18.43%. These results indicate that EA might promote the recovery of brain electricity after ischemia. Similar results were also obtained in the monkey MCAO model (Gao et al. 2002). In this model, the EEG was suppressed after ischemia and slowly recovered after reperfusion. After EA treatment, the ischemic suppression of EEG was significantly attenuated when compared with that in the ischemia group. Xu et al (2001) also observed that the amplitude of brain electricity increased after EA at GV meridian acupoints on the MCAO rats. Furthermore, the EA is also presumed to affect changes in the SEP. Jin et al (1998a) reported that SEP disappeared during ischemia in MCAO rats. In the animals treated with

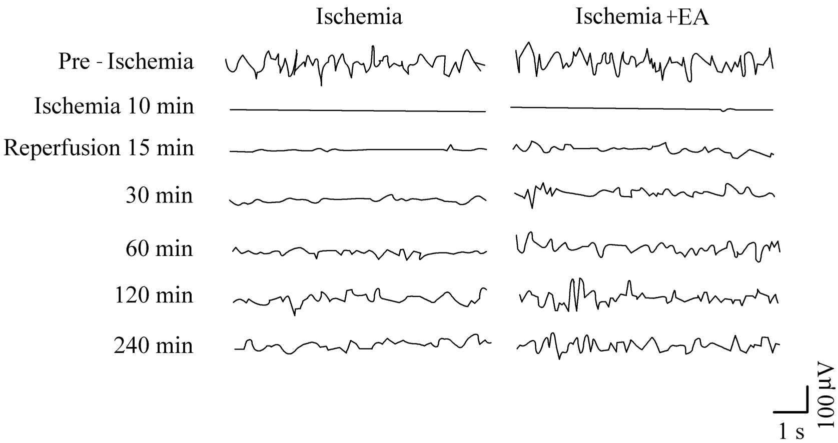

Figure 9.6 Effect of EA on EEGs in ischemic brain of gerbil. The EA was delivered at Fengfu (GV 16) and Jinsuo (GV 8). At 10 min after the onset of global ischemia, the electricity amplitude was largely suppressed in both the ischemia group and ischemia + EA treated group. After acupuncture treatment, the brain electricity recovered faster than that in the ischemia group.

acupuncture at the acupoints of GV meridian, the SEP appeared at 30 min post-reperfusion and recovered gradually after reperfusion.

9.3.4 Optimal EA Conditions for Maximal Protection from Cerebral Ischemia

Clinical data have provided a clue that the effect of acupuncture or EA on stroke is dependent on the acupoints and other conditions (see Section 9.2.3). Owing to the limitations of the clinical studies, it is extremely difficult, if not impossible, to compare various acupuncture/EA conditions with strict controls. Although this is feasible in the experimental studies, it is unclear in terms of optimal acupuncture conditions leading to the best outcome. In fact, earlier studies have employed different acupuncture conditions in various models based on the investigators' interest. There exist many variables in timing window, acupoints, applying length, stimulation intensity, and frequency. To clarify these important issues, our recent studies have systemically determined the effect of these factors on the efficacy of acupuncture-induced protection from ischemia (Zhou et al. 2007a, 2007b, 2007c).

Our data show that EA with sparse-dense wave (5 Hz/4 s – 20 Hz/4 s) at 1.0 mA for 30 min differentially attenuated the ischemic infarction depending on the acupoints used. In the group of head acupoints, that is, "Shuigou" (GV-26) and "Baihui" (GV-20), the cerebral infarction was greatly reduced from 33.4 ± 3.1% to 4.9 ± 1.2% of the brain ($n = 30$, $p < 0.01$) with significant improvement in the neurological deficit (from 6.0 ± 1.0 to 1.0 ± 1.0 in scales of 0 – 7). Furthermore, the EA at "Quchi" (LI-11) and "Neiguan" (PC-6) on the left anterior limbs reduced the infarct volume to 8.6 ± 3.8% (n = 12, p<0.01) with the scales of neurological deficit being reduced to 2.0 ± 1.0 (n = 22, p<0.01). In sharp contrast, the EA at "Quchi" (LI-11) "Neiguan" (PC-6) on the right anterior limbs did not lead to any significant changes in the infarct volume (29 ± 6.3%, n = 9) and neurological deficit (5.5 ± 0.5, n = 9). In addition, the EA at "Yanglingquan" (GB-34) and "Sanyinjiao" (SP-6) on the left posterior limb had no protective effect on the ischemic injury. These results suggest that the EA protection from cerebral ischemia is relatively acupoints-specific.

The EA effects are considered to be critically dependent on the stimulation parameters. Therefore, we investigated whether the EA-induced protection changes with the stimulation intensity and frequency, by delivering the EA to acupoints of "Shuigou" (GV-26) and "Baihui" (GV-20). At 1.0 mA of EA stimulation for 30 min, 5 – 20 Hz (sparse-dense wave) led to a significant increase in the CBF and decrease in the cerebral infarction (– 85%, p<0.01 vs. MCAO alone). However, at 40 Hz of EA stimulation, the CBF increased, with a major increase observed between 2 and 30 Hz. At 40 Hz, the EA induced a marginal increase in the blood flow, while EA with >40 Hz stimulation led to no/little change in the CBF. On the other hand, the EA-induced increase in the CBF was sensitive to the change in the current intensity, and the intensity of <0.6 mA did not induce any significant change in the CBF. However, with a higher intensity of 0.8 mA, a slight but significant increase in the CBF was observed, and 1.0 – 1.2 mA led to a major increase in the CBF. With "optimal" intensity and "non-optimal" frequency (e.g., 1.0 mA and 70 Hz), or "optimal" frequency intensity and "non-optimal" intensity (e.g., 5 – 20 Hz and 0.4 mA), the EA was unable to induce a significant increase in the CBF. Thus, we can conclude that the EA-induced increase in CBF is largely dependent on the EA conditions, especially, the intensity and frequency.

In addition, we found that EA for 5 – 30 min significantly reduced the ischemic infarct volume and relieved the neurological deficits. This beneficial effect increased with EA length between 5 and 30 min, with the infarct volume being reduced by >80% in the 30 min group (n = 60, p<0.01). In sharp contrast, EA for 45 min or more failed to reduce the ischemic infarction with an increase in the neurological deficits and death rate. These results suggest that the EA efficacy is dependent on the appropriate EA duration.

Thus, by considering all these results, we can conclude that the EA-induced protection from experimental stroke is largely dependent on the EA conditions. The data from the experimental studies provide important indications for determining the optimal conditions at the bedside.

9.3.5 Mechanisms of Acupuncture-Induced Protection Against Cerebral Ischemia

Accumulating data in the recent years have provided critical evidences on the mechanisms of acupuncture-induced protection against cerebral ischemia. The following is a brief summary about the research in this field.

1. Acupuncture-induced increase in cerebral blood flow

After the onset of cerebral ischemia, CBF in the affected brain regions is observed to decline rapidly, and is considered to be the first stage and the initiating factor of ischemic-cascade chain-reaction. Therefore, alterations in the regional CBF can directly affect the degree of ischemic injury in the brain, and the measurement of CBF is considered to be an important marker to evaluate the ischemic consequences.

In China, since the early 1980s, rheo-encephalogram (REG) has been the conventional method to detect acupuncture-induced changes in the regional CBF (rCBF) (Wang and Jia 2001). Yang et al (1984) observed acupuncture-induced changes in the amplitude of CBF on eleven patients with stroke. Six patients showed an obvious increase in the CBF after acupuncture at head acupoints, and one showed a decrease in the CBF after acupuncture treatment. The other four patients suffered from severe asymmetry of bilateral CBF. However, after acupuncture treatment, the asymmetry was improved with an increased CBF in both the sides of the brain. However, a few groups (Gao et al. 1987) observed no significant change or even decrease in REG after acupuncture treatment on patients with stroke sequel. Again, these controversies could be attributed to the differences in the patients, treatment window, and acupuncture conditions as discussed earlier in Sections 9.2.3 and 9.3.4 of this chapter.

Laser Doppler Flowmetry (LDF) is another commonly used apparatus to evaluate the changes in the local CBF (lCBF). Luo and Zhou (1994) observed that EA induced a rapid but transient upregulation of the cortical blood flow, and similar results were obtained by other researchers as well. In our work, we placed a laser probe on the surface of the parietal cortex and measured the changes in lCBF. Immediately after MCAO onset, lCBF decreased to about 15% – 25% of the baseline (pre-ischemic) level. However, when we delivered EA to Baihui (GV-20) and Renzhong (GV-26) acupoints 10 min after ischemia, the lCBF level increased to 40% – 50% of the baseline level and sustained till the EA was withdrawn. Nevertheless, after EA treatment, the lCBF level rapidly decreased to the pre-acupuncture level. Interestingly, we observed different lCBF levels as a response to EA treatment at different pairs of acupoints. Apart from acupuncture at specific acupoints, non-acupoint acupuncture barely produced any upregulation of CBF. These results imply a transient, partial, and acupoint-specific effect of EA on CBF in the ischemic brain. In the study carried out on monkey MCAO model (Gao et al. 2002), lCBF in the dorsal lateral striatum was also observed to increase after EA delivery.

Several researchers (Uyama et al. 1992; Aronowski et al. 1997) have noted the contribution of blood reperfusion after ischemia to brain damage resulting from the increased oxygen supply and metabolism owing to the blood flow after reperfusion. Considerable number of reactive oxygen species (ROS) produced during reperfusion is considered to exacerbate the ischemic brain damage, known as reperfusion injury. Pang et al (2003) reported a decreased effect of EA against a transient increase in the CBF, induced by reperfusion after 5 min of ischemia onset in gerbils. They observed that during ischemia, the hippocampal CBF decreased to around 40% of its pre-ischemic level. However, after reperfusion, rCBF increased immediately and was 2.5 folds higher than its pre-ischemic level at 10 min after reperfusion. The EA stimulation was delivered on acupoints Fengfu (GV-16) and Shendao (GV-11) acupoints during pre-, intra-, or post-ischemia. They found that intra-ischemia acupuncture could increase the rCBF of the hippocampus, and that all the three acupuncture applications could suppress the hyperemia induced by reperfusion.

Recently, many researchers observed cerebrovascular responses to acupuncture treatment for stroke, using direct and scatheless techniques such as functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), and single-proton emission computed tomography (SPECT). Lee et al (2003) carried out a study on acupuncture-induced changes in the rCBF after its treatment for stroke by using SPECT perfusion imaging with subtraction and MRI co-registration. They observed rCBF changes in six patients with MCAO and eight volunteers, before and after acupuncture. Six acupoints, namely, Hegu (LI-4), Shousanli (LI-10), Quchi (LI-11), Jianyu (LI-15), Jugu (LI-16), and Waiguan (TE-5), in the affected arm were acupunctured. The results showed that the cerebrovascular responses to acupuncture in patients were different from those in the normal volunteers. In all the patients, the CBF increased with regional specificity, especially in the hypoperfused zone; whereas, in the normal subjects, the rCBF increased in both the hemispheres.

The mechanisms by which acupuncture activates the blood flow are still unknown. Uchida et al (2000) reported that acupuncture-like stimulation increases the cortical blood flow by activating the cholinergic vasodilators and that the increase in blood flow is independent of the blood pressure. Kagitani et al (2000) found an increase in the hippocampal blood flow by activating the nicotinic receptors. Furthermore, some research reports published in Chinese journals have also reported acupuncture-induced alterations in hemorheology in the experimental cerebral ischemia animals. Some researchers detected a dramatic decrease in the shear viscosity of the whole blood and the rate of plastocyte aggregation after acupuncture (Wang et al. 1996). These results imply that acupuncture promotes an improvement in the microcirculation, and that abnormal hemorheology is one of the inducing factors of stroke. However, irrespective of the mechanisms, an increase in the blood flow is observed to be a beneficial factor for the ischemic brain.

2. The role of delta opioid receptors in electroacupuncture protection

The increase in CBF may not be solely responsible for the EA-induced protection against ischemic injury. This conclusion is based on the following observations: in the animal stroke model, an "over-length" (inappropriate) EA stimulation failed to induce any protective effect on the brain, though it did increase the blood flow (Zhou et al. 2007a), suggesting that the EA protection is critically dependent on other mechanisms apart from the increase in CBF.

It has been well documented that acupuncture/EA activates the opioid system in the brain (see Chapter 4). As the delta opioid receptors (DOR) are neuroprotective against hypoxic-ischemic stress (Zhang et al. 2000, 2002, 2006; Ma et al. 2005; Chao et al. 2007; Tian et al. 2008a; Zhu et al. 2008), we tested the role of DOR in EA protection. We determined the effect of EA on DOR expression in the ischemic brain, as DOR could be significantly decreased after ischemic stress or prolonged hypoxia (Boutin et al. 1998, 2000; Zhang et al. 2000). We observed that EA increased the DOR expression in the ischemic cortex. Hence, to test whether DOR is functionally involved in the EA protection, we applied DOR antagonists to the brain and found that the inhibition of DOR significantly attenuated the EA effect (Zhao et al. 2002; Tian et al. 2008b, 2008c). Our data suggest that the EA-induced brain protection against ischemia is associated with DOR function. Furthermore, it is important to note that following our work indicating that DOR plays a role in EA protection from ischemic injury (Zhao et al. 2002), another independent laboratory study recently demonstrated that DOR is critically involved in the EA-induced protection from ischemic infarction (Xiong et al. 2004, 2007), which strongly supports our finding.

In a series of experiments with multiple approaches, we further elucidated the role of DOR in neuronal protection and the mechanism in cortical neurons. Our results demonstrated that (1) DOR, but not mu- or kappa-opioid receptors, protected the neurons against excitotoxic, hypoxic, and chemical hypoxic injury (Zhang et al. 2000, 2002; Chao et al. 2007; Zhu et al. 2008); (2) the expression of DOR was associated with neuronal tolerance to stress (Ma et al. 2005; Zhang et al. 2006; Chao et al. 2006b; Zhu et al. 2008); and (3) protein kinases and MAP kinases were involved in the DOR signaling during neuroprotection (Ma et al. 2005; Hong et al. 2007). On exploring the mechanism of ionic regulation under hypoxic-ischemic stress, we observed that DOR activation attenuates the hypoxic and ischemic disruption of K^+ homeostasis (Chao et al. 2006a, 2007), that is, it causes massive K^+ leakage, which is a major event in the neurons in response to hypoxia and ischemia, triggering neuronal apoptosis and death (Yu et al. 1997; Wei et al. 2003; Burg et al. 2006). More recently, our studies showed that transgenic upregulation of DOR makes cortical neurons more tolerant to hypoxic stress (Chao et al. 2006b).

Taken together, DOR activation is considered to be neuroprotective and the upregulation of brain DOR system is observed to play an important role in the EA-induced protection against hypoxic-ischemic injury.

3. Effect of acupuncture on other neuroactive factors

Acupuncture/EA may affect many neurotransmitter systems in the brain (see Chapters 4 and 5). Therefore, the acupuncture/EA-induced protection against stroke may involve the regulation of multiple neurotransmitter systems at different levels in the brain, besides the DOR system.

Excitatory and inhibitory amino acids

Owing to energy insufficiency, functional disruption may occur on some ATP-dependent membrane proteins, such as Na^+/K^+ ATPase, Ca^{2+}-ATPase, and H^+-ATPase. This event may lead to rapid membrane depolarization and the subsequent excessive outflux of the neurotransmitters from the pre-synapse to the synaptic cleft. Excessive release of glutamate during ischemia is widely regarded as a key factor in the pathogenesis of ischemic neuronal injury. Normally, the membrane protein, Na^+-dependent glutamate transporter, maintains the extracellular glutamate concentration at a very low level (1 – 2 μM) to prevent overexcitation of the cells. During ischemia, besides the over-release of glutamate from pre-synapse, Na^+-dependent glutamate transporters also become reverse-functional owing to the dissipation of Na^+ gradient. Thus, glutamate accumulates in the cleft and continuously stimulates the excitatory amino acids in the postsynaptic membrane, which subsequently results in an increase in the calcium influx and ultimately causes neuronal death.

The biochemical levels of the excitatory and inhibitory amino acids were detected in multiple ischemic models exposed to acupuncture. Several researchers reported that acupuncture could significantly decrease the ischemia-induced increase in the extracellular excitatory amino acids in acute ischemia (Ying et al. 1994b; Zhao and Cheng 1997; Guo and Cheng 2000). Pang et al (2003) observed the change in the extracellular glutamate in the hippocampus of gerbil, through real-time monitoring of the electroenzymatic microdialysis. However, owing to the fact that the microdialysis samples represent the neurotransmitters in the extracellular fluid resulting from both release and reuptake, further studies are needed to evaluate whether the acupuncture can also affect the release of amino acid neurotransmitters. Furthermore, some researchers reported that EA could also attenuate the $NMDAR_1$ (a kind of excitatory amino acid receptor) mRNA overexpression induced by ischemia (Shi 1999). All these above-mentioned studies indicate a possible downregulation of the excitatory amino acids by acupuncture, which consequently attenuates the neuronal toxicity.

Inhibitory amino acid neurotransmitters are also released in abundance during ischemia, which may compensate for the increased excitatory amino acids to counterbalance excitotoxicity. Zhao and Cheng (1997) observed that in addition to the attenuation effect on the excessively increased level of extracellular aspartate, EA at acupoints of GV meridian also substantially enhances the elevation of taurine during ischemia and reperfusion. These results demonstrate the biphasic effects of acupuncture on alterations of both the excitatory and inhibitory amino acids—acupuncture markedly attenuated the over-released excitatory amino acids, and simultaneously enhanced the release of inhibitory amino acids further. These findings are, to a certain degree, consistent with and might partially elucidate the ancient Chinese acupuncture theory that acupuncture is able to rebalance the imbalanced microenvironment. More interestingly, a recently published paper reported the relationship between EA and taurine (Xia et al. 2003). The study demonstrated that depletion of brain taurine owing to the taurine transporter inhibitor, alanine, could attenuate the protective effect of EA against MCAO-induced ischemia in rats. These results imply that the inhibitory amino acid, taurine, might be an important mediator involved in the anti-ischemic effect of acupuncture.

Nitric oxide synthase

Nitric oxide synthase (NOS) is activated upon binding to the Ca^{2+}-calmodulin complexes, and catalyses the reaction of arginine to nitric oxide (NO). There are three different isoforms of NOS in the brain: Neuronal NOS (nNOS), expressed exclusively in the neurons; endothelial NOS (eNOS), which was originally identified in the endothelial cells; and inducible NOS (iNOS), which was originally identified in certain immune system cells. The gaseous signal molecule, NO, plays multiple roles on ischemic injury owing to its multiple sources. Particularly, NO produced by eNOS is most likely to exert its beneficial effect by prompting the reperfusion of the ischemic area, whereas NO from nNOS and iNOS displays its deleterious effect by reacting with oxygen or O_2^- and producing free radicals.

Several studies have investigated the possible effect of acupuncture on NOS system. Using RT-PCR, Jin et al (1998b) detected the mRNA expression of three NOS isoforms at 4, 12, 24, and 48 h post-reperfusion in the rats exposed to 1 h of MCAO with acupuncture treatment. Two GV meridian acupoints, Renzhong (GV-26) and Shangxing (GV-23), were stimulated by EA, from 15 min prior to ischemia to 3 h after reperfusion, with 2-min intervals every 15 min. In the ischemic rats, the expression of nNOS mRNA increased to its peak level at 4 h post-reperfusion, and decreased to baseline at 48 h post-reperfusion; whereas, the expression of iNOS mRNA did not appear till 48 h post-reperfusion. After acupuncture, the expression levels of both nNOS and iNOS mRNA in the cortex and striatum decreased significantly, although the levels were still higher than those in the pre-ischemia phase. However, no changes in the eNOS mRNA expression were observed at any time point in the ischemic or acupuncture-treated rats. Another study reported by Zhao et al (2000) showed the relationship between EA and NO. They detected real-time changes in NO production in the rats exposed to 2 h MCAO after acupuncture treatment with an NO-sensitive microelectrode inserted into the dorsal lateral striatum of the ipsilateral ischemic hemisphere (Zhao et al. 2000). The EA was delivered on the acupoints Rengzhong (GV-26) and Baihui (GV-20), starting at 10 min post-ischemia and lasting for 1 h. The results showed that NO levels were significantly increased upon the onset of ischemia and reperfusion. The EA significantly was observed to antagonize the ischemia-elicited rise of NO, although it could not bring the NO level to the baseline.

Effect of acupuncture on neurotrophic factors

Two general strategies can be used to compensate for the loss of neurons that are destroyed by an ischemic attack: (1) to promote the self-repair of the damaged neurons and (2) to promote the neurogenesis of the stem cells in the brain. Several neurotrophic factors or growth factors are believed to have the potential to improve cell survival and proliferation, which are beneficial to the ischemic brain tissues. It is observed that the immunoreactive distribution of the basic fibroblast growth factor (bFGF) is widely but unevenly distributed throughout the central nervous system. Increased expression of bFGF mRNA has been detected in the brain after cerebral ischemia or hypoxia. There are evidences showing that bFGF promotes neuronal survival against hypoxia-ischemia insults both in vitro and in vivo (Kiyota et al. 1991; Baldauf et al. 2005; Liu et al. 2006). Neurotrophic factors such as BDNF and glial cell line-derived neurotrophic factor (GDNF) are also reported to be protective against ischemic injury (Wang et al. 1997; Schabitz et al. 2004).

Furthermore, the EA treatment on ischemic rats may regulate the expression of several neurotrophic factors or growth factors in the brain. With RT-PCR and immunohistochemistry, Wei et al (2000) detected the expression of GDNF mRNA and protein in the brain, and observed that they increased in penumbra cortex after 2 h of ischemia and reached peak at 2 h after reperfusion. However, acupuncture immediately after the onset of ischemia did not change the expression peak, but notably depressed the descending tendency. Similarly, Ouyang et al (2001) investigated the expression of bFGF during ischemia/reperfusion period with or without EA intervention in the ischemic model with 2 h of MCAO. In their study, the expression of bFGF was increased in the striatum and frontoparietal cortex after ischemia/reperfusion, and was further enhanced by EA application. However, although supplementation of bFGF produced similar protective effect as EA, against neuronal injury induced by cerebral ischemia in the rat, the EA-induced protection was not enhanced by the application of bFGF (Li et al. 2002). Furthermore, single EA application after ischemia also improved the BDNF expression with the levels reaching the peak at 12 h post-reperfusion. Interestingly, researchers also observed that the high expression level of BDNF appeared 7 days after reperfusion, when EA was repeatedly administered to the animals (Chen and Huang, 2000). As GDNF, BDNF, and bFGF supplementation are all observed to be beneficial to the ischemic brain, these results indicate that there might be a relationship between acupuncture-induced neuroprotection and growth factors (Fig. 9.7).

4. Acupuncture-induced intracellular regulation

Besides the modulation effects on some neurotransmitters and neurotrophic factors, acupuncture may also affect several intracellular events in the brain.

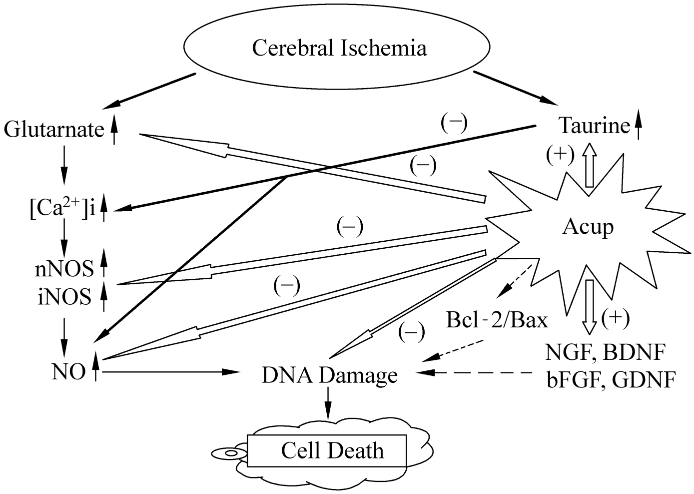

Figure 9.7 Bidirectional modulation of neuroactive factors and other bioactive substances by EA.

Immediately responsive genes

The c-Fos and c-Jun, the two immediately responsive genes, are transcription factors and important markers of injury-response cascades in the hypoxic-ischemic brain. Increased induction of c-Fos and c-Jun by ischemia is a well-documented phenomenon. The rapid and transient activation pattern of such genes and their proteins initiated by hypoxic-ischemic injury is complex, and is often linked to the promotion of cellular recovery, as well as neural death and apoptosis. As an immediately early gene, c-Fos may produce different responses to different ischemic extents. Hence, proper expression of c-Fos might be an important factor in the protective effects of acupuncture against ischemia.

Several articles reported the effect of acupuncture on c-Fos or c-Jun expression. Ying et al (1994c) performed EA at acupoints Fengfu (GV-16) and Jinsuo (GV-9) in global ischemic gerbil and observed substantial induction of c-Fos in the hippocampal neurons. Furthermore, EA was observed to prevent most of the CA1 cells from delayed degeneration after ischemia. These results indicate that there might be some possible links between the neuroprotective effect of acupuncture and c-Fos induction. However, several other researches showed an inconsistent and complex alteration in the c-Fos expression. In gerbils with transient global ischemia, Jang et al (2003) delivered acupuncture twice a day, starting from the third day of the experiment and lasting for 8 days. They observed that at the tenth day of the experiment, c-Fos expression increased in the hippocampal CA1 region after ischemia, which could be suppressed by acupuncture treatment on Zusanli (ST-36) or Hegu (LI-4) acupoints. In addition, decreased caspase-3 expression and TUNEL positivities were concurrently observed after acupuncture. These results indicated that acupuncture could suppress the increase in c-Fos expression and extent of apoptosis induced by ischemia.

In another study, the expression of c-Fos and c-Jun was investigated in the model of glibenclamide-induced (an ATP-sensitive potassium channel blocker) hypoxic-ischemic brain injury (Jiang et al. 2004). The EA on the acupoint Hegu (LI-4) was carried out before the hypoxic-ischemic injury. The results demonstrated lower c-Fos and c-Jun expressions in both the EA and diazoxide-treated (a K_{ATP} channel opener) groups, 24 h after the hypoxic-ischemic injury. These results are somewhat consistent with those obtained by Dong and Chen (2001). In a 90 min MCAO rat model, Dong and Chen (2001) performed EA on the acupoints Renzhong (GV-26) and Baihui (GV-20) immediately after the onset of ischemia, and observed an increased expression of c-Fos in the ipsilateral cortex with a peak at 4 h after reperfusion. Acupuncture was observed to suppress the overexpression of c-Fos at each time point that they studied and reduce the volume of ischemic infarction. Furthermore, in the acupuncture-treated group, after the microinjection of c-Fos antisense oligonucleotide into the ischemia core, there was an increased infarction volume with the overexpression of c-Fos being completely blocked, when compared with the acupuncture-treated group without antisense oligonucleotide microinjection. These results indicate that the inhibitory effect of EA on the superfluous expression of c-Fos in the brain may partially account for the mechanisms of the EA-induced tolerance of the cerebral neurons to ischemic injury.

Inflammatory factors

Recent evidences suggest that cerebral ischemia triggers inflammatory responses in the brain which are associated with the induction of a variety of cytokines, including tumor necrosis factor-α (TNFα), interleukin-1 (IL-1) and interleukin-6 (IL-6), which play crucial roles in the initiation of inflammatory cascades and potentiation of neurotoxicity (Adibhatla and Hatcher 2007; Arekelian et al. 2005; Huang et al. 2006; Rallidis et al. 2006; Rubattu et al. 2005; Zaremba and Losy 2001). The therapeutic correction directed toward modulation of inflammatory immune response at the level of cytokine expression may be a necessary factor for the prevention and treatment of stroke, as well as for the successful rehabilitation of stroke patients (Arekelian et al. 2005). Therefore, neurologists tried to develop some antibodies, such as anti-ICAM-1, anti-IL-1, and anti-IL-6 to protect the neurons from ischemic inflammation. However, the current results available are inconsistent.

Some studies showed that acupuncture may have the potential to regulate inflammatory processes of ischemia or stroke (Chen et al. 2003; Jeong et al. 2003). In patients with chronic headache, researchers observed that acupuncture could significantly reduce the levels of TNF-α (Jeong et al. 2003). In contrast, in a rat model with transient focal cerebral ischemia, acupuncture dramatically upregulated the mRNA expression of IL-6 in cortex and striatum, 24 h post-reperfusion (Chen et al. 2003). It has been reported that IL-1 beta plays a key role in the pathogenesis of cerebral ischemia. Cerebral ischemia is observed to trigger a rapid expression of IL-1 beta and IL-1 Ra mRNA (the latter is an inner antagonist of IL-1 beta receptor). However, after EA stimulation, the mRNA expression of IL-1 beta was notably reduced, while that of IL-1Ra was further enhanced (Xu et al. 2002).

Free radicals formation

With an unpaired electron in the outer shell, free radicals are very unstable and highly reactive, and in turn, can cause serious damage to the neurons. Accumulation of ROS, particularly superoxide anion and hydrogen peroxide, causes damage to the membrane phospholipids, proteins, and DNA. Furthermore, the production of large numbers of free radicals is frequently associated with excitotoxicity.

Many of the ischemia-related events can lead to the formation of free radicals. During reperfusion, along with the transiently increased cerebral blood flow, excess of ROS, such as hydroxyl radicals and superoxide radicals, are also produced. In the 1 h MCAO rats, Siu et al (2004) carried out single EA application on the acupoint Fengchi (GB-20) for 30 min following ischemia, and then investigated the activities of the antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPx) after acupuncture treatment. They observed that ischemia-reperfusion caused significant increases in the SOD and GPx activities. The EA was not observed to alter the activities of the antioxidant enzymes in the non-ischemic normal rat brains; however, it further increased the activities of the antioxidant enzymes in the ischemic-reperfused brain tissues, with a concomitant decrease in the extent of lipid peroxidation. These results are consistent with other studies published in some Chinese journals (Bai et al. 2003; Huo et al. 2003), which reported that EA could enhance the activities of SOD and decrease the malondialdehyde level.

Under normal circumstances, antioxidant enzymes, such as SOD and GPx, can effectively scavenge the ROS. However, the normal functioning of these antioxidant enzymes may be insufficient for the prevention of oxidant-induced peroxidation of the membrane lipid. Therefore, the sudden burst of ROS during cerebral ischemia-reperfusion can overwhelm the antioxidant defense, resulting in lipid peroxidation and consequently, cerebral infarction. The abovementioned studies suggest that the increase in the activities of SOD and GPx to remove the excessive free radicals might be one of the underlying mechanisms responsible for the protective effect of EA.

Apoptotic signals

Several articles showed that acupuncture may have a potential to reduce the number of neuronal cells undergoing apoptotic cell death (Shi 1999; Wang et al. 2002; Li et al. 2003). Using PI or TUNEL labeling, significantly reduced positive cells could be seen after acupuncture treatment.

Cell survival is regulated by the balance of survival and death signals under normal and pathologic conditions. It is hypothesized that acupuncture has the potential to rebalance such signals in stroke therapy. In MCAO rats, Wang et al (2002) delivered EA stimulation for 1 h on the acupoints Baihui (GV-20) and Renzhong (GV-26) immediately after the onset of reperfusion. They observed that after 90 min of transient MCAO, the immunoreactivities of both phospho-Akt (p-Akt) and cleaved caspase-9 (c-cas 9) increased in the ipsilateral penumbra and peaked at 8 h post-reperfusion. Subsequently, the expression progressively decreased and almost reached the baseline at 24 h post-reperfusion. In the EA-treated rats, the pAkt expression was enhanced in both ipsilateral and contralateral hemisphere, mainly in the ischemic penumbra at 8 and 24 h, whereas c-cas 9 expression was suppressed at 8 and 24 h after reperfusion, especially in the ipsilateral penumbra. Furthermore, they detected a number of TUNEL-positive cells in the model with or without EA application. These cells were observed at 8 h post-reperfusion and increased at 24 h post-reperfusion. However, after EA performance, the number of TUNEL-positive cells reduced at 24 h in the cerebral cortex. These results indicate that EA enhances the activations of Akt and suppresses that of caspase-9. In another study published in Chinese, Li et al (2003) detected apoptotic-related proteins, Bcl-2 and Bax, and showed that acupuncture could dramatically upregulate the expression ratio of Bcl-2/Bax and reduce the percentages of TUNEL-positive cells.

5. Effect of acupuncture on neurogenesis

It is confirmed that neural stem cells are also distributed in the adult brain, and are able to proliferate and finally differentiate into neurons or glial cells. Cerebral ischemia is observed to induce cell proliferation, migration, and maturation. However, it is still a challenge for neurologists to develop a method to promote the neurogenesis and neural functional recovery. A few studies have been attempting to implant exo-stem cells or provide stimulants to trigger inherent proliferation of the stem cells to compensate for the dead neurons in the injured brain region. This might be a direct therapy method for stroke patients. However, there are still many problems and side effects that need to be resolved.

In clinical practice, acupuncture is commonly used to promote functional recovery in the treatment for paralysis. However, does acupuncture truly promote neurogenesis? Can acupuncture enhance cell proliferation and differentiation? Few studies have focused on these issues. In an earlier study (Kim et al. 2001a), researchers observed that BrdU (a cell proliferation marker) immunoreactivities increased significantly in the dentate gyrus after the application of auricular acupuncture. Moreover, acupuncture on acupoint Zusanli (ST-36) resulted in notable increase in the number of BrdU-positive cells in the dentate gyrus after transient global ischemia (Kim et al. 2001b). Furthermore, in TCM, the acupoint Zusanli (ST-36) has been commonly used for the improvement of functional recovery in stroke therapy. These findings indicate that acupuncture might have the ability to promote cell proliferation after ischemia. Another study (Yang et al. 2005) showed evidence on the notion that EA could enhance stroke-induced striatal neurogenesis in rat brains. The authors delivered EA on the acupoints Fengfu (GV-16) and Jinsuo (GV-8), and detected cell proliferation and differentiation using multiple fluorescence immunostaining. The results revealed that EA could increase the number of BrdU-positive cells, as well as increase $BrdU^{+}/CRMP\text{-}4^{+}$ and $BrdU^{+}/MAP\text{-}2^{+}$ cells. The CRMP-4 and MAP-2 are the markers of immature and mature neurons, respectively, and the BrdU, colocalized with CRMP-4 or MAP-2, indicates the maturation of the newly generated neurons. Moreover, most of the $BrdU^{+}/CRMP\text{-}4^{+}$ or $BrdU^{+}/MAP\text{-}2^{+}$ cells in the striatum showed DiI^{+} staining. The DiI is a lipophilic neuronal tracer and was intravenously injected after ischemia. The tri-labeling of these cells suggest that newborn striatal neurons might migrate mainly from the cells lining the ventricle. Therefore, based on this evidence, the authors concluded that EA can improve the neuronal regeneration, newborn neuron migration, and their maturation in the striatum of adult rat brains after stroke. Recently, a study (Cheng et al. 2008) showed that combination treatment with nerve growth factor (NGF) and EA further increase $BrdU^{+}$ cells after focal cerebral ischemia, suggesting that a possibly synergistic effect of NGF and EA might contribute to the improvement in neuronal survival and function. The research data also present another interesting and important question: what is the relationship between EA, neurogenesis, and neurotrophic factors? More studies are needed to clarify this issue.

6. Effect of acupuncture on blood brain barrier and edema

Ischemia or stroke can affect the function and structure of blood brain barrier (BBB) and produce cerebral edema. Thus, the integrity of BBB is important for the treatment of cerebral ischemia. An earlier study (Wu et al. 2001) used the Evans Blue dye as a tracer for assessing the permeability of BBB, and showed that there was a type of biphasic opening of BBB after ischemia. Evans Blue extroversion reached its first peak at 6 h post-reperfusion and second peak at 48 h post-reperfusion. After EA stimulation, both the area and intensity of Evans Blue were suppressed. This research data give us a hint that EA could depress the BBB disruption induced by cerebral ischemia/reperfusion.

Our previous studies also showed that along with the depressed BBB rupture, EA application to the ischemic rats could also reduce cerebral edema (Peng et al. 2007). As aquaporins (AQPs) are regarded as water channel proteins, and responsible for the formation and elimination of cerebral edema in ischemia/reperfusion proceeding (Frydenlund et al. 2006), we further tested whether AQPs is modulated by EA intervention. Our results showed that EA not only reduced the AQP-4 expression, but also redistributed the cellular location of AQP-4 in the astrocyte endfoot. However, whether the redistribution of AQP-4 in the astrocyte is associated with the neuroprotective effect of EA or not, requires further investigations.

9.4 Concluding Remarks

In this chapter, we discussed the clinic application and experimental study of acupuncture treatment on stroke. Currently, there is no promising therapy for stroke. Physicians are advocated to perform multiple interventions of combined agents and give prescriptions personally, as multiple factors including inflammatory, excitotoxicity, and free radicals are involved, which cross-react in the injury cascade of ischemia. Acupuncture, unlike chemical drugs, may be a useful option, because it is a convenient and cost-effective modality with low side effects. In fact, acupuncture has been widely used for stroke therapy in oriental countries, and has become more and more popular in the western countries. Most studies suggest that patients show better outcome and require less nursing and rehabilitation therapy after acupuncture treatment. In some clinic trials as well as experimental studies in China, the combination of acupuncture and other neuroprotective agents has been observed to exert better outcome than acupuncture or neuroprotective agents alone. Therefore, a therapy combined with acupuncture and drugs may be a more effective way to treat stroke patients. However, there are several shortfalls in the currently published clinical data that render physicians unwilling to consider acupuncture therapy at the bedside. A multiple-center clinical trial with strict control is in urgent need to validate the efficacy of acupuncture therapy for stroke.

In contrast to the extensive clinical application, experimental studies on acupuncture therapy with current techniques are still in its early stage. Although several groups have demonstrated acupuncture/EA-induced brain protection from experimental stroke, and have indicated multiple alterations in the cellular and molecular events in the brain triggered by acupuncture, there is still a lack of deep and direct evidence to elucidate the mechanisms underlying the neuroprotective effect of acupuncture. However, the available data do suggest that acupuncture might be a regulator to mobilize the mechanisms of self-regulation and self-repair in the brain, that is, ischemia is considered to trigger injury/death signals, while acupuncture is believed to augment the inherent survival mechanisms and antagonize the signals harmful to the brain. Indeed, studies on gene expression profile (Guo et al. 2004) provide supporting evidence for this hypothesis. More comprehensive and mechanistic investigation will certainly generate invaluable information for better clinical practice of acupuncture therapy against stroke, and may even provide novel clue for the development of new solutions for the treatment of hypoxic-ischemic encephalopathy.

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10 Effects of Acupuncture on Arrhythmia and Other Cardiac Diseases

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Summary This chapter reviews the clinical and laboraotry research on acupuncture therapies for arrhythmia and other cardiac diseases (e.g., coronary atherosclerotic heart disease, heart failure, and viral myocarditis). Clinical data suggest that the efficacy of acupuncture therapy varies depending on multiple factors, including the type of diseases, acupoints selected, and the manner of manipulation used. In general, acupuncture induces a much better efficacy in the patients with arrhythmia related to neural dysfunction than in those with pathological changes in the heart. The mechanistic research shows that acupuncture signal is mainly transferred to the central nervous system by afferent nerve fibers. The input signal leads to serial changes in electrical and chemical activities in the brain. Subsequently, the body corrects cardiovascular dysfunctions through neural regulation, endocrine secretion, humoral and dielectric regulation, intracellular modulation of signal transduction, and even gene expression. Thus, acupuncture induces a therapeutic effect on cardiovascular system through an integrated and complex mechanism.

Keywords *cardiac diseases, arrhythmia, acupuncture therapy, correction, mechanism*

10.1 Introduction

Cardiovascular diseases are often observed to be presenting with palpitations, vertigo, choking sensation in the chest, and precordial pain. Acupuncture has been used for a long time to relieve these symptoms in the history of traditional Chinese medicine (TCM). As early as in the *Huangdi Neijing* (*the Section of Lingshu·Wuxie*)*,* it was perceptively recorded that "*if there is evil in the heart, epigastric pain is felt and the patient is susceptible to sorrow, often feels dizziness or falls in asphyxia or syncope. Specific acupoints should be adopted to regulate*

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meridian according to its state of excess or deficiency". In the Wei and Jin dynasties, Huangfu Mi had already mentioned *cardiodynia*, and had referred to dizziness and cardiopalmus in his work, *Zhenjiu Jiayi Jing* (*Acupuncture A & B Guidelines*, Fig. 10.1). In the past 50 years, much attention was paid to TCM in China with very supportive policies to encourage the integration of TCM and western medicine. Thus, remarkable progress has been made in TCM, especially in acupuncture and moxibustion as well as herbal medicine. It is noteworthy that in the 1960s – 1970s, fruitful results in the field of acupuncture analgesia and anesthetization greatly promoted clinical and basic research on acupuncture therapy for cardiovascular diseases to a high level. In the recent years, acupuncture has increasingly become an active modality for cardiovascular diseases in China as well as other countries (Shi 1998; Zhu 1998; Cao 2001; Li and Man 2004; Tan 2005; Liu 2005; Chen and Xu 2009).

Figure 10.1 Classical work of TCM. *Yellow Emperor's Classic of Medicine* (*Huangdi Neijing*) is the most important book on ancient Chinese medicine. It consists of two parts, the *Suwen* and the *Lingshu*. Another book called Zhenjing (Classic of Acupuncture) is a classic book describing the Yellow Emperor's Classic of Medicine. *Zhenjiu Jiayi Jing* and *Zhenjiu Da Cheng* are both specialist manuals on acupuncture.

There are many types of cardiovascular diseases, including arrhythmia, myocarditis, coronary heart disease (CHD), etc. Because of rapid progress in research on acupuncture therapy for arrhythmia, this chapter will mainly focus on the acupuncture treatment for arrhythmia and the underlying mechanism, though we will also review the effect of acupuncture on other cardiovascular diseases, such as CHD and myocarditis. We will seek to broadly reflect the profile of the studies in this field, in spite of the fact that we do not necessarily agree with all the views and conclusions in the original articles.

10.2 Clinical Application of Acupuncture for the Treatment of Cardiac Diseases

Many clinical studies have been carried out to determine the effects of acupuncture on cardiovascular diseases, and have generated substantial data regarding the efficacy of acupuncture on different cardiovascular diseases with various acupoints and different types of manipulation (e.g., lifting, thrusting, and rotating in manual acupuncture) or electrical stimulation (e.g., current parameters in electroacupuncture (EA)) (Fig. 10.2).

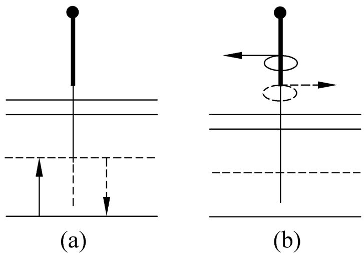

Figure 10.2 Two basic acupuncture manipulations. (a) lifting and thrusting; (b) rotating.

10.2.1 Arrhythmia

A variety of acupuncture approaches, including manual acupuncture, EA, ear acupuncture, acupoint-injection combination of acupuncture and medicine, and wrist-ankle acupuncture, have been used in acupuncture therapy for arrhythmia (Xia 1983; Wu and Lin 2006). The acupoints selected are often located at the Shaoyin Heart Meridian of the hand and Jueyin Pericardium Meridian of the hand, sacral region, and legs. The acupoints used include Xinshu (BL-15), Juque (RN-14), Shenmen (HT-7), Neiguan (PC-6), Zusanli (ST-36), and Sanyinjiao (SP-6) (Lin 1980; Tan 2005; Liu 2005; Wang et al. 2005). In particular, acupoint Neiguan (PC-6) has been demonstrated to be the most effective in reducing or raising the heart rate, and reverting the cardiac rhythm (Chen and Xu 2009).

Acupuncture has shown appreciable effects on both simple arrhythmias (e.g., extrasystole and paroxysmal tachycardia) and complicated arrhythmias owing to heart and/or lung disorders, such as myocardial infarction, rheumatic heart disease, and viral myocarditis. Jiang (1994) treated 30 cases of children with premature systole, using acupuncture therapy. Among the sick children, 12 cases suffered from atrial extrasystole and 18 cases had ventricular extrasystole. When Shenmen (HT-7) was selected as the therapeutic acupoint, the effective rate was 77% with “excellent” efficacy in 7 cases, “effective” efficacy in 16 cases, and no appreciable effect on the remaining 7 cases. Ma (1996) reported that in 68 cases of intermittent supraventricular tachycardia, acupuncture at the acupoints Neiguan (PC-6) and Sanyinjiao (SP-6) induced a beneficial effect in 45 cases after 2 – 5 min, and the effect was observed to last for a long period. In other 23 cases, the heart rate decreased after 5 – 10 min of acupuncture and completely returned to normalcy after 2 – 3 times of treatment, without relapse during the follow-up period. Sui (1999) compared the therapeutic effects of the acupoints Taiyuan (LU-9), Taiyuan (LU-9) and Tanzhong (RN-17), and Neiguan (PC-6) and Shenmen (HT-7) in 64 patients with extrasystole (40 cases of ventricular extrasystole and 24 cases of atrial extrasystole). The results showed that acupuncture treatment at the acupoint Taiyuan (LU-9) or combined with Tanzhong (RN-17) had a better effect than that at the acupoints Neiguan (PC-6) and Shenmen (HT-7) (93.7% effective rate vs. 71.9%, $p<0.05$). Zheng (2005), using acupuncture, treated 76 cases of arrhythmia caused by CHD, high blood pressure, myocarditis, etc., and observed a total effective rate of 96.5%. In addition, Xing and Wang (2000) reported that acupuncture at the acupoint Neiguan (PC-6) combined with finger-pressing (acupressure) on the acupoints Tanzhong (RN-17), Shendao (DU-11), Zhiyang (DU-9), and Xinshu (BL-15) could stop supraventricular tachycardia in all the 5 cases. Qiu and Chen (2003) treated chronic cardiopulmonary disease with arrhythmia by combining acupuncture and medical drugs, and demonstrated an efficacy rate of 93.55%. All these data suggest that acupuncture has a broad effect on arrhythmia resulting from various causes. Furthermore, there are data suggesting that acupuncture has a better effect on "rapid" cardiac arrhythmia (e.g., extrasystole and tachycardia) than other arrhythmia, and has little or no effect on cardiac conduction defects or chronic atrial fibrillation (Xia 1983). Table 10.1 lists the common acupoints used for the treatment of arrhythmia.

Table 10.1 Acupoints commonly used for treating arrhythmia*

Acupoints	Location	Other Applications
Xinshu (BL 15)	1.5 cun lateral to the lower border of the spinous process of the 5th thoracic vertebra	Main point for cardiac disorders, such as palpitation, cardiac pain, arrhythmia; also for insomnia, dreaminess, mental disorder, and backache
Juque (RN 14)	6 cun above the umbilicus	Stomachache, vomiting, cramp of diaphragm, mental disorder, and epilepsy
Shenmen (HT 7)	At the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of m. flexor carpiulnaris	Main point for cardiac disorders, such as palpitation, cardiac pain, arrhythmia tachycardia; also for insomnia, epilepsy, psychosis, pain in wrist joint, and numbness of the ulnar nerve
Neiguan (PC 6)	2 cun above the transverse crease of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis	Main point for cardiac disorders, such as tachycardia, bradycardia, arrhythmia, angina pectoris; also for insomnia, epilepsy, mental disorder, regulation of blood pressure in favorable directions, chest pain, asthma, stomachache, vomiting, retching, hiccup, fever caused by deficiency of *Yin*; main point for acupuncture anesthesia in chest operations

(Continued)

Acupoints	Location	Other Applications
Zusanli (ST 36)	3 cun below Dubi, one finger breadth from the anterior crest of the tibia	Main point for the gastro intestinal diseases, cough, asthma; regulating blood pressure in favorable directions; for treating fainting and insomnia; strengthening the body's resistance and restoring vital energy; for treating diseases in the head and face; also for treating paralysis of the lower extremities; often used with Hegu acupoint
Sanyinjiao (SP 6)	3 cun directly above the tip of the medial malleolus, on the posterior border of the tibia	Used for deficiency of the spleen and stomach, borborygmus; abdominal distension; irregular menstruation; leucorrhea; nocturnal emission; impotence; flaccidity; obstructive pain in the foot; eczema; and insomnia
Tanzhong (RN 17)	On the midline of the sternum, at the level with the 4th intercostal space	For treating chest stuffiness, chest pain, asthma, cough, often used with acupoint Neiguan; main point for treating breast diseases, such as early mammitis and agalactia
Zhiyang (DU 9)	Below the spinous process of the 7th thoracic vertebra	Used for treating jaundice, cough, asthma, and lumbago
Shendao (DU 11)	On the posterior midline, in the depression below the spinous process of the 5th thoracic vertebra	For palpitation, pain in the back and shoulder, cough, asthma, and epilepsy

*The contents of this table refer to the relevant internet resources and related contents of the following two monographs: (1) Jin SX. Chinese-English Learning and Memory Manual of Meridians and Acupoints. Zhengzhou University Publishing House, Zhengzhou, 2002; and (2) Shen XY and Wang H. Acupuncture and Moxibustion. People's Medical Publishing House, Beijing, 2007.

10.2.2 Other Cardiac Disorders

Clinical data also show that acupuncture has a therapeutic effect on other cardiovascular diseases, such as CHD, heart failure, viral myocarditis, and rheumatic heart disease, thus, improving the patients' quality of life.

CHD is a severe heart disorder caused by cardiac ischemia owing to atherosclerosis. Clinically, CHD can be divided into five types: symptomless, angina, myocardial infarction, ischemic cardiomyopathy, and sudden death. In TCM, CHD is considered as thoracic obstruction and cardiodynia. Several ancient books on TCM have records of this disease in terms of its etiopathogenesis, pathogenesis, and clinical symptoms (Xu 2003). In the recent years, there have been significant progresses in the acupuncture treatment of this disease. According to a clinical study in 2001 (Cao 2001), the total rate of "efficacy" was 56.7%–96.5% in all the patients receiving acupuncture treatment. Among them, most showed decreased level of glyceryltrinitrate, with 46.6% – 87.4% exhibiting improved electrocardiogram. After the treatment, 62.5% – 91.7% of the patients maintained the beneficial effect.

Specific acupoints are required for the treatment of CHD. The common acupoints selected are located on the Meridian of Hand-Shao Yin and Hand-Jue Yin, such as Neiguan (PC-6), Jianshi (PC-5), Daling (PC-7), Ximen (PC-4), Tanzhong (RN-17), Juque (RN-14), Xinshu (BL-15), Jueyinshu (BL-14), Shenmen (HT-7), and some ear acupoints in the cardiac area (Wu 1995; Shi 1998). In manual acupuncture, it has been suggested that the acupoints should be strongly stimulated by hand manipulation (Shi 1998).

Some clinical reports showed that heart failure could be improved by acupuncture treatment. Hu (1997) applied acupuncture at the acupoints Lieque (LU-7) and Neiguan (PC-6) to treat 15 patients with acute left heart failure and observed that 14 of them improved shortly after the treatment, and that the heart rates were reduced by about 20 times/min. Li and Man (2004) randomly divided 60 patients with symptomless heart failure into two groups (30 patients per group) and treated them with western medicine and acupuncture, respectively. The acupuncture was applied at the acupoints Neiguan (PC-6), Ximen (PC-4), Tanzhong (RN-17), Xinshu (BL-15), Jueyinshu (BL-14), and Geshu (BL-17). The efficacy was evaluated by determining the left ventricle ejection fraction, shortening fraction, and plasma brain natriuretic peptide before and after the treatment. Interestingly, they observed almost equal efficacy in these two groups ($p>0.05$). Thus, they concluded that acupuncture treatment could improve cardiac function, like western medicine. Apparently, it may be a better option for some patients, as acupuncture is convenient and cost-effective with producing little side effects.

Some researchers observed the therapeutic effect of acupuncture on viral myocarditis and rheumatic heart disease (Zhu 1998; Deng et al. 2001; Li et al. 1996). The total effective rate was more than 88% in 150 patients with viral myocarditis. However, the efficacy needs to be further verified, because the patients received the treatment along with the Chinese herbal medicine (Li et al. 1996; Zhu 1998; Deng et al. 2001).

Nevertheless, all the above mentioned data strongly suggest that acupuncture could induce a therapeutic effect on various cardiovascular diseases, including arrhythmia, coronary artery disease, and cardiac failure. Thus, the subsequent question is to determine whether there is a scientific basis for acupuncture treatment, and the following contents of this chapter will explore the potential mechanisms.

10.3 Mechanisms of Acupuncture Therapy for Cardiac Disorders

It has been well documented that manual acupuncture/EA signals can regulate cardiovascular function through nervous system, endocrine secretion, humoral factors, and electrolyte balance (Fig. 10.3). Among the complex mechanisms, neural regulation plays a critical and unique role in the regulation of cardiovascular function and the correction of cardiovascular abnormality. For example, electrical stimulation of certain brain regions was observed to induce arrhythmia and elevated blood pressure with an increase in the sympathetic activity, including cardiac sympathetic discharges, which could be attenuated by simulated EA on the deep peroneal nerve (Xia et al. 1985, 1986, 1987, 1988a, 1988b, 1989a, 1989b, 1989c). In a study on the effect of the acupoint Neiguan (PC-6) on rat myocardial ischemia, Yan et al (1998) observed that stimulation of the median nerve, cubital nerve, and muscle under the acupoint yielded differential effects. The stimulation of the median nerve significantly improved the electrocardiogram of acute myocardial ischemia. In contrast, the stimulation of the cubital nerve induced little effect on the myocardial ischemia, and the muscle stimulation had no effect at all. The median nerve is presumed to play a major role in transferring Neiguan (PC-6) generated acupuncture signals that regulate cardiac system. Furthermore, there has been evidence suggesting that the regulatory signals of the acupuncture at the acupoint Neiguan (PC-6) may be mediated by Group Ⅱ and III fibers of the median nerve (Li 2002). In addition to neural regulation, other mechanisms such as endocrine and humoral factors also play a role in the acupuncture-induced regulation of cardiovascular system.

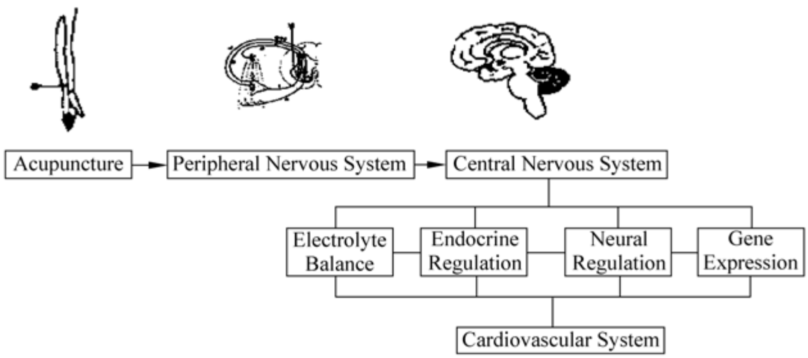

Figure 10.3 Neural and other factors involved in the acupuncture treatment for cardiovascular diseases.

10.3.1 Mechanisms Underlying Acupuncture Correction of Arrhythmia

Besides clinical observations, experimental studies from several independent laboratories have also demonstrated that acupuncture can attenuate arrhythmia (Xia 1983; Xia et al. 1985, 1986; Jiang 1994; Ma 1996; Sui 1999; Cao 2001; Wang et al. 2005; Tan 2005; Liu 2005; Chen and Xu 2009). Accumulating evidence suggests that the mechanisms underlying acupuncture correction of arrhythmia mainly involve nervous system and endocrine-humoral system, leading to cellular, intracellular, and ionic regulation of the cardiovascular system.

10.3.1.1 Regulation of nerve activity

Neural dysfunction plays an important role in the etiology of arrhythmia, either in myocardial ischemia or other conditions (Schwarz 1978; Xia 1983; Gantenberg and Hagemen 1992). For example, an electrical stimulation of the medial portion of the hypothalamus was observed to increase the cardiac sympathetic discharges and arrhythmia (especially, premature ventricular contraction) in naive animals (Xia et al. 1984). Arrhythmia almost completely disappeared after the removal of ganglion stellares on both the sides (Xia et al. 1984, 1985). At the bedside, cerebrovascular disorders often cause cardiovascular dysfunction or even morphological changes in the cardiac muscles, which is the so-called cerebrocardiac syndrome. These patients exhibit neurological symptoms and arrhythmia, as well as abnormal electrocardiogram (Fu and Zhao 1997).

Many studies have shown that EA could adjust the autonomic nerve function in humans (Cao et al. 1981) and animals (Liu and Wang 2003). Lin et al (1980) considered that it was the activity of the body surface-internal organ reflex through acupuncture regulation of the autonomic nervous system. Gao et al (1980) observed that in the rat models of tachyarrhythmia and bradyarrhythmia induced by the injection of aconitine or cordilox, EA induced a therapeutic effect. However, the effect of EA disappeared after vagotomy. In the same study, the therapeutic effect of EA was also eliminated by blocking the humeral nerve of the anterior limb with aethocaine hydrochloride (Fig. 10.4). Thus, they concluded that the integrity reflex path in the body surface-internal organs and the telotism of the cardiac nerves were critical for the acupuncture therapy for experimental arrhythmia. Recent evidence obtained by Uchida et al (2008) shows that acupuncture signal may transmit through the Group Ⅳ muscle efferent fibers, and activate the γ-aminobutyric acid (GABA) neurons in the brainstem, thus, inhibiting the sympathetic output and decreasing the heart rate.

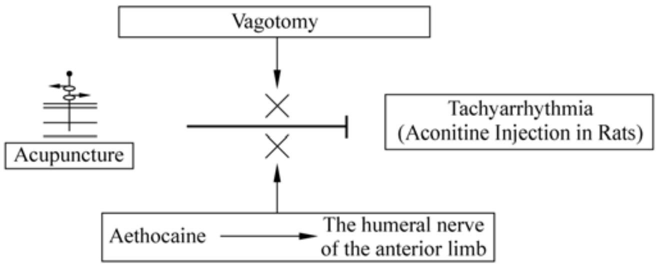

Figure 10.4 The roles of the vagus and humeral nerves in acupuncture treatment for tachyarrhythmia.

The heart is mainly innervated by Thorax 1-5 of the spinal cord. Neiguan (PC-6) is a common acupoint used for the treatment of arrhythmia in clinical practice. It is mainly innervated by the median nerve that belongs to the spinal cord segments at Cervicum 7 (C-7) ~ Thorax 2 (T-2). Acupuncture at the acupoint Neiguan (PC-6) was observed to excite the afferent nerve fiber (Groups Ⅱ and Ⅲ) of the median nerve, which may eventually affect the vagus and sympathetic nerves, and thus regulate the cardiac function. Indeed, some experiments showed that acupuncture at the acupoint Neiguan (PC-6) had little/no effect on the cardiac regulation after the median nerve was cut (Lin 1994). In a rat model of acute myocardial ischemia caused by pituitrin, Yan et al (1998) observed that after cutting the right ventral roots and dorsal roots of the spinal cord segments C-6 ~ T-2, stimulating the median nerve under the acupoint Neiguan (PC-6) in the right side could still improve the ECG. This observation provided additional evidence that the intact nerve pathway in one side can transfer acupuncture signals in this particular side and induce cardiac reaction.

Based on our previous work and literature search, we believe that the dysfunction of the nervous system significantly contributes to the generation of arrhythmia, and acupuncture therapy for arrhythmia is dependent on the regulation of this system. The acupuncture signals are processed in the central nervous system, and subsequently regulate the activity of the cardiovascular centers and autonomic nervous system, thereby adjusting the heart function and inhibiting arrhythmia (Xia 1983; Xia et al. 1985, 1987, 1988a, 1988b, 1989b, 1989c; Uchida et al. 2007).

10.3.1.2 Role of neurotransmitters

The nervous system is a functional integrity with chemical and electrical connections at all levels. In most of the cases, afferent signals and outgoing signals of acupuncture are regulated and integrated by the superior position of the brain. As a result, many neurotransmitters in the brain undergo significant changes in their activity in response to acupuncture.

Central neurotransmitters are the important substances to regulate the cardiovascular activity. The signals of acupuncture may activate a series of actions in the central nervous system, including the activity of the central neurotransmitters (Xia and Cao 1985). For example, EA increases the content of the endogenous opioid peptide (EOP) in the cerebrospinal fluid (Pert et al. 1981). Indeed, both manual acupuncture and EA can activate the endogenous opioid system in the brain (see Chapter 4). This activation may attenuate the sympathetic nervous activity and enhance the parasympathetic nervous activity (Holaday 1983; Xia et al. 1985). We (Xia and Li 1984; Xia et al. 1985, 1986) found that opioid peptides in the periaqueductal gray matter and brain stem play an important role in the inhibition of hypothalamic stimulation-induced ventricular extrasystoles (HVE) by simulated EA, i.e., deep peroneal nerve stimulation (DPNS) with low-frequency and low-intensity currents. These early observations have been confirmed by other independent investigators. For example, Li et al (1997) found that DPNS with square wave at low frequency and low intensity could inhibit HVE. Moreover, morphine microinjected into the hippocampus was also observed to attenuate HVE, while the microinjection of naloxone (an antagonist of the opioid receptor) increased HVE, suggesting that opioid receptor in the hippocampus may participate in the DPNS-induced inhibition of HVE (Li et al. 1997).

Yu et al (1999) observed tachycardia in morphine-withdrawn rats and studied the effect of EA on such arrhythmia. Morphine dependence was induced in Wistar rats by injecting morphine for 8 days. Subsequently, the heart rate and blood pressure of the rats were recorded 18 – 24 h after morphine withdrawal. They observed that tachycardia was ameliorated by 100 Hz EA, which was reversed by injecting the opioid receptor antagonist, naloxone (1 mg/kg) or κ-opioid receptor antagonist, nor-binaltorphimine (nor-BNI, 2 mmol). You et al (2005) observed that the effect of scalp EA on the lateral line 1 of the forehead on the experimental arrhythmia was also dependent on the opioid system in the brain. They applied scalp EA on the Wistar rats with experimental arrhythmia induced by barium chloride and observed that arrhythmia was significantly ameliorated by scalp EA, and this effect was reversed by naloxone injected into the periaqueductal gray matter ($p<0.01$).

All these studies demonstrate that the opioid peptide system in the brain is very important for acupuncture therapy for experimental arrhythmia. Acupuncture is believed to evoke the release of EOP and activate the opioid receptors in the brain, thus regulating the tonic of the cardiac sympathetic center and the output signals, subsequently inhibiting arrhythmia. This may be especially true for rapid arrhythmia resulting from an increase in the sympathetic activity (Fig. 10.5).

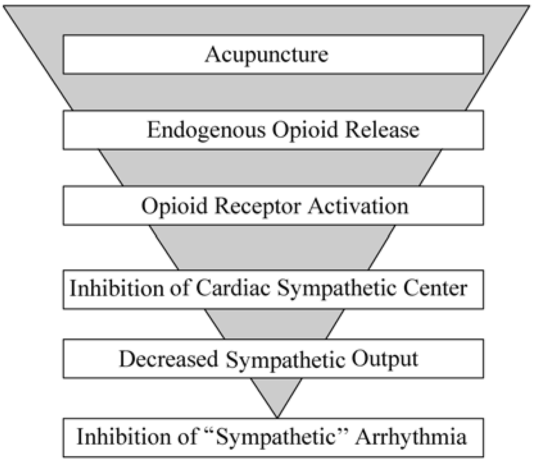

Figure 10.5 Acupuncture-induced inhibition of the sympathetic activity through the opioid system.

However, there is also evidence suggesting that the opioid system may be involved in the effect of acupuncture on bradycardia. For example, Zou et al (2000) reported that acupuncture at the acupoints Quchi (LI-15) and Neiguan (PC-6) could effectively suppress bradycardia, while intraventricular injection of naloxone could block the suppression. If this phenomenon can be verified, the mechanisms underlying acupuncture therapy for arrhythmia may be more interesting, i.e., endogenous opioid system may play a biphasic role in the regulation of "rapid" and "slow" arrhythmia.

In addition to the opioid peptide, a variety of other neurotransmitters have been observed to be involved in acupuncture suppression of arrhythmia. For example, we (Xia et al. 1985) observed that not only EOP, but also 5-hydroxy-tryptamine (5-HT) participated in the process in which DPNS inhibited HVE.

Studies by Li and Longhurst (Li 2002; Longhurst 2002) on the treatment of experimental arrhythmia with EA showed that EA at the acupoint Neiguan (PC-6) or Zusanli (ST-36) with low-frequency and low-intensity current could activate some brain regions to release the neurotransmitters or modulators, including the opioid peptide-like substances and GABA. These substances could inhibit the neuronal activity in the rostral ventrolateral medulla and the adrenergic nerve output, with the amelioration of arrhythmia and myocardial ischemia. They also showed that the opioid peptides, 5-HT, and acetylcholine (ACh) participated in the mechanism of acupuncture.

In the study on acupuncture therapy for bradycardia, Zou et al (2000) observed that the acupuncture-induced attenuation of bradycardia was blocked by the intravenous (i.v.) injection of propranolol, a β-receptor antagonist, but not by prazosin or yohimbine, which are α1- and α2-receptor antagonists, respectively, suggesting that the β-adrenergic receptors may be involved in the effect of acupuncture on bradycardia.Taken together, the mechanism underlying acupuncture therapy for arrhythmia is presumed to involve endogenous opioids and many other neurotransmitters, including 5-HT, noradrenalin, and ACh (Fig. 10.6).

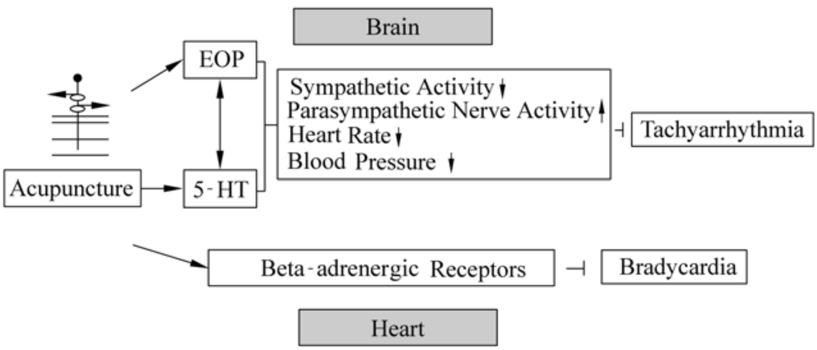

Figure 10.6 Some neurotransmitters and receptors involved in acupuncture therapy for cardiac arrhythmia.

10.3.1.3 Humoral and electrolyte mechanisms

Catecholamine (CA) in the blood is an active substance in increasing sympathetic activity of the cardiovascular system (Chen, 1984; Sandblom and Axelsson 2006; Liu et al. 2006). It has been found that acupuncture influences the level of CA in the blood. Liu et al (1997) developed an animal model of acute myocardial ischemia by ligating the left ventricle branch of the coronary artery, and tested the effect of EA on it. Their results showed that EA at the acupoint Neiguan (PC-6) significantly reduced the plasma level of norepinephrine. Fu et al (2004) found that acupuncture could decrease plasma norepinephrine and dihydroxyphenyl ethylamine to normal level in patients with cerebrocardiac syndrome, sustain neuroendocrine and body-fluid equilibrium, and thus protect the cardiac muscle from injury. Acupuncture is likely to improve myocardial ischemia and attenuate arrhythmia by regulating the level of CA in the plasma.

Clinical observations show that patients are sensitive to transient hypopotassemia or hypomagnesemia, which often causes disruption of the bioelectrical activity and physiological integrity of the cardiac muscle cells, especially during myocardial ischemia (Nordrehaug 1985; Zheng and Zhao 1991). Thus, patients who suffer from acute myocardial infarction, complicated with hypopotassemia or hypomagnesemia, have more chances to suffer from arrhythmia, such as premature ventricular contraction, ventricular tachycardia, and ventricular fibrillation (Solomon 1984). However, could acupuncture regulate arrhythmia via the regulation of potassium and/or magnesium level? An investigation carried out by Bao et al (2000) provided a negative answer. In a rabbit model of acute myocardial ischemia by the left anterior descending branch of the coronary artery ligation, they examined the effect of EA on ventricular fibrillation threshold (VFT) and serum levels of K^+ and Mg^{2+}. The results showed that the coronary artery ligation lowered VFT with transient hypopotassemia. EA was observed to remarkably raise VFT at the early stage of acute myocardial ischemia, but did not alter hypopotassemia at all. They concluded that EA could raise VFT at the early period of acute myocardial ischemia, and that this effect was not correlated with any changes in hypopotassemia.

10.3.1.4 Local cardiac regulation

Some researchers examined whether acupuncture could directly regulate the physiological characteristics of the cardiac cells when it is employed for the treatment of arrhythmia. Liu et al (2005) induced acute myocardial infarction in rats by the ligation of the anterior descending coronary artery, and subsequently recorded the monophasic action potential (MAP) in vivo. They found that after acupuncture at the acupoints Neiguan (PC-6), Sanyinjiao (SP-6), and Shenmen (HT-7), the monophasic action potential amplitude (MAPA) in the ischemic region significantly increased when compared with the control group, and the monophasic action potential duration (MAPD) was close to the normal level. On the other hand, the second-phase platform and the third-phase slope rate recovered and almost reached the normal level. These observations suggest that acupuncture might improve the MAP course of depolarization and repolarization, and thus relieve ischemic stress to cardiac cells. In addition, they speculated that acupuncture could increase the coronary blood flow, reduce the resisting power, and enhance the responsiveness of fast channels, thus improving the stability of the cardiac cell membrane.

The changes in the Ca^{2+} concentration in the myocardial cells have a direct effect on arrhythmia, especially during ischemia. Myocardial ischemia can cause arrhythmia as a result of remodeling of Cx43 gap-junction protein of the ventricular muscle, changes in the electrical conductivity between the myocardial cells, and damages to the electro synchronism of the heart. Therefore, ischemic arrhythmia may be at least partially attributed to the disruption of the electric conductance in Ca^{2+}-Cx43 gap junction. Some investigators considered that acupuncture might improve the electric conductance in Ca^{2+}-Cx43 gap junction, and subsequently enhance the cardiac function and attenuate arrhythmia (Qin et al. 2007). Consequently, their study showed that pretreatment of EA can effectively inhibit arrhythmia induced by myocardial ischemia and reperfusion (MIR) in rats, and the effect was partially owing to a decrease in the intracellular calcium oscillation (Qin et al. 2008).

Cyclic adenosine monophosphate (cAMP) and cyclic guanylic acid (cGMP) are widely present in the cells. Both participate in the physiological and pathophysiological process of the cells, including cellular growth, differentiation, and reaction to hormones. However, in some tissues, their physiological effects are found to be contrasting. For example, cAMP is observed to break down amylon and fat, promote cardiac muscle contraction, and smooth muscle relaxation, while cGMP is found to carry out the opposite function. Under normal conditions, the contents of cAMP and cGMP are relatively stable in the tissues and body fluid at an appropriate ratio. Once the balance is broken, a series of physiological and biochemical processes may occur. Therefore, some scholars suggested that cAMP and cGMP may be the "*Yin-Yang*" regulatory system of the body and may be the physical basis of "*Yin-Yang*" hypothesis in TCM (Goldberg et al. 1975) (Fig. 10.7). Gao et al (1980) measured the levels of cAMP and cGMP in the left ventricular muscle of the rats using protein-binding assay and radioimmunoassay, and found that acupuncture could adjust the abnormal ratio of cAMP and cGMP, and bring it to the normal level. This regulation is biphasic. When the level was higher than the normal level, acupuncture was observed to decrease it, and vice versa. Wu et al (1999) investigated the influence of EA on the contents of cAMP and cGMP in the blood plasma, cardiac muscles, and medullae in the rabbit model of acute myocardial ischemia induced by hypophysin (2.5 Units/kg, i.v.). They observed that EA at the acupoint Neiguan (PC-6) inhibited excessive increase in cGMP level in the tissues studied, and restored the ratio of cAMP and cGMP to the normal level. Therefore, acupuncture seems to attenuate arrhythmia by regulating the level of cAMP and cGMP.

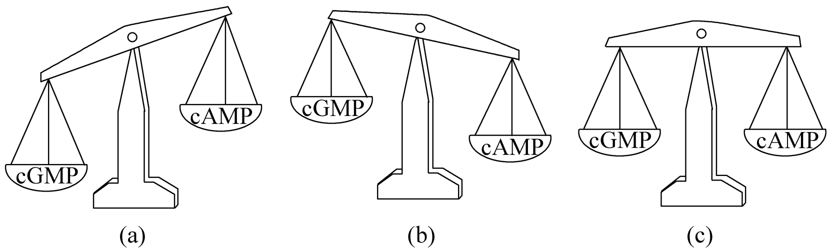

Figure 10.7 Schematic diagram of cAMP and cGMP balance in the body. According to the theory of the authors (Goldberg et al. 1975), an imbalance in cAMP and cGMP may lead to a disease state (a, b), while acupuncture may modulate the abnormal ratio of cAMP and cGMP, and reset their balance (c).

In the studies on the mechanisms, Gao et al (2006) investigated the pathways of signal transduction. They induced MIR in rats by ligation of the left anterior descending coronary artery, followed by reperfusion. Arrhythmic score and the content of cAMP and Gsα (the α-subunit of stimulatory guanine nucleotide-binding protein) protein in the ischemic myocardium were compared among the normal control (NC), ischemia and reperfusion (IR), IR+EA, and IR+EA plus propranolol (EAP) groups. The results showed that the arrhythmic score of the IR group at 10 min after reperfusion was significantly higher than that of the NC group ($p<0.01$); the score was lower in the EA group ($p<0.01$ vs. the IR group) and the score of the EAP group was similar to that of the IR group and much higher than that of the EA group ($p<0.01$). Similar results were also observed with regard to the contents of cAMP and Gsα protein in the ischemic myocardium group. Such attenuation was significantly inhibited by the intraperitoneal injection of propranolol, a specific β-adrenoreceptor antagonist. These results suggest that EA pretreatment could significantly attenuate arrhythmia and enhance the contents of myocardial cAMP and Gsα protein induced by MIR, which is possibly related to the activity of β-adrenergic receptors.

10.3.1.5 Other possible mechanisms

Concentration of Ca^{2+} at the stimulated acupoints. Ca^{2+} is one of the important ions that participate in multiple functions of the body, including cardiac activity. Indeed, it is essential for heart beat. Changes in the Ca^{2+} concentration greatly influence the cardiac rhythm. Therefore, some studies tried to determine whether acupuncture could alter Ca^{2+} concentration when attenuating arrhythmia. Interestingly, some investigators noticed changes in the Ca^{2+} concentration at the acupoints. Zhang et al (1995) established two models of experimental arrhythmia in rabbits, by injecting aconitine and electrically stimulating the hypothalamus. They found that acupuncture could reduce arrhythmia. However, after chelation of Ca^{2+} at the acupoint Neiguan (PC-6) with ethylenediamine tetraacetic acid (EDTA) solution, the effect was eliminated. Hu et al (1998) carried out a more exhaustive study. They induced arrhythmia in rabbits by i.v. injection of aconitine (0.002% dissolved in physiological saline solution, pH: 6.5 – 7.0), and then continuously monitored the changes in the Ca^{2+} concentration at several acupoints with an ionic activity meter in four experiment groups: (1) acupuncturing at the left Quze (PC-3) acupoint and monitoring the Ca^{2+} concentration at the left Quchi (LI-15) and left Zusanli (ST-36) acupoints of the arrhythmic rabbits, and those without acupuncture; (2) acupuncturing at the left Neiguan (PC-6) acupoint and monitoring the Ca^{2+} concentration at the left Quze (PC-3) acupoint; (3) monitoring at a point 2 cm away from the left Neiguan (PC-6) acupoint in rabbits with experimental arrhythmia; and (4) acupuncturing at the left Neiguan (PC-6) acupoint and monitoring at a point 2 cm away from the left Neiguan (PC-6) acupoint in rabbits with experimental arrhythmia. The experimental data showed that Ca^{2+} at Quze (PC-3) and Neiguan (PC-6) acupoints decreased and then recovered gradually during the period of arrhythmia. However, its level could not be restored to the normal level. Acupuncturing at the acupoint Neiguan (PC-6) inhibited the decrease in Ca^{2+} level at the acupoints and restored it to the normal level. This demonstrated a change in Ca^{2+} along the Pericardium Meridian. Thus, the authors believed that Ca^{2+} ions might partially form the basis of the functional activity of the meridians and collaterals; their change may be related to the mechanism of acupuncture therapy for arrhythmia. However, it is difficult to correlate the changes in the level of Ca^{2+} at the acupoints with those in arrhythmia in the heart.

Hydrogen ion at the stimulated acupoints. Similar to the studies on Ca^{2+}, Guo et al (1994) monitored the changes in the hydrogen ion concentration, using a pH sensor, at the left Neiguan (PC-6) acupoint, 0.3 cm away from the left Neiguan (PC-6) and Zusanli (ST-36) acupoints in rabbits with experimental arrhythmia, after confirming the therapeutic effect of acupuncture on arrhythmia at the acupoint Neiguan (PC-6). They showed that the hydrogen ion concentration at the left Neiguan (PC-6) acupoint suddenly increased with the occurrence of experimental arrhythmia and then decreased to a low level. When arrhythmia was attenuated by acupuncture, the hydrogen ion concentration at the left Neiguan (PC-6) acupoint increased to the normal level. However, the hydrogen ion concentration at the other two acupoints (left Zusanli acupoint and 0.3 cm away from the left Neiguan acupoint) did not change. This observation suggests that hydrogen ion concentration at some meridians and acupoints might have specific changes when "zangfu" organs exhibit pathological changes. Again, the precise mechanism is still unknown. Further experiments are needed to validate the results and deepen the investigation.

Guanine nucleotide-binding protein in the medulla. Zhen et al (2006) acupunctured at the Neiguan (PC-6) acupoint of rats with tachyarrhythmia induced by aconitine, and subsequently detected the heart rate and mRNA of the stimulant G-protein of the guanine nucleotide-binding protein in the medulla oblongata before and after acupuncture treatment. The results showed that the mRNA markedly increased in the group of arrhythmia, which could be reduced by acupuncture at the acupoint Neiguan (PC-6). The authors concluded that tachyarrhythmia might be partially attributed to the gene expression of guanine nucleotide-binding protein in the medulla, and that acupuncture at the acupoint Neiguan (PC-6) might attenuate tachyarrhythmia by decreasing its expression. Soon after, however, other investigators (Chen et al. 2006; Zheng et al. 2006; Cao et al. 2007a, 2007b; Yan et al. 2007; Zhang et al. 2007; Zheng et al. 2007; Hu P et al. 2008; Hu TT et al. 2008) made different observations in the rat models of experimental arrhythmia, and they believed that the guanine nucleotide-binding protein and its signal pathway may play an important role in acupuncture therapy for cardiac arrhythmia.

The abovementioned reports showed some interesting observations. However, the exact meaning and accurate explanation remain unclear. This is because the simultaneous changes in the body do not necessarily signify that they have any inevitable relationship.

10.3.2 Mechanisms of Acupuncture Therapy for Other Cardiac Disorders

When compared with the studies on arrhythmia, much less data have been generated on the mechanisms of acupuncture therapy for other cardiac disorders. However, there have been some reports initially elucidating the mechanism of acupuncture-induced effects on coronary heart disease.

10.3.2.1 Mechanisms of acupuncture therapy for coronary heart disease

Acupuncture treatment for coronary heart disease has made a rapid progress in recent years. Cui and Cao (1995) observed the influence of EA at the acupoint Neiguan (PC-6) on ischemic myocardia through the analysis of adenine nucleotides and two components of the monophasic action potential. The results suggested that ATP and ADP were significantly lower with electrical disturbance in ischemic myocardia. EA at the acupoint Neiguan (PC-6) could ameliorate such condition. Specifically, the level of ATP and ADP at the marginal area of ischemic myocardia was increased by EA. However, it is still unclear whether the changes in the adenine mononucleotide form the basis for improving the electrical stability of the cardiac muscles.

Researchers also found that myocardial ischemia promoted the release of catecholamines (CA) in the myocardial adrenergic nerve endings, thereby activating the corresponding receptors. Acupuncture was observed to inhibit the release of CA, thus lowering the CA activity and reducing the damage to the cardiac muscle cells (Wen et al. 1993). In addition, Liu's experiment (1997) showed that the contents of norepinephrine in the plasma was significantly increased ($p<0.05$) after acute myocardial ischemia induced by ligation of the left ventricle of the coronary artery for 20 min. Furthermore, EA at the acupoint Neiguan (PC-6) was observed to largely decrease the content of norepinephrine ($p<0.05$), but failed to change the content of 5-HT and adnephrin ($p>0.05$). Clearly, such change may be beneficial for the ischemic cardiac cells.

Another report (Sun et al. 1996) indicated that EA at the acupoint Neiguan (PC-6) had a protective effect on the electric-activity stability of acute myocardial ischemia. This effect was observed to be related to the activation of the opioid receptors located at the ventrolateral medulla. Chen et al (2000) established acute myocardial ischemia in rabbits by ligation of the left ventricular coronary branch and then examined the ST segment and the damage size of myocardial ischemia. The control group, the EA on the acupoint Neiguan (PC-6) group, and the naloxone plus EA group, were divided randomly. The results showed that EA at the acupoint Neiguan (PC-6) could promote the restoration of ST segment in acute myocardial ischemia and attenuate myocardial ischemia. This effect could be blocked by naloxone microinjected into the lateral cerebral ventricle. Thus, the authors concluded that EOP played an important role in reducing myocardial injury by acupuncture at the acupoint Neiguan (PC-6). In another study, after EA at the acupoint Neiguan (PC-6), Wang et al (2004) measured the contents of β-endorphin in the medullae of the rabbits with acute myocardial ischemia. They found that EA at the acupoint Neiguan (PC-6) could adjust the content of β-endorphin in the brain tissues and improve the blood supply in the cardiac muscle tissues. Hence, it was inferred to be one of the important mechanisms in acupuncture therapy.

Zheng et al (1999) acupunctured the acupoints Zusanli (ST-36), Sanyinjiao (SP-6), Neiguan (PC-6), and Xinshu (BL-15) to treat 20 cases of CHD patients, and then detected the plasma endothelin (ET), lipid peroxidation (LPO), superoxide dismutase (SOD), and the whole-blood glutathione peroxidase (GSH-Px). They showed that ET and LPO were significantly higher and GSH-Px was much lower ($p<0.01$) in patients with CHD than the control level. After acupuncture, ET and LPO significantly decreased ($p<0.01$), while GSH-Px increased ($p<0.01$). It seems that acupuncture could regulate ET in patients with CHD. The mechanism might be related to improving coronary circulation, reducing LPO on the endothelial cell injury, and enhancing the antioxidant enzyme activity in hypoxic-ischemic myocardial cells. Han (1999) determined the serum activity of SOD and the content of LPO in 40 cases with coronary heart disease before and after acupuncture therapy, with 30 control cases. It was found that after acupuncture treatment for about 1 month, the activity of SOD increased markedly ($p<0.05$) with a significant decrease in the content of LPO ($p<0.05$), when compared with the control group. These observations suggest that acupuncture may elevate the activity of SOD and degrade LPO during the treatment of coronary artery disease with acupuncture, which improves the ability of the antioxidant and anti-lipid peroxidation. Undoubtedly, it has a positive role in the prevention and treatment of coronary heart disease.

Li (1999) found that acupuncture therapy on angina pectoris patients could decrease the plasma Thromboxane B2 (TXB2) and the ratio of TXB2/6-Keto-PGF (T/P). This suggests that acupuncture may adjust TXB2 and T/P, thus relieving coronarospasm and coronary artery occlusion, increasing coronary blood flow, and attenuating angina pectoris induced by coronary artery disease. Liu et al (2004) found that acupuncture could improve variant angina pectoris and increase the plasma nitric oxide (NO) levels in variant angina pectoris patients. Similar result was also observed by Xiao et al (2002) who showed that acupuncture could reduce ET levels, prevent the decline of NO, improve imbalance between ET and NO, and relieve coronary capillary vessel spasm.

These data provide initial information on the mechanism of acupuncture therapy for CHD and suggest that acupuncture can improve neurohumoral regulation, increase coronary blood flow and myocardial oxygen supply, and reduce myocardial oxygen consumption, thus improving myocardial ischemia.

10.3.2.2 Mechanisms of acupuncture treatment for other cardiac diseases

Some clinical reports show that acupuncture can improve the symptoms of cardiac failure, viral myocarditis, and rheumatic heart disease (Hu 1997; Li and Man 2004; Zhu 1998; Deng et al. 2001; Li et al. 1996; Liu and Liu 1994). However, currently, there is a lack of research on its mechanism. Some TCM researchers believe that acupuncture can circulate qi and blood of the meridian, tranquilize the mind, and tonic cardiac qi. Our laboratory as well as other groups have found that δ-opioid receptors play an important role in the protection of brain and heart from hypoxic/ischemic condition (Zhang et al. 2000, 2002, 2006; Lim et al. 2004; Ma et al. 2005; Su et al. 2007; Charron et al. 2008; Borlongan et al. 2009). As acupuncture can activate the endogenous opioid system, we speculate that acupuncture may protect the heart and brain from damage, especially in the hypoxic ischemic injury, via δ-opioid receptor system.

10.4 Concluding Remarks

Clinical practice and basic research on acupuncture treatment for cardiac diseases have demonstrated that: (1) acupuncture has a therapeutic effect on a variety of cardiac diseases; (2) the effect of acupuncture treatment depends on the types of the diseases, the acupoints selected, and the manner of acupuncture manipulation and EA stimulation; and (3) acupuncture signals are transferred via the neural pathway, and regulate a number of neurotransmitters and modulate the sympathetic and parasympathetic outputs, endocrine outputs, body fluids, and local cardiac muscles, thus improving the cardiac function and ameliorating the disease conditions.

Although major progresses have been made in clinical and basic studies on acupuncture therapy for cardiac diseases, many problematic issues still remain to be clarified in this field.

First, many of the clinical reports lack data on multiple-center and large-scale observations. Second, most reports are based on an immediate or short-term effect after acupuncture therapy. A long-term follow-up is needed for a better evaluation of the effect of acupuncture. Third, acupoint selection and application are very limited in the past studies. It is important to obtain more convincing evidence with the comparison of multiple acupoints, to define the specificity of acupoints. Lastly and most importantly, majority of the previous clinical studies lack strict control. Thus, more rigorous studies are needed with standardized treatment protocols, diverse patient populations, and long-term follow-up (Van Wormer et al. 2008).

Previous basic studies have been limited to certain cardiac disorders such as arrhythmia. As clinical acupuncture has shown its broad effects on various cardiac diseases, such as cardiac failure, viral myocarditis, and rheumatic heart disease (Liu and Liu 1994; Li et al. 1996; Hu 1997; Zhu 1998; Deng et al. 2001; Li and Man 2004), it is important to expand the scope of the basic research to various cardiac diseases, which may provide experimental validation and mechanistic understanding of acupuncture therapy for serious cardiac disorders. Moreover, some of the previous studies require validation through additional experiments with better protocol design. In fact, certain conclusions were somehow based on unreliable results or two simultaneous events. We presume that two simultaneous events seen in the body may not necessarily mean that they have any causal relationship.

With regard to the mechanistic research on acupuncture therapy for arrhythmia, we have drawn a relatively clear picture, though many details are still far away from our vision. However, we have much less information today regarding the mechanisms of acupuncture treatment for other heart diseases. Our recent work as well as those of the others have demonstrated that δ-opioid receptors play an important role in the protection of brain and heart in the hypoxic/ischemic conditions (Zhang et al. 2000, 2002, 2006; Peart et al. 2003; Lim et al. 2004; Ma et al. 2005; Patel et al. 2006; Huang et al. 2007; Su et al. 2007; Charron et al. 2008; Borlongan et al. 2009; Chao et al. 2009; Yang et al. 2009). As we have previously shown that acupuncture can activate the endogenous opioid system in the body and influence the cardiovascular activity (Xia and Li 1984; Xia et al. 1985, 1986, 1988a, 1989c, also refer to Chapter 4), we speculate that acupuncture may, at least partially, protect the heart and brain from damage, especially hypoxic/ischemic injury, through the unique δ-opioid receptor system.

Acupuncture has a history of thousand years and still plays a role in today's health care around the world. With more efforts on clinical and basic research at the molecular, cellular, and the whole body levels, we may be able to better understand the mechanisms of acupuncture for treating cardiac diseases, which may lead to better applications of acupuncture at the bedside and potentially provide novel clues for new solutions to cardiac diseases.

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11 Acupuncture Therapy for Hypertension and Hypotension

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Summary This chapter summarizes the clinical practice and mechanistic exploration of acupuncture therapy for hypertension and hypotension. Numerous clinical reports have shown that the therapeutic efficacy of acupuncture on abnormal blood pressure is dependent on the acupoints, acupuncture manipulation or stimulation parameters in the case of electroacupuncture, applying window, times of treatment, and other factors. The mechanistic research has established the idea that acupuncture signals initiated at the acupoints are transferred to the brain through the nervous pathway, thus, modulating multiple neurotransmitter systems at different levels. The output signaling cascades correct abnormal blood pressure, mainly through neural regulation. In addition, acupuncture-induced correction of abnormal blood pressure is also observed to be dependent on the endocritic, humoral, and dielectric regulation. Collectively, acupuncture induces a comprehensive modulation of the cardiovascular activity, consequently, adjusting the blood pressure. Lastly, we will comment on several unsolved issues and future directions of the research concerning acupuncture treatment for abnormal blood pressure.

Keywords *acupuncture mechanism, hypertension, hypotension, blood flow, neural regulation*

11.1 Introduction

Blood pressure is continuously regulated by the autonomic nervous system through an elaborate network of nerves, receptors, and hormones, to balance the effects of the sympathetic and parasympathetic nervous systems. The ability for the vast and rapid compensation of the autonomic nervous system allows normal individuals to maintain normal blood pressure over a wide range of activities (Bettencourt et al. 2008; Chen et al. 2008).

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Abnormality of blood pressure, either hypertension or hypotension, is a very common cardiovascular condition. It can be primary or secondary to other diseases, especially cardiovascular and cerebrovascular disorders. In many disease states, the blood pressure may be out of control owing to complex pathological changes.

The most common abnormality of blood pressure is primary (or essential) hypertension. Unlike secondary hypertension, there is no known cause of primary hypertension. Approximately 90% – 95% of the patients diagnosed with hypertension have primary hypertension (JNC, 1997).

Acupuncture has been used to treat abnormal blood pressure for a long time in traditional Chinese medicine (TCM). Although there are currently a variety of effective drugs to treat abnormal blood pressure, especially hypertension, it is still very valuable to explore the mystery of the mechanism of acupuncture therapy for abnormal blood pressure. This is not only because of the fact that acupuncture is a convenient, safe, and cost-effective strategy, but also because of the notion that the understanding of its mechanism may provide novel insights into the mechanism of cardiovascular regulation and better treatment options for cardiovascular and cerebrovascular disorders in the future. Hence, many Chinese clinicians and scientists have performed clinical and bench studies on acupuncture therapy for abnormal blood pressure.

Interestingly, many studies, either using human or animal subjects, have demonstrated that acupuncture and EA have little effect on normal blood pressure, while they significantly adjust abnormal blood pressure, i.e., hypertension or hypotension. In other words, with appropriate acupoints and stimulation, acupuncture and EA can either decrease or increase the blood pressure depending on the condition of blood pressure, suggesting a delicate mechanism underlying the effect of acupuncture on blood pressure.

11.2 Clinical Application of Acupuncture for Treating Abnormal Blood Pressure

Numerous clinical studies have shown that acupuncture is effective in adjusting the blood pressure in hypertensive and hypotensive patients. These reports indicate that the efficacy of acupuncture therapy for abnormal blood pressure is largely dependent on the acupoints, acupuncture manipulation (e.g., lifting, thrusting, or rotating for manual acupuncture, and current parameters for EA), applying windows, and times of the treatment.

11.2.1 Hypertension

Acupuncture therapy is unique because it produces few side effects and is cost-effective (Zhang 1999) (Fig. 11.1). The therapeutic effect of acupuncture on hypertensive disease has been well confirmed by many clinical studies, though most of the clinical data suggest that the efficacy of acupuncture depressurization varies with the acupoints, acupuncture manipulation or EA parameter, and applying windows.

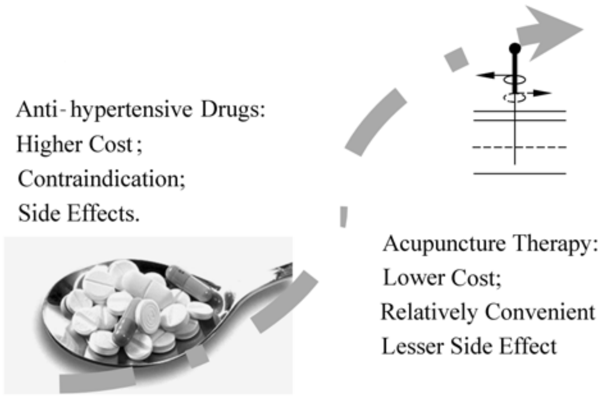

Figure 11.1 Major advantages of acupuncture vs. drug therapy for hypertension.

Acupoints such as Tinggong (Sl-19), Quchi (Ll-15), Fenglong (ST-40), Yongquan (KL-1), Zusanli (ST-36), Baihui (DU-20), Fengchi (GB-20), Fuliu (KL-7), Neiguan (PC-6), Gongsun (SP-4), Sanyinjiao (SP-6), and Taichong (LR-3) have been reported to induce a better effect than other acupoints (Wang 1996; Zhang et al. 1999; Huang 2000; Chen et al. 2006; Huang et al. 2007). Among these acupoints, some have been used as main acupoints, while others have been employed as supporting acupoints (Huang 2000). For example, Wang (1996) treated various types of hypertension in 95 patients using acupoints Baihui (Du-20), Fengchi (GB-20), Neiguan (PC-6), and Sanyinjiao (SP-6) as the main acupoints. For patients with the symptom of "hyperactivity of liver-YANG", acupoints Taichong (LR-3), Taixi (KL-3), Ganshu (BL-18), and Shenshu (BL-23) were chosen as the supporting acupoints. On the other hand, for patients with the symptom of "*phlegm stagnation*", acupoints Zhongwan (RN-13), Fenglong (ST-40), Touwei (ST-8), and GongSun (SP-4) were selected as the supporting acupoints. For patients with the symptom of "*deficiency of both Yin and Yang*", acupoints Guanyuan (RN-7) and Zusanli (ST-36) were adopted as the supporting acupoints. The acupuncture was performed once a day with warmed needle. After 2~4 weeks of acupuncture treatment, 10 patients demonstrated a major decrease in high blood pressure and 74 cases exhibited significant improvement, among the 95 patients treated.

Zhang et al (1999) separately acupunctured at a single acupoint, and subsequently compared the effects of several common acupoints in acupuncture depressurization. They observed that: (1) acupoints Fengchi (GB-20), Dazhui (DU-14), Quchi (LI-15), Neiguan (PC-6), Zusanli (ST-36), Taichong (LR-3), and Taixi (KL-3) produced a better effect than the acupoint Fenglong (ST-40) ($p<0.05$); (2) there were no differences among the acupoints Zusanli (ST-36), Taichong (LR-3), and Quchi (Ll-15) ($p>0.05$); (3) there were no differences among the acupoints Taichong (LR-3), Zusanli (ST-36), Neiguan (PC-6), Dazhui (DU-14), and Fengchi (GB-20); and (4) acupoint Quchi (LI-15) produced a better effect than the acupoints Neiguan (PC-6), Dazhui (DU-14), and Fengchi (GB-20). However, some clinical investigators believe that acupoint Zusanli (ST-36) does not play a significant role in acupuncture depressurization. For example, Chen (2002) conducted a blind clinical trial in patients with hypertension. The patients were divided into A and B groups, simply based on acupuncture at acupoint Zusanli (ST-36) or not. Both the groups were treated with general acupoints, such as Zhongwan (RN-13), Qimen (LR-14), Tianshu (ST-25), Tianzhu (BL-10), Fengchi (GB-20), Dazhu (BL-11), Jianjin (GB-21), Feishu (BL-13), Jueyinshu (BL-14), Pishu (BL-20), Shenshu (BL-23), and Dachangshu (BL-25). After the treatment, the blood pressure was decreased in both the groups, which showed no significant difference between the two groups of patients. Thus, the author concluded that acupuncture at the acupoint Zusanli (ST-36) had no antihypertensive effect (Chen 2002). However, this conclusion is contradictory to that of many other reports (Wang 1996; Zhang et al. 1999; Huang 2000; Guo and Ni 2001; Pan and Hu 2000). We consider that this controversy may be attributed to the different approaches in their studies. In this study (Chen 2002), several depressurization-effective acupoints were stimulated in both the groups to lower the blood pressure. In such situation, the additional stimulation of the acupoint Zusanli (ST-36), though may be effective for depressurization, might not lower the blood pressure further. This is because acupuncture signal leads to an integrated regulation of the cardiovascular system in the body. The biological activity in response to acupuncture may not be changed by simply adding or reducing a single acupoint. To better determine the role of a given acupoint in acupuncture depressurization, it may be a better strategy to stimulate that acupoint and compare it with other single acupoint without any interference from multiple acupoints. Table 11.1 lists the common acupoints used for the treatment of hypertension.

Table 11.1 Acupoints commonly used for treating hypertension*

Acupoints	Location	Other Applications
Tinggong (SI 19)	Between the targus and the mandibular joint where a depression is formed when the mouth is slightly open	Tinnitus; deafness; purulent tympanitis; toothache; epilepsy
Quchi (LI 15)	When the elbow is flexed, the point can be located in the midpoint between the lateral end of the transverse cubical crease and the lateral epicondyle of the humerus	Febrile disease; swelling and pain in the throat and the upper extremities; abdominal distention; vomiting; diarrhea; toothache; urticaria; insanity; mania; susceptibility to fright; swelling and pain in the arm

(Continued)

Acupoints	Location	Other Applications
Fenglong (ST 40)	8 cun superior and anterior to the external malleolus, one finger breadth from the anterior crest of the tibia	Cough; asthma; dizziness; mental disorder; indigestion; numbness of the lower limbs
Yongquan (KL 1)	Approximately at the junction of the anterior and middle third of the sole (excluding toe)	Waking up a patient from unconsciousness; syncope; hysteria; treating both shock and high blood pressure; terminal neuritis; pain and numbness of the toe
Zusanli (ST 36)	3 cun below Dubi, one finger breadth from the anterior crest of the tibia	Main point for the gastro intestinal diseases; cough; asthma; fainting; insomnia; strengthening immunity; reviviscence; treating disorders in the head and face; paralysis of the lower extremities
Baihui (DU 20)	7 cun directly above the midpoint of the posterior hairline	Main point to treat neurological diseases, such as dizziness, cerebral apoplexy; epilepsy; various kinds of headache; neurasthenia; faintness; and insomnia
Fengchi (GB 20)	In the posterior aspect of the neck, below the occipital bone, in the depression between the upper portion of musculus sternocleidomastoideus and musculus trapezius	Headache; dizziness; pain in the eyes; eye redness; pain in the neck; apoplexy; deviated mouth; common cold
Fuliu (KL 7)	2 cun directly above acupoint Taixi (KL 3), anterior to the Achilles tendon	Edema; abdominal distention; diarrhea; febrile disease without sweat or ceaselessly sweating; night sweating; weakness; numbness; pain in the lower extremities
Neiguan (PC 6)	2 cun above the transverse crease of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis	Main point for treating heart diseases, such as tachycardia, bradycardia, arrhythmia, and angina pectoris; also used for insomnia; epilepsy; mental disorder; chest pain; asthma; stomachache; vomiting; retching; hiccup; fever caused by deficiency of *Yin*; common point for acupuncture anesthesia in chest operations
Gongsun (SP 4)	In the depression, distal and inferior to the base of the 1st metatarsal bone, at the junction of the red and white skin	Main point for gastro intestinal diseases, such as stomachache, abdominal pain, vomiting, and diarrhea
Sanyinjiao (SP 6)	3 cun directly above the tip of the medial malleolus on the posterior border of the tibia	Deficiency of the spleen and stomach; borborygmus; abdominal distension; irregular menstruation; leucorrhea; nocturnal emission

(Continued)

Acupoints	Location	Other Applications
Taichong (LR 3)	On the dorsum of the foot, in the depression distal to the junction of the 1st and 2nd metatarsal bones	Hepatitis; cholecystisis; cholelithiosis; ascariasis of the gallbladder; fainting and headache caused by high blood pressure; convulsion of epilepsy; spermatorrhea; enuresis; amenorrhea; headache caused by hepatic fire; redness and pain in the eye
Taixi (KL 3)	In the depression between the prominence of the medial malleolus and heel tendon	Dizziness; tinnitus; insomnia; headache; toothache and sore throat caused by deficiency of Yin and excess of Fire; spermatorrhea; impotence; irregular menstruation
Ganshu (BL 18)	1.5 cun lateral to the lower border of the spinous process of the 9th thoracic vertebra	Main point for treating hepatic diseases, such as jaundice, pain in the hypocondriac region; dizziness, headache; epilepsy; madness; convulsion; pain due to the depression of hepatic energy or gastric energy, such as gastritis and ulcer; main point for eye diseases; deficiency syndrome; backache
Shenshu (BL 23)	1.5 cun lateral to the lower border of the spinous process of the 2nd lumbar vertebra	Main point for treating disorders in urinary system, such as frequently micturation, pain in urination, urgent micturation, retention, diguria, and edema; main point for diseases in genital system, such as impotence, spermatorrhea, and irregular menstruation; tinnitus deafness; chronic lumbago
Zhongwan (RN 13)	4 cun above the umbilicus	Main point for treating stomach diseases, such as stomachache, fullness of the stomach, regurgitation of acid, belching, nausea, and vomiting; cough with phlegm
Touwei (ST 8)	0.5 cun above the hairline of the forehead, 4.5 cun lateral to the anterior hairline	Headache; pain in eyes; dizziness; lacrimation with wind; twitching of the eyelids
Guanyuan (RN 7)	3 cun below the umbilicus	Main point for diseases of urinary and genital system, such as pain caused by polyuria, urine retention, incontinence of urine, nocturnal enuresis, impotence, spermatorrhea, irregular menstruation, and dysmenorrheal; chronic abdominal pain; chronic diarrhea; aged chronic bronchitis; collapse of the uterus; health point for keeping the body fit

(Continued)

Acupoints	Location	Other Applications
Dazhui (DU 14)	Below the spinous process of the 7th cervical vertebra	Fever; cold; malaria; controlling the symptom of malaria; mania
Qimen (LR 14)	Below the nipple, in the 6th intercostal space	Distension and pain in the chest and hypochondrium; feverish sensation in the chest; diarrhea; vomiting; cough; asthma
Tianshu (ST 25)	2 cun lateral to the centre of the umbilicus	Pain around the umbilicus; vomiting; abdominal distension; borborygmus; diarrhea; dysentery; constipation; abdominal mass; dysmenorrheal and irregular menstruation
Tianzhu (BL 10)	0.5 cun directly above the midpoint of the posterior hairline, 1.3 cun lateral to the anterior posterior midline in the depression of the lateral border of m. trapezium	Neck rigidity; cervical spondylopathy; cold caused nose stuff; sore throat
Jianjin (GB 21)	Midway between the acupoint Dazhui and the acromion, at the highest point of the shoulder	Stiffness and pain in the neck; pain in the shoulder and back; paralysis of the extremities; scrofula; acute mastitis; apoplexy; difficult labor
Feishu (BL 13)	1.5 cun lateral to the lower border of the spinous process of the 12th thoracic vertebra	Main point for gastric disorders, such as fullness of the stomach, stomachache, retching with sore water, hiccup, and vomiting; backache
Jueyinshu (BL 14)	1.5 cun lateral to the lower border of the spinous process of the 4th thoracic vertebra	Angina; palpitation; stuffy chest; cough; vomiting
Pishu (BL 20)	1.5 cun lateral to the lower border of the spinous process of the 11th thoracic vertebra	Gastric disorder such as fullness of the stomach, nausea, vomiting, retching, hiccup, chronic diarrhea; anemia;, bleeding, menorrhagia; cough and asthma with whitish watery phlegm; edema; scanty urination
Dachangshu (BL 25)	1.5 cun lateral to the lower border of the spinous process of the 4th lumbar vertebra	Main point for treating large intestinal diseases, such as diarrhea, dysentery, and constipation; main point to treat lumbar muscle strain or sprain

* The contents of this table refer to the relevant Internet resources and the following two monographs: (1) Jin SX. Chinese-English Learning and Memory Manual of Meridians and Acupoints,. Zhenzhou University Publishing House, Zhengzhou, 2002; and (2) Shen XY and Wang H. Acupuncture and Moxibustion. People's Medical Publishing House, Beijing, 2007.

There is evidence showing that the intensity of acupuncture signals is important for acupuncture-induced depressurization of hypertension. In a clinical study on hypertensive patients with "*sthenia syndrome*", Zhou and Jin (2004a) applied EA and compared the antihypertensive effects induced by higher (3.7 mA) and lower (2.7 mA) intensity EA with all other factors being the same, including acupoints, wave pattern, and frequency. The results showed that the systolic blood pressure increased slightly from 22.0 to 26.2 kPa (p<0.01) in the group administered with higher intensity EA, while in the group administered with lower intensity EA, the systolic blood pressure declined from 22.3 to 20.7 kPa (p<0.01) and the diastolic blood pressure declined from 11.9 to 11.3 kPa (p<0.01). Although the optimal intensity still needs to be better defined at the bedside, these observations suggest that the intensity of acupuncture stimulation is a critical factor determining the effect of acupuncture on blood pressure. A high intensity EA may excite the body and increase the blood pressure, instead of decreasing it.

There are also studies showing that the efficacy of acupuncture depressurization is dependent on the acupuncture-applying window or the status of the patients. The blood pressure of the hypertension patients is observed to vary at periodic cycles with a peak phase (the time point with the highest blood pressure) and a low phase (the time point with the lowest blood pressure) during a day. For example, acupuncture applied at the peak phase may induce an effect that is different from that applied at other phases during the fluctuation of blood pressure. Wang (1989) used acupuncture to treat 21 patients with primary hypertension at different phases with the same approach, and observed that the blood pressure declined more at the peak phase than at the non-peak phase, in response to acupuncture treatment, suggesting that cardiovascular sensitivity to acupuncture varies from time to time during the day. At a relatively high level of blood pressure, acupuncture may induce a greater decrease in high blood pressure (Fig. 11.2).

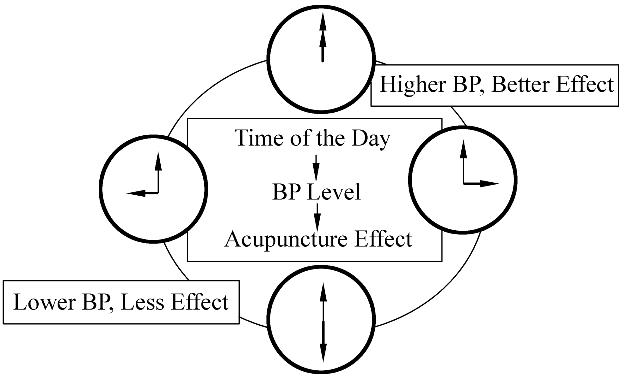

Figure 11.2 Schematic representation of acupuncture effects on blood pressure (BP) at different time points. Note that BP fluctuates during the day and the effect of acupuncture on hypertension varies with BP levels. Acupuncture induces a better effect on relatively higher level of BP.

Consistent with these observations, some studies demonstrated that acupuncture can lower high blood pressure and may not have a significant influence on normal blood pressure. Guo and Ni (2001) observed that in 87 patients, who were subjected to acupuncture therapy for various disorders, the systolic pressure declined in those with hypertension, while the diastolic or systolic pressure showed little change in patients with normal blood pressure. Ni et al (2001) also reported that acupuncture had no appreciable effect on the normal blood pressure in both male and female subjects. These observations demonstrate that acupuncture may adjust "abnormal", but not "normal" blood pressure.

There is also preliminary evidence implying that the efficacy of acupuncture depressurization may vary with genders. For example, Ni et al (2001) showed that acupuncture could lower the systolic pressure, but not the diastolic pressure in women. Owing to the lack of other solid evidence at this stage, there still exists a need to verify the presence of any major gender difference in terms of acupuncture depressurization.

In general, the therapeutic effect of acupuncture on hypertension is better at the early and middle stages than at the later stage in hypertensive patients. Yin (1994) analyzed the data of 48 hypertensive patients who underwent acupuncture therapy, and found that acupuncture induced satisfactory depressurization in patients with stage-II hypertension, but had limited effect on those with stage-III hypertension (Table 11.2). Thus, acupuncture may have a therapeutic effect on mild or moderate hypertension, but not on severe hypertension.

Table 11.2 Effects of acupuncture on hypertension in different conditions

Effect	Strong EA	Mild EA	Stage II hypertension	Stage III hypertension	Normal BP
Excellent (++)		++	++		
Good (+)				+	
None ( )					

Taken together, the clinical data demonstrate that acupuncture could induce depressurization in patients with hypertension, especially at the earlier stage. In contrast, acupuncture has been observed to produce no significant effect on normal blood pressure in either the normal subjects or patients with non-hypertensive diseases. The efficacy of acupuncture depressurization is greatly dependent on the acupoints, stimulation intensity, and applying window. However, the optimal conditions of acupuncture or EA therapy for lowering high blood pressure are not well defined yet.

11.2.2 Hypotension

In most of the individuals, a slight decrease in blood pressure, even as little as 20 mmHg, can result in transient hypotension with clinical symptoms. Hypotension can be secondary to hypovolemia (reduced blood volume as seen in excessive use of diuretics), decreased cardiac output, excessive vasodilation, and acute life-threatening allergic reaction. Primary hypotension can also occur, and the cause of low blood pressure is unclear. Hypotension is often associated with cardinal symptoms, such as lightheadedness or dizziness, headache, shortness of breath, chest pain, profound fatigue, loss of consciousness, and seizures. In TCM, hypotension belongs to the category of "megrim, heart-throb, or fatigue" (Mao and Wang 2003).

When compared with acupuncture therapy for hypertension, only limited research has been carried out on acupuncture effect on hypotension at bedside. As modern modalities provide relatively quick and effective treatment for hypovolemia, allergic reaction, and other disorders, there are only limited clinical studies on the application of acupuncture therapy for secondary hypotension. However, several published reports suggest that acupuncture could significantly improve primary hypotension. For example, EA on the acupoints Neiguan (PC-6) and Gongsun (SP-4) with slow wave (2 – 5 Hz) yielded a significant therapeutic effect on patients with hypotension (Yin et al. 2000). After 10 – 20 days of EA treatment (20 min/day), 32 out of 100 patients were completely cured (32%) and 66 of them showed marked improvement (66%). Only 2 patients did not respond to EA therapy (2%). The total effective rate was 98%. As the control, 110 patients were exposed to Chinese herbal medicine without acupuncture. They daily received "Bazhen Soup" containing "Decoction of Eight Ingredients", which comprised *angelicae sinensis radix, paeoniae alba radix, rehmannia glutinosa, ligustici rhizome, Codonopsis pilosula, poria cocos, atractylodes macrocephala,* and *glycyrrhizae radix*. After 10 days of treatment, 21 of the 110 patients completely recovered (19.1%) and 75 of them showed improvement (68.2%). However, the remaining patients (14) did not respond to herbal treatment. The effective rate of the herbal treatment was 87.3%, which is significantly lower than that of the EA group ($p<0.05$, Fig. 11.3). Wang (2000) reported similar results in support of this observation, although using different acupoints, e.g., Baihui (DU-20). The effective rate was 94.7% in patients subjected to acupuncture therapy (Wang 2000). These clinical studies suggest that EA or manual acupuncture is effective in the treatment of hypotension. Table 11.3 lists the common acupoints used for the treatment of hypotension.

These available data suggest that acupuncture may induce a therapeutic effect on hypotension; however, more scientific testing with strict control is needed to determine the clinical efficacy and long-term effect of acupuncture.

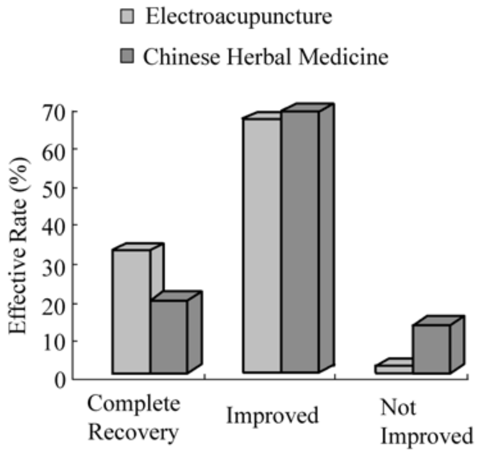

Figure 11.3 Therapeutic efficacy of EA vs. Chinese herbal medicine in patients with hypotension.

Table 11.3 Acupoints commonly used for treating hypotension*

Acupoints	Location	Other Applications
Baihui (DU 20)	7 cun directly above the midpoint of the posterior hairline	See Table 11.1
Gongsun (SP 4)	In the depression, distal and inferior to the base of the 1st metatarsal bone, at the junction of the red and white skin	See Table 11.1
Neiguan (PC 6)	2 cun above the transverse crease of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis	See Table 11.1
Renzhong (DU 26)	At the junction of the superior and middle third of the philtrum	Main point to increase the blood pressure and excite respiration; used for relief of shock in first aid and also used for treating schizophrenia, hysteria, and facial paralysis
Hegu (LI 14)	On the dorsum of the hand, midway between the 1st and 2nd metacarpal bones, approximately in the middle of the 2nd metacarpal bone on the radial side	Main point for treating diseases of the head and face; for relieving pains in the whole body, especially toothache; hyperhidrosis
Sujie (DU 25)	In the center of the tip of the nose	Nasal polyp; nasal obstruction; nasal sinusitis; epistaxis; nasal abscess; syncope due to fright; coma
Shaoze (SI 1)	On the ulnar side of the little finger, about 0.1 cun posterior to the corner of the nail	Coma; fever; breast carbuncle; numbness of the finger tip

(Continued)

Acupoints	Location	Other Applications
Renying (ST 9)	At the level of the thyroid cartilage, on the anterior border of the sternocleidomastoideus	Swelling and pain in the throat; inability to swallow; headache; scrofula; goiter
Lianquan (RN 23)	Above the Adam's apple, in the midpoint of the upper border of the thyroid bone	Sore throat; harsh voice; difficulty in swallowing; aphasia caused by stiffness of the tongue; salivation with glossoplegia; aphasia due to apoplexy
Quchi (LI 15)	When the elbow is flexed, the point can be located in the midpoint between the lateral end of the transverse cubical crease and the lateral epicondyle of the humerus	See Table 11.1

* The contents of this table refer to the relevant Internet resources and the following two monographs: (1) Jin SX. Chinese-English Learning and Memory Manual of Meridians and Acupoints,. Zhenzhou University Publishing House, Zhengzhou, 2002; and (2) Shen XY and Wang H. Acupuncture and Moxibustion. People's Medical Publishing House, Beijing, 2007.

11.3 Mechanisms of Acupuncture Therapy for Abnormal Blood Pressure

If acupuncture therapy is effective in treating hypertension and hypotension, then it is important to understand the scientific basis for such simple treatment. Although the nature of the acupoints is not yet fully understood, considerable studies have shown that the local afferent nerves play an important role in the signal transmission of the acupoints. We previously observed that the brain stimulation-induced increase in blood pressure could be attenuated by simulated EA at the acupoint Zusanli (ST-36), i.e., stimulation of the deep peroneal nerve (Xia et al. 1985, 1989a, 1989b, 1989c). In the study of acupuncture-induced regulation of the cardiovascular system, Li (2002) showed that the input nerve impulses generated by acupuncture at the acupoint Neiguan (PC-6) were transferred through Group II and Group III of the fibers of nervus medianus, and the signals were subsequently integrated to the spinal cord and at higher level, leading to output impulses via the efferent fibers of the sympathetic-adrenergic nerve. This suggests the importance of neural regulation in acupuncture therapy for hypertension, though multiple mechanisms are believed to be involved. Acupuncture signals are presumed to be transmitted through the afferent nerves and processed in the central nervous system, and might subsequently regulate the blood pressure through the nerve output signals, along with the humoral and endocrine regulation and balance of the electrolyte.

11.3.1 Mechanisms of Acupuncture-induced Decrease in Lowering High Blood Pressure

Accumulating evidence shows that appropriate stimulation of the acupoints can lead to major changes in the hemodynamics and hemorheology. In particular, manual acupuncture/EA may reduce the sympathetic tonic, adjust insulin resistance, regulate rennin-angiotonin-aldosterone system (RAAS), and promote the release of vasoactive substance, atrial natriuretic peptide, and prostacyclin. Consequently, the integrated modulation decreases the peripheral resistance and blood viscosity, leading to a decrease in the blood pressure.

11.3.1.1 Modulation of peripheral resistance of the blood flow

In the 1960s, a research group at Anhui Medical College in China studied the effect of acupuncture therapy on experimental hypertension in dog and rabbit models, and found that acupuncture could significantly decrease the blood pressure in animals with high blood pressure, and the effect was observed to last for a relatively long duration (>10 days). However, in the normal animals, acupuncture caused an instantaneous and temporary increase in blood pressure, which could be attributed to the pain stimulation when the needles penetrate the skin (Research group at Anhui Medical College, 1960). These results show that acupuncture could induce a profound and long-lasting decrease in the blood pressure in animals with hypertension, although it may not affect the normal blood pressure in a major way. Similarly, Xiao and Li (1983) noticed that EA could decrease experimental hypertension evoked by intravenous (i.v.) injection of noradrenalin, and increase experimental hypotension induced by i.v. injection of nitroprusside sodium. All these observations suggest that acupuncture may regulate blood pressure in two ways (decrease or increase), depending on the states of blood pressure.

In a rabbit hypertensive model, Zhang (1985) observed that acupuncture at the acupoint Zusanli (ST-36) lowered experimental hypertension, but did not affect the normal blood pressure. The antihypertensive effect was observed to be owing to blood vessel vasodilation. Similarly, in a rat hypertensive model with one of the kidneys being occluded, Pan and Hu (2000) showed that after 10 days of daily treatment with acupuncture at the acupoint "Zusanli" (ST-36), the tail arterial pressure was significantly lower than that of the hypertensive rats without acupuncture treatment ($p<0.01$), and showed no difference when compared with the blood pressure in the normal control group ($p>0.05$) (Fig. 11.4). As acupuncturing at the acupoint "Zusanli" (ST-36) had no influence on the heart rate while decreasing the blood pressure, the acupuncture-induced decrease in the blood pressure is presumed to be related to the mechanism of reducing the resistance of peripheral blood vessels.

Wang and Yin (1993) studied the hemodynamic changes in 49 patients with stage-II primary hypertension before and after acupuncture at Fengchi (GB-20), Taichong (LR-3), and other acupoints. They observed that the systolic blood

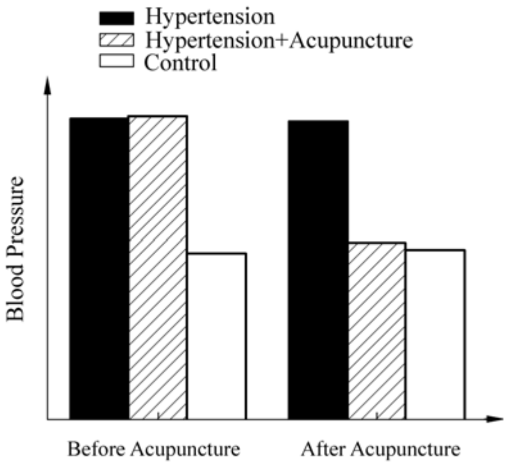

Figure 11.4 Anti-hypertensive effect of acupuncture in a rat model. Acupuncture was applied at the acupoint "Zusanli" (ST 36) daily for 10 days. The arterial pressure was monitored. Note that the acupuncture significantly reduced the blood pressure in the hypertensive rats (p<0.01), but had no effect on the control rats with normal blood pressure (p>0.05).

pressure was 3.2 kPa lower (p<0.001), the diastolic blood pressure was 2.0 kPa lower (p<0.001), and the peripheral resistance was 0.03 kPa*s/ml lower after acupuncture treatment, than immediately before acupuncture, while the arterial compliance, stroke volume, and cardiac output did not change significantly (p>0.05). The results suggest that the acupuncture-induced depressurization is mainly through lowering the peripheral resistance of small arteries, but not by influencing the compliance of large and middle arteries and cardiac output. On the other hand, Zhou (1993) showed that the blood viscosity of patients with hypertension was higher than that of the healthy persons, and that acupuncture could decrease high blood pressure as well as blood viscosity. Indeed, there has been evidence showing that acupuncture could promote tonicity of the micrangium and reduce peripheral resistance, thus improving microcirculation (Qi 1994). However, neural regulation may play a more important role in the modulation of peripheral resistance of the blood flow.

11.3.1.2 Neural regulation

The vasodilation and contraction of the peripheral vessels are tightly controlled by the autonomic nervous system that is regulated by the brain and spinal cord. The central sites responsible for the control of blood pressure are located at multiple levels of the brain, with the medulla oblongata playing a critical role. In an experimental animal model, the animal exhibited critical hypertension, when its brain was cut at the level of medulla oblongata. In contrast, no major change was observed in the animal's blood pressure, when the brain was cut at the level above the brainstem (Reis and Dobs 1974). Thus, the brainstem is essential for the maintenance of normal blood pressure. Indeed, a change in the function of the brainstem is observed to significantly affect the blood pressure. For example, microinjection of 5-hydroxytryptamine (5-HT) or γ-aminobutyric acid (GABA) into the ventrolateral medulla is found to decrease high blood pressure elicited by the stimulation of the "defense reaction area" of the hypothalamus or deutocerebrum (Li 1986). Li et al (2008) also reported that opioids and GABA in the rostral ventrolateral medulla (rVLM) and glutamate in the reciprocal excitatory projections between the arcuate nucleus and ventrolateral periaqueduct gray (vlPAG) are involved in the long-lasting effect of EA on experimental hypertension.

Acupuncture is observed to induce nerve signal inputs to the central nervous system, and thus, regulate the blood pressure. Early studies demonstrated that the brain stimulation altered the neural activity and increased the blood pressure, while simulated acupuncture, e.g., stimulation of the skeletal muscle or even nerves with low-frequency and low-intensity currents, caused depressurization (Li 1986; Xia 1985; Xia et al. 1983, 1984, 1985, 1989a, 1989b, 1989c). Similar effect was also reported in some later studies (Xie et al. 1997; Wang et al. 1997; Yu and Xia 2001; Ouyang et al. 2004). In other work, Yao (1993) specifically described the relationship between acupuncture and somatic nerve stimulation in the regulation of cardiovascular and renal activities. The process of depressurization involves the activation of small myelinated fibers in the muscles, transmission of afferent nerve signals, and regulation of various kinds of neurotransmitters and neuropeptides (Wang et al. 1997; Yu and Xia 2001; Li 2002) (Fig. 11.5).

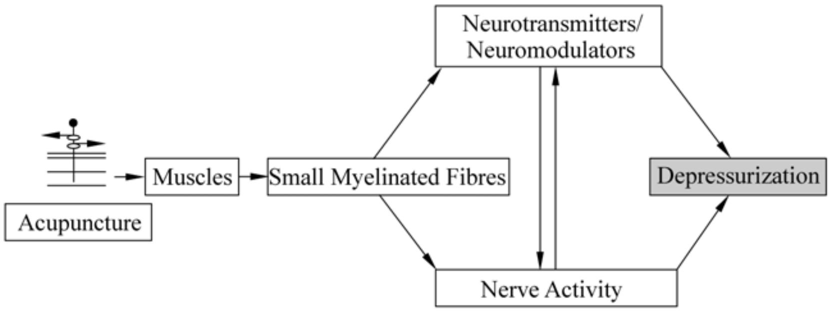

Figure 11.5 Signal pathway of acupuncture therapy for hypertension.

Nerve signals. Yao et al (1982) showed that a prolonged stimulation of the somatic afferents with low-frequency currents significantly affected the cardiovascular function and sympathetic nerve activity. In unanesthetized spontaneously hypertensive rats, an elevation of blood pressure, heart rate, and splanchnic nerve outflow were elicited during a 30-min period of sciatic nerve stimulation. Following the cessation of the stimulation, depressor response and bradycardia slowly developed and lasted for up to 12 h. Activation of the Group III or A-delta afferent fibers was found to be essential for this post-stimulatory response. The progressive depressor response and paralleled reduction of the splanchnic nerve activity reached the maximal level at about 1 h after the termination of the sciatic stimulation. The magnitude of the post-stimulatory depressor response was correlated with the blood pressure level before the stimulation. In addition, behavioral changes accompanying the depressor response were also observed. Both cardiovascular as well as behavioral depressions were immediately reversed by naloxone (10 – 15 mg/kg, i.v.). The post-stimulatory depressor response was still present after bilateral sino-aortic denervation, but was absent in animals anesthetized with chloralose and urethane. Emotional stress produced by air-blowing on the animal resulted in pressor response and tachycardia during the period of stressful stimulation. However, there was no decrease in the blood pressure following the termination of air-blowing. The authors indicated that the sympathetic and cardiovascular depression was induced by a prolonged stimulation of the somatic Group Ⅲ or A-delta afferent fibers. The naloxone reversibility suggests the involvement of endogenous opioids in the mechanism of this response. Such cardiovascular and sympathetic inhibition induced by the simulated acupuncture (somatic afferent stimulation) may partially account for the mechanisms of acupuncture-induced depressurization in humans.

In a recent work, Li et al (2009) reported that EA at P 5 – 6 (overlying the median nerves) could activate the arcuate (ARC) neurons containing β-endorphin, which excites the vlPAG and inhibits the cardiovascular sympathoexcitatory neurons in the rVLM. They observed that ARC neurons could be antidromically activated by stimulating the rVLM, and that ARC perikarya could be labeled with the retrograde tracer that had been microinjected into the rVLM. Thus, vlPAG, particularly, the caudal vlPAG, is required for ARC inhibition of rVLM neuronal activation and the subsequent EA-related cardiovascular activation. It seems that the long-loop pathways, i.e., direct projections from the ARC to the rVLM, which serve as a source of β-endorphin, exist in the cardiovascular EA responses (Li et al. 2009).

Heart rate variability. Heart rate variability (HRV) is a cardiac index of the autonomic nerve function and contributes to the maintenance of blood pressure. In a rat model of renal hypertension with the occlusion of one-side kidney artery, Wang and Tang (2003) determined the changes in the HRV, and observed that an increase in the sympathetic activity, as indicated by an increased HRV, might initiate the onset of high blood pressure in the early days. However, the progress of the renal hypertension did not rely on the increased sympathetic activity, as subsequently, HRV gradually returned to the normal level. They observed that acupuncture at the acupoint Shenshu (BL-23) or Zusanli (ST-36) could improve hypertension by regulating the nerve activity (Wang and Tang 2003). In another study, Xie et al (1997) observed that the buffer nerve has a role in acupuncture-induced depressurization.

Endogenous opioids. Yao et al (1982) provided initial evidence that endogenous opioids participate in depressurization induced by acupuncture or simulated acupuncture, as depressurization could be reversed by opioid receptor blocker, naloxone, in spontaneously hypertensive rats. Furthermore, in another animal model, Xia et al (1985, 1989a, 1989b, 1989c) found that in response to increased sympathetic activity and blood pressure induced by stimulating the hypothalamic "defense reaction area", the release of the endogenous opioids increased; and the simulated acupuncture (mild stimulation of deep peroneal nerve) attenuated the increase in the sympathetic activity and blood pressure. The attenuation was observed to be dependent on the opioid system in the brain, because i.v. injection of naloxone or microinjection of it into the brain could block the attenuation by the simulated acupuncture. The upregulation of the opioid system may regulate other neurotransmitter systems, such as the monoamine neurotransmitters like noradrenaline, dopamine, and 5-HT, thus modulating the sympathetic activity and blood pressure (Fig. 11.6). These observations have also been confirmed by other independent investigators in the recent years (Xie et al. 1997; Wang et al. 1997; Yu and Xia 2001; Zhou et al. 2003).

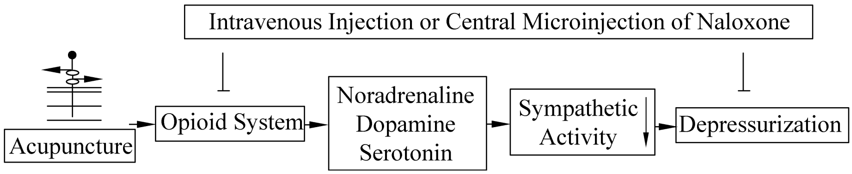

Figure 11.6 The central role of the endogenous opioid system in acupuncture-induced depressurization.

Noradrenaline and dopamine. In the rabbit model with the stimulation of the hypothalamic "defense reaction area", the increase in the sympathetic discharges and blood pressure was observed to be associated with an enhanced release of the monoamine transmitters such as noradrenaline (Xia et al. 1989a). Simulated acupuncture reduced the release of noradrenaline via the regulation of the endogenous opioid system, while naloxone reversed the simulated acupuncture-induced attenuation of noradrenaline release, sympathetic discharges, and blood pressure with no major effect on the dopamine system (Xia et al. 1989c). However, the mechanism of noradrenaline and dopamine may be different in different models. In the rat model with the microinjection of α_1-, α_2-, and β-receptor blockers into the cerebral ventricles, Zou et al (2000) observed that EA at the acupoints Quchi (LI-11) and Tinggong (SI-19) with a low-frequency current (2 Hz) reduced the blood pressure. The EA-induced depressurization could be significantly decreased by propanolol, a β-receptor blocker, injected into the brain intracerebroventricularly (i.c.v.), but could not be affected by the central application of α_1- and α_2-receptor blockers, suggesting that EA at the acupoints Quchi (LI-11) and Tinggong (SI-19) could decrease the blood pressure via adrenergic β-receptors. Interestingly, Zhou et al (1995) acupunctured spontaneously hypertensive rats at the bilateral Quchi

(LI-11) and Zusanli (ST-36) acupoints for three periods of treatment (10 min per day, 5 days per treatment, with one day interval between the periods), and observed that: (1) the systolic blood pressure decreased remarkably; (2) the plasma levels of noradrenaline and 5-HT were lowered, while that of dopamine was increased; and (3) the content of noradrenaline was significantly increased in the brainstem, hypothalamus, and cerebral cortex, while that of dopamine remarkably increased in the brainstem and cerebral cortex. These results imply that the mechanism of acupuncture-induced depressurization in spontaneously hypertensive rats, is related to the regulation of the monoamine system at both central and plasma levels.

5-hydroxytryptamine. 5-HT is a central neurotransmitter and is actively involved in the regulation of the cardiovascular activity. In several animal models, including rats, cats, and dogs, microinjection of 5-HT into the brain has been shown to decrease blood pressure by reducing the activity of the efferent adrenergic nerves (Li and Fu 2000). Our previous work suggests that the central 5-HT partially participates in the simulated acupuncture-induced correction of the cardiovascular abnormality elicited by the stimulation of the hypothalamic "defense reaction area" (Xia et al. 1985, 1989a, 1989b, 1989c). In an autoradiographic study, Zhu et al (1982) demonstrated that acupuncture could increase 5-HT uptake in the nucleus raphe dorsalis and nucleus raphe central of the deutocerebrum. Furthermore, Zhou et al (1995) observed that the acupuncture-induced depressurization is associated with an increase in the content of 5-HT in the brainstem, hypothalamus, and cerebral cortex. Thus, acupuncture is presumed to upregulate 5-HT activity in the brain, and subsequently decreases the blood pressure (Li and Fu 2000).

Amino acids. Gu et al (1998) observed that acupuncture at the acupoint Tinggong (SI-19) decreased the blood pressure, which was related to the activity of GABA receptors in rVLM, where GABAergic inter-neurons were observed to inhibit the excitatory sympathetic neurons. In the rat under anesthesia with urethane, EA at the acupoint Tinggong (SI-19) and Quchi (LI-11) with a low-intensity (3 V) and low-frequency (2 Hz) current induced a decrease in blood pressure, which could be prevented by prior injection of bicucullin, a blocker of GABA receptor, into the bilateral sides of rVLM (Gu et al. 1998). Prior injection of GABA into the bilateral A1 or A2 regions in the brainstem could decrease or even reverse the EA-induced decrease in blood pressure. Some studies (Wei and Gu 1989a, 1989b) indicated that the excitation of A1 or A5 regions decreased the blood pressure through the GABAergic inter-neurons that inhibit the excitatory sympathetic neurons of rVLM. Thus, it is likely that A1 and A2 regions are involved in the EA-induced reduction of blood pressure through the integration between GABAergic inter-neurons and rVLM.

Wang et al (2004) investigated the effect of EA on blood pressure as well as the mechanism of the central amino acids in rats by microdialysis and high-performance liquid chromatography combined with fluorescent detection for the detection of amino acid neurotransmitters. They observed that the microinjection of angiotensin-(1-7) into the caudal ventrolateral medulla (CVLM) decreased the blood pressure, which was accompanied by an increase in the glutamate release and a decrease in the taurine release in the CVLM. In contrast, the microinjection of angiotensin-(779) elevated the blood pressure, which was accompanied by a decrease in the glutamate release and an increase in the taurine release. EA at the acupoint "Zusanli" (ST-36) for 20 min was observed to reverse the angiotensin-(1-7) and angiotensin-(779)-induced effects, with partial reversal of the changes in the glutamate and taurine release in CVLM. They believed that EA could regulate the blood pressure by, at least partially, altering the release of glutamate and taurine in the CVLM.

Nitrogen monoxide. Several reports have shown that nitrogen monoxide is involved in the acupuncture-induced depressurization. Li et al (2001) observed that in the urethane and chloralose anesthetized rats that had hypertension induced by chronic stress of electric foot-shocks and noises, EA at the bilateral "Zusanli (ST-36)" acupoint for 20 min resulted in a decrease in both the systolic and diastolic pressure as well as the heart rate, as well as the attenuation of the maximal left ventricular pressure and the end diastolic pressure. These effects could be greatly reduced or eliminated by the microinjection of *N* (omega)-Nitro-L-Arginine, a blocker of the formation of nitric oxide (NO) into the ventral vPAG, suggesting that NO in the vPAG plays a role in the acupuncture-induced depressurization.

Huang et al (2005) observed the changes in the neuronal and inducible nitric oxide synthases (nNOS and iNOS), as well as their mRNAs in the rVLM of rats with stress-induced hypertension before and after acupuncture therapy. They showed that the increase in the systolic blood pressure was accompanied by an increased expression of nNOS in the rVLM, as indicated by the increased number of immunoreactive neurons, and mRNA density, while iNOS mRNA and protein were significantly reduced. EA at the acupoints Zusanli (ST-36) and Lanwei (EXTRA-37) on the same hind limb with dense-sparse wave (4 – 20 Hz) was observed to bring the blood pressure as well as both the nNOS and iNOS to the normal level. These results suggest that the effect of acupuncture on stress-induced hypertension is also related to the regulation of nNOS and iNOS in the rVLM.

Urotensin Ⅱ. Sun et al (2005) investigated whether urotensin Ⅱ and its receptor (GPR14) in the rVLM were involved in the acupuncture therapy for hypertension. They microinjected urotensin Ⅱ into the rVLM and examined its effect on the blood pressure and heart rate and used semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) and immunohistochemistry for detecting the expression of GPR14 mRNA and protein in the rVLM. The foot-shock combined with noise was utilized to establish the animal model of chronic stress- induced hypertension. Their results showed that microinjection of urotensin Ⅱ into the rVLM produced a dose-dependent increase in the blood pressure and heart rate. Acupuncture at the acupoint Zusanli (ST-36) decreased the tail systole pressure in chronic stress-induced hypertensive rats, but failed to induce any significant change in the expression of GPR14 protein in the rVLM. Thus, the authors concluded that urotensin Ⅱ can activate its receptor in the rVLM to increase the blood pressure and heart rate; however, this system may not be involved in the mechanism of acupuncture therapy for chronic stress-induced hypertension. However, it is still unclear whether acupuncture could alter the release of urotensin Ⅱ and/or modulate the function of GPR14 receptors based on this study.

11.3.1.3 Humoral and other mechanisms

Accumulating evidence suggests that acupuncture may induce endocrine-humoral regulation, and alter the contents of vasoactive substances and ions in the heart and blood vessels, thus decreasing high blood pressure.

Renin-angiotensin-aldosterone system. RAAS plays a critical role in cardiovascular function. Angiotensin Ⅱ, the major effector molecule of the RAAS, is important in maintaining the blood pressure, fluid homeostasis, and humoral electrolytes by acting on the G-protein-coupled Angiotensin Ⅱ type 1 and 2 receptors, in both the periphery and the central nervous system (Sun et al. 1998). The angiotensin and angiotensin Ⅱ receptors are broadly distributed in many organs of the body, including the heart, blood vessel wall, and kidney. They participate in many functions, e.g., causing arteriole smooth muscle contraction and renal artery contraction, affecting the zona glomerulosa of the adrenal cortex, promoting aldosterone secretion, enhancing the reabsorption of sodium ions in the distal convoluted tubule, and discharging potassium ion from the body. Dysregulation of this system is one of the factors leading to the dysfunction of the cardiovascular system, including both chronic and acute hypertension (Liu 2001). Indeed, plasma angiotensin Ⅱ is the initial factor in renal vascular hypertension (Yang et al. 1985). Owing to the increase in the level of sodium in the extracellular fluid, the osmotic pressure increases, thus stimulating the secretion of the antidiuretic hormone, encouraging tubular reabsorption, and increasing the capacity of the extracellular fluid, in turn resulting in high blood pressure. Recent studies have shown that acupuncture may affect the RAAS system, thus decreasing the blood pressure. Sun et al (1998) applied acupuncture, moxibustion, or acupuncture combined with moxibustion, on rats with renal hypertension, and observed that all the three approaches could decrease high blood pressure, which was associated with a significant decrease in the plasma rennin, angiotensin Ⅱ, and aldosterone. This suggests that acupuncture and/or moxibustion can lower blood pressure by reducing the activity of RAAS, thus decreasing the vascular tension, peripheral resistance, and water-sodium retention. It was also noted that acupuncture combined with moxibustion was the most effective, while acupuncture alone was better than moxibustion alone (Sun et al. 1998). In a rat model of renal vascular hypertension using Goldblatt's method (Goldblart 1934), Liu et al (2003) showed that acupuncture could significantly decrease high blood pressure and reduce the contents of angiotensin Ⅱ. In addition, some researchers found that acupuncture at the acupoint Shixuan (EX-UE11) or Shuiquan (KL-5) could decrease high blood pressure as well as plasma hyperten- sinogenase (Lee and Kim 1994; Li 1995; Ji and Ma 2004). All these results indicate that acupuncture can effectively improve renal hypertension by regulating RAAS system, reducing vascular tension, inhibiting aldosterone secretion, reducing water-sodium retention, and restoring the stability of the intravascular environment.

Vasoactive substances. There are studies showing that monolayer endothelial cells in the surface of the lumen of the blood vessels have the function of secretion. The secreted vasoactive substances were observed to regulate the vascular smooth muscle and participate in the regulation of blood pressure. These substances include prostacyclin (PGI_2), endothelium-derived relaxing factor (EDRF), and endothelium-derived contracting factor (EDCF).

Eedothelin (ET) is a strong vasoconstrictor substance in the EDCF. Several studies suggest that acupuncture may affect these factors, thus regulating the blood pressure. Zhang and Wang (2002) investigated 60 patients with primary hypertension who were diagnosed according to the WHO criteria of diagnosis for primary hypertension. These patients were randomly divided into acupuncture and control groups (30 cases per group). The acupuncture group was treated with a simple method of acupuncture, i.e., acupuncture at the bilateral Xingjian (LR-2) and Fengchi (GB-20) acupoints once a day. The patients of the control group were treated with oral drug administration (*Tablets of Compound Reserpine and Hydrochlorothiazidec*) daily (one tablet thrice a day). After 15 days of treatment, the plasma ET level was determined and compared with that before treatment. The results showed that the plasma ET level was significantly lower (p<0.01) after 15 days of acupuncture therapy, when compared with those of the control as well as before the acupuncture therapy (p<0.01). Thus, the authors believe that acupuncture at the acupoints Xingjian (LR-2) and Fengchi (GB-20) may have the function of repairing the vascular endothelial cells and inhibiting the sympathetic nerve activity, thus reducing the plasma ET levels and eventually leading to vasodilation. Following this work, several other studies (Zhang et al. 2004; Wu et al. 2004a; Wu et al. 2004b; Wang 2006) also showed that acupuncture at the acupoints Hegu (LI-4), Baihui (DU-20), Quchi (LI-11), and Taichong (LR-3) could regulate the plasma ET level and improve hypertension.

The endogenous NO is another cell messenger in the vascular smooth muscle cells, and its precursor is L-arginine. The vascular endothelial cells could produce NO catalyzed by NO synthase (Palmer et al. 1987). NO is observed to increase the cGMP levels and lead to the relaxation of the vascular smooth muscles (Cai et al. 1998a). Cai (1998b) investigated 28 cases of patients with hypertensive disease, and found that after acupuncture treatment, the blood pressure and circulating endothelial cells (CEC) were markedly reduced, while the level of serum NO was significantly raised with a negative correlation with the change in the blood pressure. It was suggested that acupuncture may regulate NO to lower blood pressure by targeting L-arginine-NO pathway (Cai et al. 1998b). In another study, Cai et al (1997) showed that auriculo-therapy also affected the blood pressure through the L-arginine-NO pathway. Wang and Tang (2003) performed acupuncture on a model of renal hypertension and found that acupuncture at the acupoint Zusanli (ST-36) or Shenshu (BL-23) significantly decreased the blood pressure (18.1 ± 2.5 kPa at ST-36 and 19.1 ± 1.1 kPa at BL-23 vs. 21.6 ± 1.7 kPa in the control group, $p<0.01$) with a significant reduction in the ET and an increase in the NO in the plasma. More recently, Hwang et al (2008) showed that EA could attenuate the blood pressure elevation in spontaneously hypertensive rats, as well as enhance the NO/NOS activity in the mesenteric artery in these rats. These results suggest that acupuncture could decrease high blood pressure by regulating the dynamic balance of vasoconstriction and vasodilation via ET and NO.

Moreover, Sun et al (1998) found that acupuncture, acupuncture plus moxibustion, or moxibustion could significantly decrease the plasma atrial natriuretic peptide, thus improving hypertension. Zhao and Wang (1997) and Li (1999) investigated the changes in the levels of thromboxane A_2, prostaglandin I_2, thromboxane B_2, and 6-keto-prostacyclin in patients with stroke, and observed that the level of thromboxane B_2 increased and that of 6-keto-prostacyclin decreased in the plasma of these patients. Acupuncture could restore the abnormal level of active substances in the blood vessel endothelium to "normal" level. Hence, acupuncture seems to affect the release of active substances in the blood vessel endothelium, thus regulating the blood pressure.

Insulin. There has been evidence indicating the relationship between the dysfunction of the insulin system and hypertension (Ching and Beevers 1991; Wang and Huang 2003). Essential hypertension is often associated with insulin resistance and compensatory hyperinsulinemia that may play a role in the development of the disease. The potential mechanisms of insulin resistance/hyperinsulinemia-related hypertension include the following: (1) Insulin can stimulate RAAS, promote sodium recrement in the nephric tubule, increase the reabsorption of water in the proximal convoluted tubule, and maintain the retention of sodium and water; (2) Insulin can excite the sympathetic nervous system, stimulate the secretion of catecholamine, and increase the cardiac output and vascular contraction; (3) Insulin can induce hyperplasia and hypertrophy of the arterial smooth muscle cells directly or indirectly through the parainsulin factor, narrow the small arterial lumens, inhibit the production of endogenic vasodilators such as PGI_2 and PGE_2, and thereby increase the peripheral vascular resistance; and (4) Insulin can affect the ion transport across the membrane, increase the intracellular concentration of sodium and calcium ions, and consequently, increase the sensitivity of the small arterial smooth muscle cells to the vasopressor substance (Hwang et al.1987; Ching and Beevers 1991; Rutherford et al. 1991; De Fronzo

1992; Lithell 1995; Reaven et al. 1996; Tack et al. 1996). Some studies suggest that acupuncture not only lowers high blood pressure, but also improves insulin resistance. For example, Zhou et al (1996) investigated the effect of acupuncture on blood pressure in rats with spontaneous hypertension. They randomly divided the spontaneously hypertensive rats into two groups, i.e., "heart meridian" group and "lung meridian" group, and observed that acupuncture at the acupoints of both "heart and lung meridians" could lower hypertension, with the acupoints of "heart meridian" producing better effect than those of the "lung meridians" (p<0.05). Moreover, acupuncture along the heart meridian significantly increased the atrial natriuretic peptide and decreased the serum insulin and C-peptide, with an increased ratio of C-peptide/insulin. Similarly, another study (Xu and Liang 1997) showed comparable results. Thus, the mechanisms of anti-hypertension effect of acupuncture might involve the improvement of insulin resistance and increase in the atrial natriuretic peptide.

Ca^{2+}, Na^{+}, and Mg^{2+}. In a rat model of hypertension induced by chronic stress, Dong et al (1997) observed that simulated EA (electrical stimulation of deep peroneal nerve with low-intensity and low-frequency current) significantly decreased the blood pressure, which could be blocked or attenuated by the microinjection of cordilox, a calcium channel antagonist, into the lateral cerebral ventricle. However, in the control, the same treatment with the physiological saline failed to affect the EA efficacy. Xie et al (1998) examined the effects of EA on hypertension and measured the concentrations of the cardiac muscle cytosolic-free calcium ($[Ca^{2+}]i$) and free magnesium ($[Mg^{2+}]i$) in rabbits. Experimental hypertension was induced by i.v. injection of norepinephrine. Their results showed that when norepinephrine increased the blood pressure, $[Ca^{2+}]i$ significantly increased, while $[Mg^{2+}]i$ decreased with an increased ratio of $[Ca^{2+}]i/[Mg^{2+}]i$. EA was observed to depress the blood pressure and $[Ca^{2+}]i$. Thus, they suggested that acupuncture could decrease the blood pressure, partially by regulating the cardiac function through the modulation of cytosolic-free calcium. However, more studies are needed to verify these observations and elucidate the precise meaning of this phenomenon.

There has been evidence showing that an increase in the renal perfusion pressure could increase the expulsion of sodium and water. This could lead to hypovolemia and restore the arterial pressure to the control level. In addition, changes in the sympathetic nerve activity and vasoactive substances can alter natriuresis. A sympathetic hyperactive and vasoactive substance release can alter natriuresis and induce high blood pressure. It has been reported that in rabbits, acupuncture at the bilateral "Shenshu" (BL-23) acupoint could increase the volume of renal uropoiesis and sodium excretion. The efficacy of EA is usually evident after 2-week EA treatment, suggesting a long-term effect needed for the rectification of high blood pressure (Li and Fu 2000).

The potential mechanisms of acupuncture therapy for hypertension are briefly summarized in Fig. 11.7.

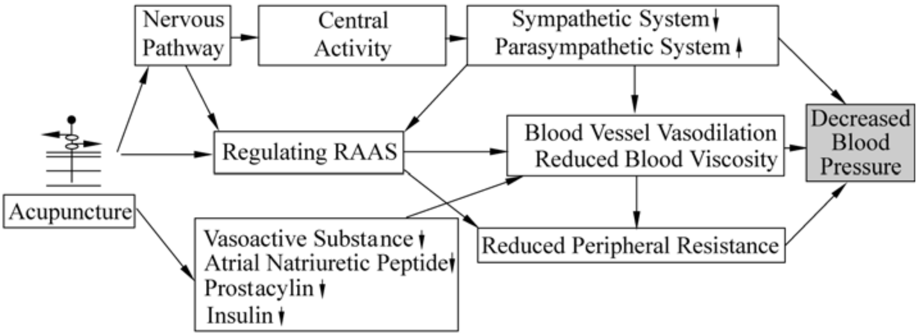

Figure 11.7 Potential mechanisms of acupuncture therapy for hypertension.

11.3.2 Mechanisms of Acupuncture Therapy for Low Blood Pressure

Numerous studies suggest that acupuncture improves hypotension by regulating the cardiovascular system at multiple levels.

11.3.2.1 Peripheral pathway of signal transmission

Acupuncture has no appreciable pressor effect on the normal animals, but has been observed to induce a beneficial effect on the hypotensive shock in the animal model of hypotension (Deng and Huang 1981; Weng et al. 1982; Song et al. 1990a; Wang et al. 1994; Zhou and Jin 2004b). The beneficial effect is relatively acupoint-specific and sensitive to the stimulation parameters (Song et al. 1990a; Zhou and Jin 2004b).

Huang and Deng (1981) found that the electrical stimulation of the rat's vagus nerve led to a decrease in the blood pressure for more than 20 mmHg with the cessation of the heart beat, and that acupuncture at the acupoint Renzhong (DU-26) could significantly elevate the blood pressure. This effect was observed only when the blood pressure was lower than the "normal" level, and acupuncture had no effect on the normal blood pressure in the control rats. On the other hand, they observed that stimulation at the central region of the pedal plate, as a control for EA at the acupoint Renzhong (DU-26), had no significant effect on hypotension. Thus, they believed that acupuncture at the acupoint "Renzhong" (DU-26) could generate a specific signal to elevate the blood pressure by enhancing the role of "self-stabilizing" in the body. In a rabbit model with hemorrhagic shock, Song et al (1990a) observed that EA at the acupoint Neiguan (PC-6) markedly increased the blood pressure, which was dependent on the stimulation intensity. However, when it reached a certain level, the blood pressure did not increase further with the intensity. Zhou and Jin (2004b) applied 2.5- and 4.5-mA EA at the acupoints Renzhong (DU-26) and Tianmen (DU-20) in two separate groups. After EA therapy, the group with 4.5-mA EA showed a greater increase in the blood pressure than the group with 2.5-mA EA. Hence, they presumed that the suitable EA intensity was essential for the anti-hypotension effect by EA. In addition, Wang et al (1994) investigated the role of stimulation intensity in the EA-induced increase in blood pressure. In 20 healthy adult rabbits under urethane anesthesia, a decrease in the blood pressure was induced by cutting the bilateral vagus nerves and aortic nerves. They observed that the electrical stimulation of the acupoint Renzhong (DU-26) significantly increased the blood pressure. The pressor effect was increased with the current intensity within a certain range. However, an intensity beyond that range could not increase the blood pressure further. As the infraorbital nerve is considered to be the major pathway of the signals from the acupoint Renzhong (DU-26) (Wang et al. 1994), the authors studied the relationship between the EA stimulation and the excitement of the infraorbital nerve endings, and found that a lower-intensity current partially excited the infraorbital nerve endings, while a moderate-intensity current excited all the infraorbital nerve endings. Apparently, acupuncture-induced anti-hypotension depends upon appropriate stimulation intensity, besides specific acupoints (e.g., Renzhong).

In a rat model of hypotension induced by vagus nerve stimulation, Deng and Huang (1981) investigated the relationship between the trigeminal nerve and Renzhong acupoint. They observed that the pressor effect of acupuncture at the acupoint Renzhong (DU-26) was inhibited by aethocaine infiltrated into the maxillary nerve stem, and was not inhibited at all by normal saline (Fig. 11.8). Hence, the authors concluded that the acupuncture signals generated from the acupoint Renzhong (DU-26) were transmitted along the trigeminal nerve. With a rabbit model of hemorrhagic shock, Weng et al (1982) observed that EA at the bilateral Neiguan (PC-6) acupoint increased the average blood pressure by 14.62 mmHg after 10 min of EA stimulation. This effect could be blocked by injecting propanolol into the ear vein or cutting the bilateral brachial plexus, which suggests that the transmission of the acupuncture signals from the acupoint Neiguan (PC-6) is dependent on the adrenergic nerve of the brachial plexus. Thus, it is evident that the nerve-based signals are critical in acupuncture-induced pressor.

11.3.2.2 Central regulation

Acupuncture is well known to activate the central opioid system, which may play a role in manual acupuncture/EA-induced decrease in the blood pressure. Indeed, endogenous opioid system has been observed to actively inhibit the sympathetic tone and negatively regulate the cardiovascular activity. For example, electrical stimulation of the hypothalamic defense area enhanced the sympathetic activity (Xia et al. 1983, 1984, 1985, 1988, 1989a). In response to such stress, enkephalin was greatly increased in the cerebrospinal fluid (Xia et al. 1988), suggesting an increased release of endogenous opioids in the brain, which may negatively regulate

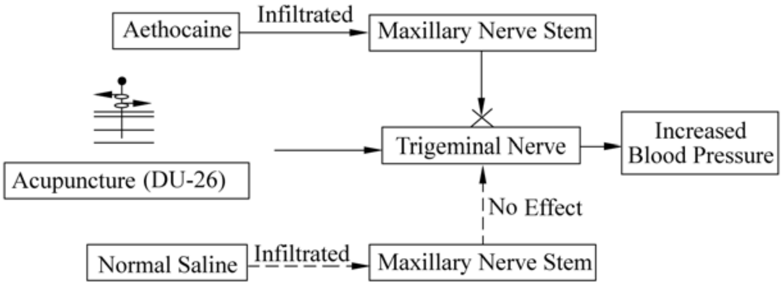

Figure 11.8 A potential mechanism for acupuncture induced increase in blood pressure. Note that acupuncture at Renzhong (DU 26) increases the blood pressure via the trigeminal nerve based on the data of Deng and Huang (1981).

the sympathetic activity. Indeed, some stressful conditions may lead to over-release of the opioids that contribute to hypotension. During trauma and hemorrhage, blockage of the opioid peptide activity might raise the blood pressure (Sun et al. 1989). Xia (1989) observed that severe trauma could seriously decrease the blood pressure, while i.v. injection of naloxone could significantly increase the blood pressure.

Manual acupuncture/EA activation of the endogenous opioids may not have any role in manual acupuncture/EA-induced increase in blood pressure. Sun et al (1983) observed that in a rat model of hemorrhagic hypotension by vein bloodletting, simulated acupuncture (i.e., sciatic nerve stimulation) raised the blood pressure significantly, which was not blocked by prior injection of naloxone. In the rat anesthetized by intraperitoneal injection of chloral hydrate, sciatic nerve stimulation still increased the blood pressure. However, sciatic nerve stimulation induced little or no increase in the blood pressure in most animals after i.v. injection of scopolamine. Therefore, the authors believed that the sciatic nerve stimulation could strengthen the sympathetic excitement, and thus increase the blood pressure through cholinergic neurotransmitter system, but not the endogenous opioid system. Xiao et al (1983) also observed that stimulation of some acupoints such as Zusanli (ST-36) and Neiguan (PC-6), or some nerves such as nervus peronaeus superficialis and radial deep nerve, could raise the blood pressure, which was found to be dependent on the cholinergic activation. However, more investigations are needed to verify the possibility, because some studies did not support the importance of cholinergic system in manual acupuncture/EA-induced increase in blood pressure (Li et al. 1993).

11.3.2.3 Humoral regulation

Several humoral factors have been suggested to play a role in the acupuncture-induced elevation of blood pressure.

Renin-angiotonin-aldosterone system. RAAS is important in maintaining the homeostatic equilibrium of the body fluid, electrolytes, and blood pressure. The protein enzyme, renin angiotensin (RA), activates angiotensinogen, generates angiotensin Ⅰ, and eventually forms angiotensin Ⅱ that is the most important element of the RAAS, which directly leads to vascular contraction, increase in peripheral resistance, and alteration in the aldosterone secretion. Song et al (1990b) studied the effect of acupuncture on angiotensin Ⅱ in 20 rabbits with hemorrhagic shock by femoral artery bloodletting. They showed that the concentration of angiotensin Ⅱ in the plasma was 23.73 + 1.01 pg/ml before hemorrhagic shock. However, 30 min after the shock, the level of plasma angiotensin Ⅱ significantly increased to 64.68 + 18.78 pg/ml. The level was even higher at 60 min after the shock, but was significantly lower in the acupuncture group. These results suggest that massive blood loss could enhance RAAS activity. This may be beneficial in the early period of shock for recovering blood volume and redistributing the blood to important organs like the brain, heart, and kidney. In the non-acupuncture group, the angiotensin Ⅱ level was high, while the blood pressure decreased. In contrast, in the acupuncture group, the blood pressure increased, while the level of angiotensin Ⅱ was relatively lower. The authors interpreted that an increase in the angiotensin Ⅱ level might be beneficial to the body at the beginning of hemorrhagic shock, but an over-increase may not be necessarily helpful to the body. Acupuncture could inhibit the over-increase in angiotensin II level. In a rabbit model of hypotension induced by electrostimulating the aorta nerve (AN), Li et al (2000) observed that EA at the acupoint Neiguan (PC-6) induced an anti-depressurization effect with alterations in the renin activity, angiotensin Ⅱ, and aldosterone at the plasma level.

5-hydroxytryptamine. The plasma 5-HT plays an important role in regulating the cardiovascular function, especially in increasing the blood pressure (Chen 1984). However, under the condition of shock, the vasoconstriction of the microcirculatory arteries deteriorates microcirculation. Acupuncture may improve the microcirculation by regulating the content of 5-HT in the initial period of shock. In a rabbit model of hemorrhagic shock, Song et al (1990b) observed that EA at the acupoint Neiguan (PC-6) significantly increased the blood pressure with a notable change in the content of plasma 5-HT. In the control group, the content of plasma 5-HT significantly increased at 30 and 60 min after the onset of hemorrhagic shock. In the EA group, the 5-HT level was lower than that of the control at 30 min after the onset of hemorrhagic shock. Hence, the authors speculated that EA could improve microcirculation by regulating the level of 5-HT, and eventually improve the circulatory function and blood pressure.

Nitric oxide. As a vasoactive substance, NO has a powerful effect on angioectasia. NO synthesis and release are critically involved in endotoxin shock, and are responsible for the decrease in the blood pressure (Kilbourn and Griffith 1992). Under normal physiological conditions, vascular endothelial cells release NO to maintain normal blood pressure. When pathogens or endotoxin invade into the blood stream, they stimulate macrophages, T-lymphocytes, and the release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α). These inflammatory cytokines stimulate the vascular smooth muscle and macrophages to produce redundant NO, which relaxes the smooth muscle and causes cytotoxic injury. Indeed, during endotoxin shock, NO synthesis and release are critically involved in decreasing the blood pressure (Kilbourn and Griffith 1992). Li et al (2003a; 2003b) observed that EA at the acupoint Neiguan (PC6) increased the arterial blood pressure and reduced the plasmic concentrations of NO and TNF-α in rats with endotoxin shock. They induced endotoxin shock by i.v. injection of lipopolysaccharide (1.5 mg/kg) and intraperitoneal injection of D-galactosamine (100 mg/kg). A catheter was inserted into the right subclavian artery to monitor the blood pressure and the blood was extracted for measuring the levels of NO and TNF-α. The group treated with aminoguanidine was used as the control. They showed that EA at the bilateral Neiguan (PC-6) acupoint increased the blood pressure and reduced the plasmic NO and TNF-α concentrations.

Oxytocin. There is evidence showing that oxytocin may be involved in the effect of EA on hypotension. Xia et al (2001) studied the therapeutic effect of EA on allergic shock in guinea pigs. They detected mean blood pressure in response to EA at the acupoint Neiguan (PC-6) with different intensities and frequencies. The contents of oxytocin in the hypothalamus, antepituitary, and postpituitary tissues were measured by radioimmunoassay. The results suggested that EA at the acupoint Neiguan (PC-6) could produce a significant and rapid increase in the blood pressure in conditions of anaphylactic shock. With the same intensity, higher-frequency stimulation was observed to be better than the lower-frequency stimulation, and with the same frequency, higher-intensity stimulation was better than the lower-intensity stimulation. They observed that the content of oxytocin was differentially regulated in the hypothalamus, postpituitary, and antepituitary tissues when EA increased the blood pressure in the model of anaphylactic shock.

These observations suggest that manual acupuncture/EA may involve multiple humoral factors for increasing the blood pressure in patients with hypotension or shock. However, current information is still very limited.

11.3.2.4 Ionic and other mechanisms

Blood pressure is influenced by the concentration of serum ions such as calcium, magnesium, and potassium (Tang 1986; Wang 1984; Zhao 1995). Hu et al (1997) noticed that in the rabbit model of hemorrhagic hypotension, the blood pressure was significantly raised by acupuncturing at the acupoints Renzhong (DU-26) and Chengjiang (RN-24) with a decrease in the plasma potassium concentration, which was higher in the model than in the control. Hu et al (1999) also detected intracellular free calcium ($[Ca^{2+}]i$) and free magnesium ($[Mg^{2+}]i$) ions in the cardiac myocytes in the same model, and found that $[Ca^{2+}]i$ was significantly decreased, while $[Mg^{2+}]i$ was increased with a significant decrease in the ratio of $[Ca^{2+}]i/[Mg^{2+}]i$. EA at the acupoints Renzhong (DU-26) and Chengjiang (RN-24) significantly increased the blood pressure and $[Ca^{2+}]i$, as well as the ratio of $[Ca^{2+}]i/[Mg^{2+}]i$. However, EA had no appreciable effect on the ratio of $[Ca^{2+}]i/[Mg^{2+}]i$

in the normal cardiac myocytes. Thus, the authors thought that free calcium and magnesium ions in the cardiac myocytes might play a role in regulating the blood pressure in hypotension during acupuncture therapy.

In a study on the effect of EA on cerebral microcirculation in a model of acute hypotension, Hu et al (2000) showed that EA could increase the blood flow and decrease the vascular resistance, which may improve the blood flow in the brain. On the other hand, Xiao et al (1985) showed that in the model of experimental hypotension induced by vasodilative drugs, the pressor effect of simulated EA (somatic nerves stimulation) resulted mainly from an increase in myocardial contractility. When the experimental hypotension or shock was induced by endotoxin, the pressor induced by simulated EA was mainly attributed to the improvement of myocardial contractile function and increase in the visceral vascular resistance. Yi et al (2003) investigated the pressor effect by EA at the acupoint Neiguan in a dog model of hemorrhagic hypotension. They hemorrhaged 36 anesthetized and thoracotomized mongrel dogs and decreased the LV end-systolic pressure (ESP) to approximately 70 mmHg (decreased by about 35%). EA at the acupoint Neiguan (PC-6) for 1 h significantly recovered the decreased ESP, end-diastolic volume, and stroke volume by $32 \pm 13\%$, $27 \pm 13\%$, and $39 \pm 17\%$, respectively ($p<0.05$), without significant changes in the heart rate and the slope of the ESP-volume relation. Furthermore, they found that EA at the acupoint Neiguan (PC-6) was much more effective than EA at the non-acupoint. They concluded that EA at the acupoint Neiguan (PC-6) achieved the anti-hypotension effect by improving the left ventricular filling with an increase in the venous return and vasomotor tone, as well as by the improved capability of the muscle pump.

11.4 Concluding Remarks

Acupuncture treatment for abnormal blood pressure has gained a significant progress in both clinical practice and basic research. It has been documented that the stimulation of specific acupoints with appropriate manipulation (manual acupuncture) or current parameters (EA) can increase or decrease the blood pressure, depending on the condition of the blood pressure. However, most studies have demonstrated that acupuncture or EA has no appreciable effect on the normal blood pressure. The mechanistic research has shown that acupuncture signals are transmitted through the nervous pathway and integrated into the brain, and the output signals regulate the balance of the body fluid and electrolytes, endocrine secretion, gene expression, and many other factors.

In spite of the remarkable achievements in this field, many shortfalls exist in the earlier studies. In the clinical literature, the main problems include the small sample size and lack of convincing data of the control. Similarly, in the basic research, there were some flaws in the design of some experiments and data interpretation. For example, some investigators misinterpreted the results or made wrong conclusions. In this chapter, we have tried to summarize and present comprehensive information on this topic. However, this does not necessarily mean that we agree with all the explanations and conclusions presented in the original articles.

A recent clinical review stated that "the notion that acupuncture may lower high BP is inconclusive. More rigorous trials are warranted (Lee et al. 2009)". However, substantial data in the literature, especially from the animal models, suggest that acupuncture/EA might regulate the blood pressure in "abnormal" conditions. Advanced studies on this interesting subject with new techniques and rigorous randomized controlled trials may provide better knowledge on acupuncture regulation of cardiovascular system and help us to better understand the mystery of acupuncture therapy, and eventually provide some clues for new solutions to cardiovascular disorders.

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12 Effect of Acupuncture on Epilepsy

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Summary Acupuncture has been used for suppression of epileptic seizure for more than two thousand years in Chinese medicine. Also, significant progress towards elucidating the biological basis of the acupuncture suppression has been made in the past several decades. This chapter will summarize the clinical applications and the experimental studies on acupuncture therapy for epilepsy. The therapeutic methods of acupuncture or simulated acupuncture include fine acupuncture, catgut implantation at acupoints, acupuncture plus Chinese herbs and many others. The commonly used acupoints are those along GV and CV meridians. Most reports showed that acupuncture induced remarkable efficacy although there was negative evidence in some of the studies. Optimizing acupuncture conditions including delivery ways, acupoints and stimulation parameters may further improve the efficacy of acupuncture therapy for epilepsy. In animal models, neurobiological insights into the underlying mechanism have been achieved by a variety of modern approaches including biochemical, molecular, electrophysiological, immunological techniques as well as electroencephalogram and power spectra. Accumulating data have showed that acupuncture suppress epileptic seizure through regulation of several neurotransmitters/modulators and their receptors including excitatory (e.g., glutamate) and inhibitory (e.g., gamma-aminobutyric acid) amino acids, neuropeptides such as cholecystokinin, somatostain, enkephalin, dynorphin, and nitric oxide. However, the cellular and molecular basis of acupuncture therapy for epilepsy is far away from well understanding.

Keywords *seizure, acupuncture, electroencephalogram, excitatory amino acids, inhibitory amino acids*

12.1 Introduction

Epilepsy is a common disease of the central nervous system characterized by excessive, episodic and synchronized activity of a group of neurons. The neurophysiologic disorder of cerebral function leads to paroxysmal derangement of epileptic seizure. Different occurrences of seizure activity in different regions of the brain cause different patterns of pathophysiologic behavior. Seizure can be involved with instant loss of consciousness that might be undetectable to the patient or a witness nearby. It can also be associated with severe symptoms, such as a several-second-lasting jerking of entire body induced by a grand mal tonic-clonic seizure.

The biologic basis underlying the abnormal and spontaneous burst-firing of neurons is likely to mainly involve imbalance between GABA ergic inhibitory amino acid system and glutamatergic excitatory amino acid system although investigation of the cellular and neurochemical mechanism has undergone slow and steady progress during the last decade. Many anticonvulsive drugs have been designed and developed to enhance the inhibitory effectiveness of GABA neurotransmission. Other mechanism considerations are related to widespread neurotransmitters, neuropeptides and receptor systems, such as imbalance of enkephalin and dynorphin, release of nitric oxide and influx of calcium. There are many types of epilepsies. There are many patterns of seizures, categorized mainly as focal or generalized. An epileptic seizure could be genetic or acquired. The traditional risk factors of acquired seizure are head injuries, lack of oxygen during birth, lead poisoning, severe infections (meningitis and encephalitis), problems during development of the brain, post-surgical seizures, stroke, multiple sclerosis, Alzheimer, neuroinfection, alcohol, drugs, cerebral tumors and many others. Seizure occurrence could be from one factor or integration of several factors.

Treatment and prevention of epilepsy have been focused on using anticonvulsants to modify neural excitability. Some anticonvulsant drugs are developed to enhance Na^+ channel inactivation, such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine, topirimate and felbamate. Some work to enhance inhibitory GABA ergic transmission, such as benzodiazepine, barbiturate, phenobarbital, vigabatrin, tiagabine and gabapentin. Unfortunately, many patients with intractable epilepsy do not respond to anticonvulsant drugs. Some drugs make unwanted side effects, such as phenobarbital and trimethadione, which have been abandoned to apply in clinic because their sedative or hypnotic properties always lead to tiredness, forgetfulness and confusion. The development of new and effective drug forms is still rather limited in spite of rapid increase in our understanding of related factors in epilepsy.

The prevalence of human epilepsy is high. One among two hundred people in Chinese population is diagnosed with epilepsy based on epidemiological studies in China. In the worldwide, the incidence is high up to about 1%. Many patients with intractable epilepsy suffer from depression of consciousness, transient blindness or even paralysis. Brain surgery resolves part of the problems but may potentially lead to new disorders, such as dysfunction of learning and memory.

Acupuncture, as an effective and a safe treatment, has been served in inhibiting epileptic seizure in clinic for thousands of years. The potential neurobiology pathway of acupuncture has been addressed using modern bio-techniques during the past half century.

In concept of traditional Chinese medicine, epilepsy is caused either by dampness in the spleen and stomach or emotional irritation. The former will be condensed into phlegm later and the latter will result in liver *Qi* stagnation and phlegm retention. Phlegm and improper *Qi* make liver, spleen and kidney unharmonious. Liver wind stirs and liver *Yang* rises. Phlegm and *Qi*, ultimately, mist the clear orifice, disturb the mind, and invade the channels, leading to the occurrence of seizure.

12.2 Clinical Practice of Acupuncture on Epilepsy

Acupuncture efficacy on clinical epilepsy was impressive in therapeutic history. Needle application methods, acupoints selection, and cooperation with Chinese herbs were several key issues for clinical improvement.

12.2.1 History

The first known document on epilepsy and acupuncture in ancient China appeared in *Ling Su* (Miraculous Pivot), Chapter *Epilepsy and Madness* of *Huang Di Nei Jing* (The Yellow Emperor's Classic of Internal Medicine), written by a group of physicians around 770 – 221 B.C. Zhu Danxi, an ancient Chinese physician, commented "epileptic seizure, is from blockage of acupoint channels by phlegm and by salvation". The treatment of acupuncture on epilepsy is believed to make *Yin* and *Yang* balance and quench convulsion via flowing through out acupoint channels, modifying life energy, blood and cerebrospinal fluid and waking brain system in traditional Chinese medicine. *Nan Jing* (Classic on Medical Problems), *Twenty Difficulties* indicated, "One suffered from severe *Yin* will be epileptic. One suffered from severe *Yang* will be mad." *Pi Wei Lun* (Theory on Spleen and Stomach) commented, "epileptic patients generally present running mouth-water, cold sweat secreted from body and clear mucus from nose. The cause of epilepsy is the bad stuff inside of body running up to the brain along Yangjiao, Yinjiao, GV and Chong channels. …Acupuncture should be performed on the above four channels with selected methods".

Acupuncture has been experienced through all the dynasties (Table 12.1). In Qin and Han dynasty (221 B.C. – 220 A.D.), *Ling Shu* (Miraculous Pivot) said that acupoint Tianzhu (BL 10) was used to treat convulsion. In Jing dynasty (A.D. 265 – 420), *Mai Jing* (The Pulse Classic) recorded that acupoint Yangjiao (GB-35) was applied and *Zhen Jiu Jia Yi Jing* (A Classic of Acupuncture and Moxibustion) mentioned Pusen and other four acupoints. In Tang dynasty (A.D. 618 – 907), researches on acupuncture and epilepsy went further. Seizures were categorized

Table 12.1 Historical documents of acupuncture and epilepsy in China

Dynasties	Documents	Authors/Editors
Qin and Han (B.C. 221 – A.D. 220)	*Ling Shu* Miraculous Pivot	A group of physicians
Jing (A.D. 265 – 420)	*Mai Jing* The Pulse Classic	Wang Shuhe
	Zhen Jiu Jia Yi Jing A Classic of Acupuncture and Moxibustion	Huangpu Mi
	Zhou Hou Fang A Handbook of Prescriptions	Ge Hong
Tang (A.D. 618 – 907)	*Qian Jin Yi Fang* Supplement to the Prescriptions Worth a Thousand Gold	Sun Simiao
	Wai Tai Mi Yao Medical Secrets of an Official (752 A.D.)	Wang Tao
North Song (A.D. 960 – 1127)	*Tai Ping Sheng Hui Fang* The Peaceful Holy Benevolent Prescriptions (992 A.D.)	Wang Huaiyin
	Yi Xin Fang Remedies of Heart of Medicine	Yasuyori Tamba (Japanese)
	Tong Ren Shu Xue Zhen Jiu Tu Jing Illustrated Manual on the Points for Acupuncture and Moxibustion as Found on the Bronze Figure (1027 A.D.)	Wang Weiyi
	Sheng Ji Zong Lu Imperial Encyclopaedia of Medicine (1111 – 1117 A.D.)	A staff of physicians under orders of the Emperor Huizong
South Song (A.D. 1127 – 1279)	*Bian Que Xin Shu* Essential Theory of Bian Que	Dou Cai
	Zhen Jiu Zi Sheng Jing Fundamentals of Acupuncture and Moxibustion (1220 A.D.)	Wang Zhizhong
Jin and Yuan (A.D. 1115 – 1368)	*Pi Wei Lun* Theory on Spleen and Stomach (1249 A.D.)	Li Dongyuan
	Wei Sheng Bao Jian Treasure References to Protect One's Life	Luo Tianyi
	Yu Long Ge Jade Dragon Song	Unknown
	Zi Wu Liu Zhu Zhen Jing Acupuncture and Time Window	Yan Mingguang
	Xi Fang Zi Ming Tang Jiu Jing Moxibustion Methods of Xifang Zi	Xifang Zi
	Zhen Jing Zhi Nan Guide to Acupuncture	Dou Hanqing
	Yu Long Jing Jade Dragon Methods	Wang Guorui

(Continued)

Dynasties	Documents	Authors/Editors
Ming and Qing (A.D. 1368 – 1911)	*Shen Ying Jing* Holy Theory	Chen Huizhuan
	Yi Xue Gang Mu Medical Contents	Lou Ying
	Zhen Jiu Da Cheng Compendium of Acupuncture and Moxibustion (1601 A.D.)	Yang Jizhou
	Lei Jing Tu Yi Illustrated Supplementary to the Classified Canon (1624 A.D.)	Zhang Jiebin
	Zhen Jiu Feng Yuan Acupuncture Meets Source	Li Xuechuan
	Shen Jiu Jing Lun Theory on Amazing Acupuncture	Wu Yiding
	Zhen Jiu Ji Cheng Acupuncture Selection	Liao Runhong
	Zhen Jiu Da Quan General Acupuncture and Moxibustion	Xu Feng
	Qi Xiao Liang Fang Wonderful Well tried Recipes. Five Seizures (1470 A.D.)	Fang Xian and Dong Su
	Yang Jingzhai Zhen Jiu Quan Shu General Acupuncture Book of Yang Jingzhai	Yang Jingzhai
	Zhen Jiu Ju Ying Essentials of Acupuncture and Moxibustion (1529 A.D.)	Gao Wu
	Yi Xue Ru Men Guide to Medicine	Li Ting
	Zhen Fang Liu Ji Six Collections of Acupuncture Prescriptions	Wu Kun
	Xun Jing Kao Xue Bian Acupoints Investigation Following Channels	Unknown
	Yi Zong Jin Jian The Golden Mirror of Medicine (1742 A.D.)	Wu Qian
	Xi Hong Fu Xihong Poems	Xi Hong
	Za Bing Xue Fa Acupoints to Different Diseases	Li Ting
	Sheng Yu Ge Better than Jade	Yang Jizhou

in *Supplement to the Prescriptions Worth a Thousand Gold* as liver seizure, heart seizure, spleen seizure, lung seizure, intestine seizure, and septal seizure according body organs or bull seizure, goat seizure, pig seizure and dog seizure according to symptoms. For different seizures, different combinations of acupoints were selected.

Therapy of childhood seizures was discussed even in details in *Supplement to the Prescriptions Worth a Thousand Gold*. In North Song dynasty (A.D. 960 – 1127), eight acupoints were supplemented to treat epilepsy in *The Peaceful Holy Benevolent Prescriptions*, a book finished by the order of an emperor. More therapies to pig seizure, goat seizure and food seizure were also supplemented. In South Song dynasty (A.D. 1127 – 1279), acupoint Zhongwan (CV-12) was emphasized to acupuncture for seizures in *Essential Theory of Bianque* and acupoints Baihui (GV-20), Zhongwan (CV-12) and Fengchi (GB-20) were acupunctured in *Fundamentals of Acupuncture and Moxibustion*. Bianque was a famous physician in ancient China. In Jing and Yuan dynasty (A.D. 1115 – 1368), Yangjiao, Yinjiao, GV and Chong channels were emphasized in *Treatise on Spleen and Stomach*. Acupoint Shenmai (BL-62) was used in daytime seizure and acupoint Zhaohai (KI-6) in night seizure in *Treasure References to Protect One's Life*. Acupoints Houxi (SI-3) and Shenmai (BL-62) were used by Dou Hanqing, a famous physician in ancient China. Acupoints Jiuwei (CV-15), Yongquan (KI-1), Laogong (PC-8), Houxi (SI-3), Shenmen (HT-7) and others were even recorded in therapeutic songs such as *Jade Dragon Song*, *Xihong Poems*, *Acupoints to different diseases*, and *Better than Jade*. Experiences and recipes from different physicians and different dynasties were summarized in Ming dynasty in *Holy Theory*, *Medical Contents*, *Acupuncture Summary*, *Illustrated Supplementary to the Classified Canon*, *Acupuncture meets Source*, *Theory on Amazing Acupuncture*, *Acupuncture Selection* and others. It was said in Ming dynasties, "One who is good at applying acupuncture, knows how to turn *Yang* into *Yin* and how to turn *Yin* into *Yang*". (Liu and Gu 2000)

Acupuncture is commonly practiced to treat epilepsy in present hospitals in China. Doctors' experiences are summarized in reports from clinics around the country, such as Shanghai Institute of Acupuncture and Meridans (Yin 1995). These summaries are generally focused on clinic methods, including acupionts and acupuncture parameters, which were evaluated by theory of traditional Chinese medicine. Most of the experiences were from individual practices after years of clinical work (Wang 2001a; Wang 2001b).

Besides in China, acupuncture is also used in Korea, Japan, Indian (Misra and Singh 2002), Israel (Gross-Tsur 2003) and other countries.

12.2.2 Current Applications of Acupuncture Therapy

The principle of acupuncture treatment in traditional Chinese medicine is to refresh the brain, eliminate wind, clear phlegm and restore consciousness using needles to acupoints of the CV and GV, liver, gall bladder and stomach channels.

12.2.2.1 Fine acupuncture

Fine acupuncture is a classic method of acupuncture. Multiple acupoints are applied, especially GV channels and CV channels. From 54 cases, 34 patients were cured and 14 improved using acupuncture on Jiuwei (CV-15), Jinsuo (GV-8), Yaoqi (Ex-B9), Jianshi (PC-5), and Fenglong (ST-40) (Guo et al. 1999; Lin 2001a). In a case, a 10-year-old child suffered from severe epilepsy. She had seven grand seizures within one year. During every convulsion, she lost her consciousness suddenly with jerking of arms and legs, tightly closing of teeth, up-looking of eye lens, running of mouth water and uncontrollable urination. The seizure lasted about 10 minutes. She waked up with knowing nothing even happened. Anticonvulsant drugs did not work for her. Doctors tried acupuncture to her. Firstly, acupuncture was applied on Renzhong (GV-26) with 1-inch fine needle by insertion of 0.5-inch. Then acupuncture on Dazhui (GV-14) and Fengchi (GB-20) plus Baihui (GV-20) and Yaoqi (Ex-B9) acupoints lasted 30 minutes every day for 15 days. The child did not have seizure again until next year. The recurred seizure lasted 2 minutes with slighter symptom than last year. Acupuncture was going on being given to her every other day for 20 times. From then on, she has not experienced seizure any more in the past 10 years (Wang 2001a). In Chinese clinic, Shi Xueming (1938 –   ), a famous acupuncturist in Tianjin city, used methods of "waking brain and getting keys" to give acupoints Neiguan (PC-6) and Renzhong (GV-26) high stimulation to treat seizure with stroke. Shao Jingming (1911 –   ), a famous acupuncturist in Henan province, performed Dazhui (GV-14), Fengchi (GB-20), Baihui (GV-20), Jinsuo (GV-8) and Yaoqi (Ex-B9) on seizures. Generally, Baihui (GV-20), Renzhong (GV-26), Hegu (LI-4) and Yaoqi (Ex-B9) are used in seizure period and Baihui (GV-20), Dazhui (GV-14), Fengchi (GB-20) and Yaoqi (Ex-B9) are used in intermittent period.

12.2.2.2 Catgut implantation at acupoints

Catgut threads were implanted under the skin in the position of acupoints to stimulate acupoints as heterogeneous proteins. 67 cases of 100 patients obtained improvement of clinical conditions after acupuncture on Jiuwei (CV-15) and Neiguan (PC-6) followed by Xinshu (BL-15) and Dazhui (GV-14) for 21 months in one report (Yan 2001). In another report, 678 cases from 816 patients improved with catgut implantation on Jizhong (GV-6) and Jinsuo (GV-8), in additional with Dazhui (GV-14), Changqiang (GV-1), Tanzhong (CV-17), Zhongwan (CV-12), Qihai (CV-6) and Neiguan (PC-6). To search an effective treatment of general paroxysmal epilepsy, Dazhui (GV-14), Jinsuo (GV-8), Fenglong (ST-40) and other acupoints were used for catgut implantation in 50 patients in a case study when other 50 patients were treated with sodium valproate only as controls (Zhuang et al. 2006). The result showed that both groups got significant improvement according to scores for epilepsy. The effective rate was 94% in catgut implantation group and 82% in control group, which lead to a conclusion that catgut implantation at acupoints has a definite therapeutic effect on general paroxysmal epilepsy. Generally, most of reports indicated that more than 67% patients showed improvement in different degrees as given treatment on different acupoints.

Clinical therapeutic effect of catgut implantation at acupoints plus small dose of anticonvulsant drugs was compared with anticonvulsant drugs only in patients with epileptic general tonic-clonic attack. The former appeared a more satisfactory result in 44 cases of 64 patients than the latter, which was observed in 65 patients (Deng et al. 2001). Catgut thread was also implanted on acupoints after soaked in tranquilizer injection (Lin 2001b, Fu and Li 2004). The efficacy was 89.4% from 160 cases of epileptic patients. Implantation of catgut thread at acupoints of GV channel lead to good efficacy (Xu 2002). In this report, Fengfu (GV-16), Dazhui (GV-14) and Yaoqi (Ex-B9) were used as main acupoints and Taodao (GV-13) and Jinsuo (GV-8) as subsidiary acupoints. 31 of 60 cases got cured. 14 improved significantly. 12 improved a little. 3 failed.

12.2.2.3 Acupuncture plus Chinese herbs

Acupuncture is also commonly applied with Chinese herbs in inhibiting epilepsy at clinic (Xu and Xu 1995). 21 patients were cured and 25 patients were improved among 54 patients in one report (Guo et al. 1999). In another report, 19 patients aged between 8 and 36 did not have seizure again after acupuncture applied on Baihui (GV-20), Fengfu (GV-16), Fengchi (GB-20), Dazhui (GV-14), Taodao (GV-13), Changqiang (GV-1), Jiuwei (CV-15), Taichong (LR-3), and Zhaohai (KI-6) plus an anticonvulsant power, which was made of Chonglou, acorus tatarinowii schott, bombyx batryticatus, pheretima aspergillum (Perrier), Buthus martensii kirsch (whole scorpion), house lizard and cryptotympana pustulata fabricius (snake skin). These patients had different frequencies of seizures before acupuncture, from one seizure every three or five days to several seizures every day (Xing and Hu 1999). Other Chinese herb medicine was also used to treat epilepsy. One is an anticonvulsant ball, which is consist of gastrodia elata bl, arisaema erubescens (wall.) schott, pinellia ternate (thunb.) breit, Fe_3O_4, Fe_2O_3, dens draconis, curcuma wenyujin Y.H.Chen et C. Ling, and scolopendra subspinipes mutilans L. Koch (Guo et al. 1999). The other one is made of $Al(SO_4)_2 \cdot 12H_2O$, curcuma wenyujin Y.H.Chen et C. Ling, arisaema erubescens (wall.) schott, bambusa textiles Mcclure, HgS, amber and mint, which was applied with acupuncture on Dazhui (GV-14), Yaoqi (Ex-B9), Jianshi (PC-5) and Fenglong (ST-40). Combination of acupuncture and Chinese herb evodia rutaecarpa (Juss.) Benth on belly button was also used (Sun 2001).

12.2.2.4 Other methods

Multiple acupuncture methods are applied to suppress epilepsy, including elongated needle, long acupuncture, head acupuncture, ear acupuncture (Shu et al. 2004, 2005), magnetic stimulation at acupoints, drug implantation at acupoints, injection of Chinese herbs at acupoints, magnetic chips implantation at acupoints, Chinese herbs-soaked catgut implantation at acupoints, capsicum patches at acupoints, moxibustion at acupoints, cupping at acupoints, vagal nerve stimulation (Cakmak 2006) and others.

For examples, phenytoin sodium, artane or lominal was implanted at acupoints and released slowly to produce its effect. Dang-gui injection solution or Galculus Bovis waking-brain injection solution was injected at acupoints when *Qi* exists. Special acupuncture techniques were even used to implant gold bead in proper location to treat seizures (Durkes 1992).

12.2.3 Acupoints

Acupoints along GV channels and CV channels are mainly used, such as Fengfu (GV-16), Jinsuo (GV-8), Renzhong (GV-26), Baihui (GV-20), Dazhui (GV-14) and Jizhong (GV-6) (Gu et al. 1998). GV and CV acupoints are also applied with acupoints out of GV and CV channels. A classic method is that several acupoints are used as main ones and other acupoints as subsidiary ones. For example, Baihui (GV-20), Dazhui (GV-14), Shenting (GV-24), Yaoqi (Ex-B9), and Taichong (LR-3) were used as main acupoints. Taiyang (Ex-HN-5), Fengchi (GB-20), Anmian (Ex-HN-22), Shenmen (HT-7), Neiguan (PC-6), Fenglong (ST-40), Taodao (GV-13), Jinsuo (GV-8) and Changqiang (GV-1) were used as subsidiary acupoints. Renzhong (GV-26) acupoint was added during seizure. Shenmai (BL-62) acupoint was added if the seizure took place in the daytime. Zhaohai (KI-6) acupoint was added if the seizure happened at night. Besides first choices of GV and CV acupoints, acupoints near or related with spine also play an important role. *Plain Questions, Su Men, Theory of Empty Bone* demonstrated, “the disease from GV channels is reflected on spine cord”. *Hundreds of Diseases* reported, “the peace of Shendao (GV-11) and Xinshu (BL-15) acupoints is necessary for the recovery of epilepsy”, “epilepsy is related to spine cord”. For another example of clinical trial, Dazhui (GV-14), Shendao (GV-11) and Yaoqi (Ex-B9) were used as main acupoints. Renzhong (GV-26), Baihui (GV-20), Neiguan (PC-6), Hegu (LI-4) and Taichong (LR-3) were added in acute seizure period. Zusanli (ST-36), Xinshu (BL-15), Ganshu (BL-18), Pishu (BL-20) and Shenshu (BL-23) were added in non-acute seizure period. Fenglong (ST-40) was added when patients had lots of sputum (Wang 2001b). Most Shu acupoints in GV channel play roles of inhibiting epilepsy, seizure and madness. Shendao (GV-11) is linked to Shenzhu (GV-12). Acupuncture on one acupoint of Shendao (GV-11) works like on two acupoints of Shendao (GV-11) and Shenzhu (GV-12), which makes the mind peaceful.

According to the statistics of ancient documents, the most common used acupoints were: Jiuwei (CV-15), Baihui (GV-20), Shaoshang (LU-11), Shenmen (HT-7), Xinshu (BL-15), Houxi (SI-3), Juque (CV-14), Yinbai (SP-1), Shenmai (BL-62), Yongquan (KI-1), Zhongwan (CV-12), Shenting (GV-24), Jianshi (PC-5), Laogong (PC-8), Shuigou (GV-26), Jinmen (BL-63), Zhaohai (KI-6), Tianjing (SJ-10) and Dazhui (GV-14). The most commonly used medilans were: bladder, GV channel, CV channel, heart, lung, spleen and kidney, Chong channel, Yinjiao channel and Yangjiao channel. The most commonly used regions were: head, chest, palm, low facet of foot, upper back, upper facet of foot, inner facet of arm. Acupoints were selected by medilans, by body regions, or by dialectics. All in all, commonly used acupoints are located on upper body, far ends of body (including palm and foot) and ventral body. For acupoints in far ends of body, strong stimulation was applied. The selection of acupoints was also related with what time the patient had seizure during a day in ancient time.

The explanation of acupoints applied in treating epilepsy is as follows in traditional Chinese medicine. Renzhong (GV-26) and Baihui (GV-20) act to eliminate the "wind" and refresh the brain. Houxi (SI-3) is connected to GV channel, which is important for epilepsy. Yongquan (KI-1), an acupoint of the kidney channel, nourishes water to restrain *Yang*. The four acupoints are applied during epileptic seizure. An attack in the daytime indicates seizure in the Yangjiao channel, that is why Shenmai (BL-62) is selected. Similarly, Zhaohai (KI-6) in the Yinjiao channel is needled for seizure attacking at night. Between seizures, Jiuwei (CV-15), the connecting acupoint of CV channel, and Dazhui (GV-14), the crossing point of all *Yang* channels, are performed to balance *Yin* and *Yang* and regulate rebellious *Qi*. Taichong (LR-3) soothes the liver and eliminates the "wind". Fenglong (ST-40) makes stomach harmonized turbid *Qi* downward, resolves phlegm and clears heat. Jianshi (PC-5) invigorates the flow of *Qi* in the pericardium channel and refreshes the mind. Yaoqi (Ex-B9), an empirical acupoint for seizure, used with Jiuwei (CV-15), exerts a very good effect (Xu et al. 1988).

12.2.4 Efficacy

The curative effect of acupuncture on certain epilepticus was remarkable (Shi and Gong 1987; Yang 1990).

In addition, acupuncture improves epileptic unconsciousness (Ren 2002). Renzhong (GV-26), Baihui (GV-20), Fenglong (ST-40), Taichong (LR-3) and Houxi (SI-3) were used in one case. Renzhong (GV-26) and Baihui (GV-20) of GV channels distinguish "wind" and arouse brain. Houxi (SI-3) is related to GV channels. Fenglong (ST-40) benefits spleen and stomach and removes sputum. Taichong (LR-3) peaces liver and quenches inner "wind".

Acupuncture could reduce the side effects and the dose of medicine. Medicine therapy is the most commonly used method to control epileptic attack at the present time. But it has severe side effects and toxic reaction. In the following case, an epilepsy patient was treated with acupuncture and moxibustion using Xinshu (BL-15) to regulate the *Qi* of heart and brain directly (Chuntian 2004). Ganshu (BL-18) and Shenshu (BL-23) have the effect of dissolving phlegm. And the moxibustion with method Goto can counterpoise the *Qi* of *Yin* and *Yang* (acupoints: Dazhui (GV-14), Changqiang (GV-1), along with their midpoint and two acupoints near the midpoint about 4 cm, all of 5 acupoints are unpyogenesis moxibustion). In addition, Benshen (GB-13) piercing Yangbai (GB-14) and Yangbai (GB-14) piercing Benshen (GB-13) can give intersectant stimulation to the forehead. The attack of epilepsy and the side effects of medicine are basically controlled with satisfied therapeutic effect after 3 months of treatment.

12.2.5 Negative and Opposite Evidences

Inconsistent data about acupuncture anti-convulsion were also coming from some investigators (Kloster et al. 1999; Stavem et al. 2000).

The effect of acupuncture on epileptic seizures in 29 patients was examined in a controlled clinical setting. Seizure frequency was used to evaluate the efficacy. The patients with chronic intractable epilepsy were randomized in two groups. 15 were given classical acupuncture and 14 were performed sham acupuncture. The seizure frequency was reduced but without statistical significance between both groups. Beneficial effect of acupuncture has not been proved in the above chronic intractable epilepsy (Kloster et al. 1999).

The effect of acupuncture on health-related quality of life was also assessed in intractable epilepsy in a randomized controlled trail. Thirty-four patients with long-standing drug resistant epilepsy were evaluated in the study with two parallel treatments. 20 acupuncture treatments were performed using bilateral needling of three acupoints plus one or two individually chosen points. Sham controls were applied using bilateral needling with smaller needles of three points outside the traditional meridians. The quality of life in epilepsy was evaluated with scores of 89-item questionnaire. There was no difference between the acupuncture and sham control groups in score changes, which suggested traditional acupuncture build no significant effect on the health-related quality of life of patients with intractable epilepsy (Stavem et al. 2000).

Even opposite reports emerged that convulsive syncope was associated with acupuncture in a case study (Cole et al. 2002). Syncope is a rare reaction to acupuncture. Convulsive syncope has even never been previously documented as a response to acupuncture until the recent report. The case study describes an episode of convulsive syncope, characterized by irregular clonic-tonic movements while the patient was unconscious. The episode emerged immediately after the insertion of acupuncture needles into the bilateral Zusanli (ST-36) acupoint.

A review concluded directly no strong evidence for acupuncture as a treatment for epilepsy (Cheuk and Wang 2006). To determine the effectiveness and safety of acupuncture in people with epilepsy, the authors of the review searched the Cochrane Epilepsy Group's Specialized Register (June 2005), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3, 2005), MEDLINE, EMBASE, CINAHL, AMED, TCMLARS, China Biological Medicine Database, Chinese Acupuncture Trials Register, National Center for Complementary and Alternative Medicine, and National Institute of Health Clinical Trials Database from inception to June 2005. Their selection criteria of trails was: include randomized controlled trials evaluating any type of acupuncture performed on any age of people with any form of epilepsy; include trails comparing acupuncture with placebo, sham treatment, and comparing acupuncture plus other therapies with the same other therapies and exclude trails only comparing different acupuncture methods and comparing acupuncture alone with other therapies. Their resulting data was that only three small trials met their inclusion criteria, which included two studied children in China and one studied adult in Norway. Acupuncture did control seizures in the two Chinese studies but did not inhibit seizure in the Norway study. The authors then pointed out that the description of randomization method in the two Chinese studies was not adequate, so they summarized that the current evidences were not enough to support acupuncture as a therapy for epilepsy and much larger high quality clinical trials with appropriate controls are needed to further prove acupuncture efficacy.

The above review was obviously unreasonable. From hundreds of thousands of trials, the authors set a sort of criteria, picked up three small trials to analyze and made a conclusion. Their slogan was scientific but their methods were not. Actually, ancient acupuncture physicians wrote down their successful cases upon clinical improvement one by one. They focused on controlling seizures and how to control seizure better by comparing different acupuncture methods and comparing acupuncture alone with acupuncture plus other therapies. To some extent, ancient acupuncture physicians were using people to perform their experiments and got precious experiences instead that nowadays scientists use animals to do trials first. It was difficult, almost impossible and unimaginable for them to set sort of controls to compare with sham trials. No doubt, denying acupuncture completely is not a scientific attitude and will lead to the loss of the heritage treasure if it is because ancient trials did not meet modern criteria.

Acupuncture was first introduced as a therapy to treat epilepsy in 1972 to the American public although it has been part of China’s medical heritage for over 2000 years. The use of acupuncture for epilepsy depends on precise acupoints, methods of acupuncture administration and the type and extent of a person’s epilepsy. Acupuncture may take some time for the effects to be felt in some patients. People who expect an immediate recovery from the illness may be disappointed. Those who stick with the therapy will have a better opportunity to success. Negative and opposite evidences were minority, a growing number of people with epilepsy are finding that this ancient therapy helps reduce the frequency and severity of seizures and control seizures.

12.3 Mechanism of Acupuncture Inhibition of Epilepsy

The last frontier of the acupuncture on epilepsy—their ultimate challenge—is to understand the biological basis of acupuncture. In the last two decades, remarkable data have emerged within acupuncture and epilepsy.

12.3.1 Effect of Acupuncture on Electroencephalogram and Power Spectra

Electroencephalogram (EEG) activity of a relaxed and awake human presents low-voltage (circa 20 μV) activity as normal alpha rhythm characteristic. Neurons are rest but excitable at this state. The abnormal amplification and synchronization of neuronal firing in epilepsy leads to discharge. The discharges of many neurons are manifest as synchronous interictal spike wave, sharp wave, spike plus slow wave complex or sharp plus slow wave complex. EEG and total power spectra of EEG are used commonly to evaluate the effect of acupuncture on epilepsy both in bed and in bench (Feng et al. 1983, Feng was the late director emeritus of Peking Union Medical College, Neuropsychiatry Department). Power spectrum is quantitative analysis of EEG using fast Fourier transform by means of software in computer. The analysis can be used to compare different EEG statistically (Shen et al. 1990) and quickly by providing energy distribution of individual cerebral electro-activity in total signals, total energy and average frequency.

Observation of EEG in 144 patients with epilepsy before and after acupuncture showed that acupuncture had definite effect in treating epilepsy. Those with normal EEG before acupuncture remained normal afterward. Of those with abnormal EEG 60.2% manifested asynchronism, i.e. reduction or cessation of epileptic discharge. Acupuncture at different points lead to different EEG changes. Performed at Shenmen (HT-7), Taichong (LR-3) and the Motor Zone of scalp, acupuncture induced pronounced EEG changes. Less change was detected while acupuncture was given at Hegu (LI-4), Zusanli (ST-36) and the thoracic zone of scalp (Chen et al. 1983). Acupuncture on some acupoints could prolong the latency of epileptic seizure besides decreasing epileptic discharge (Zhang 1998a).

72.6% of the patients with abnormal synchronized EEG were turned to be asynchronized after acupuncture in a case study (Zhang 1998b). Acupuncture could decrease epileptic discharge in inhibiting epileptic seizure. Healthy people present normal rhythm of EEG even given acupuncture.

The same situation appears in experimental animal models (Fig. 12.1 and Fig. 12.2).

For animal models, power spectrum analysis technique seems begin to be used in investigating the effect of electroacupuncture (EA) on electroconvulsive shock (ECS) and penicillin-induced convulsions in rat in 1986 (He and Cao 1986a, 1986b; He et al. 1990a). Under quiet state, delta and theta bands were found to be predominant in the power spectrum of spontaneous EEG with the peak of the main power in the delta bands. As convulsions were induced by ECS or penicillin, the percentage of EEG power from the delta bands decreased, while that of alpha and beta bands increased. Meanwhile, both shape of EEG power spectrum and intensity of EEG power changed. Bands with the peak of the main power shifted to the right. Total power was enhanced distinctly. In ECS or penicillin-induced convulsive rats, after EA treatment, the power percentage of the delta bands increased, while that of alpha

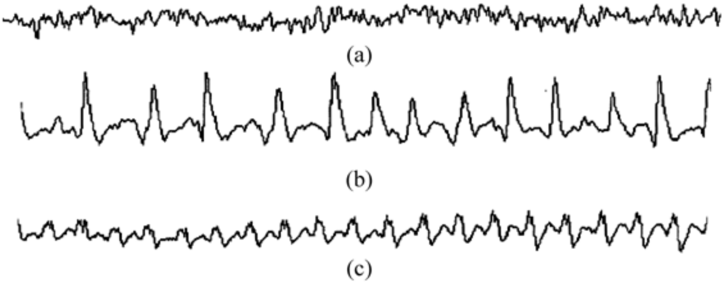

Figure 12.1 Effect of electro-acupuncture on epileptic seizure induced by injection of penicillin in rat. EEG was recorded to monitor epileptic activity. (a) Normal control (saline injection). (b) Penicillin induced epilepsy. (c) Penicillin induced epilepsy plus EA at Fengfu (GV 16) and Jinsuo (GV 8). Note that the injection of saline did not change normal EEG (a), while penicillin injection caused epileptic patterns of EEG (b) which could be largely inhibited by EA treatment (c).

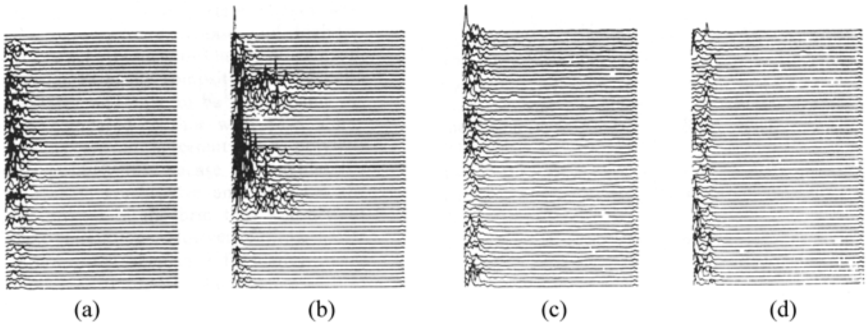

Figure 12.2 Effect of electro-acupuncture on electro-convulsive shock in rat: power spectrum analysis. (a) Normal control treated with saline. (b) Electro convulsive shock. (c) Normal control treated with EA. (d) EA treated rat with electro convulsive shock. Note that saline did not affect normal power spectrum array, while the electro convulsive shock evoked epileptiform power spectrum. Although EA had no effect on normal power spectrum, it did normalize the power spectrum in the epileptic rat.

and beta bands decreased. Interestingly, both shape of EEG power spectrum and intensity of EEG power recovered to some extent. The main power peak in EEG power spectrum returned to the delta bands. Total power decreased. In the above cases, controls were carried out using electroacupuncture stimulation only. No marked change in background EEG activity occurred in the control. No doubt, power spectrum arrays in these experiments revealed that EA suppressed animal convulsions significantly.

Upon different experimental animal models, different GV acupoints and different species of animal including rats, rabbits (He et al. 1985), dogs (Klide et al. 1987; Panzer and Chrisman 1994), mice and cats (Chen and Huang 1984), acupuncture inhibits epileptic seizure in different extents, that is consistent with clinical efficacy. For a dog-case, acupuncture therapy was used for treatment of intractable and idiopathic epilepsy in five dogs at the Veterinary Hospital of the University of Pennsylvania. The dogs were not responsive to high levels of anticonvulsants. Acupuncture was performed at acupuncture points on the Governing Vessel (GV), Gall Bladder (GB), and Bladder (B) meridians. Two of the five dogs showed a decrease in seizure frequency but the improvement reverted to their previous seizure pattern 5 months later. Other three dogs had decreased numbers of seizures and the progress maintained.

In penicillin-induced epileptic rats or rabbits, acupuncture on Fengfu (GV-16) and Jingsuo (GV-8) acupoints inhibited epileptic discharge and normalized EEG (Wang and Chen 1994a; He and Cao 1989; He et al. 1985). Compared with epileptic rats, the frequency of EEG epileptic wave decreased by 0.7 ± 0.2 Hz and the amplitude decreased by 116.16 ± 48.56 μV after acupuncture. The animals were quiet after acupuncture.

In metrozol-induced epileptic rats, acupuncture on Renzhong (GV-26) and Baihui (GV-20) inhibited abnormal EEG activity, decreased EEG pulse account, and improved total frequency ratio of EEG based on analysis of histogram of spontaneous and evoked EEG. Acupuncture also inhibited epilepsy induced by flash light (Ma 1996).

In epileptic model induced by electric stimulation, acupuncture on Baihui (GV-20), Dazhui (GV-14) and Jingsuo (GV-8) significantly decreased average wave width, maximal wave width and frequency of discharge (Zhou 1999).

In intraperitoneally pentylenetetrazol-induced petit mal epilepsy in rat, EA suppressed spike-wave discharges (Wu et al. 1999a, 1999b). EA was applied to GV acupoints of Jizhong (GV-6) and Dazhui (GV-14). Three types of electric pulses, 5 Hz, 40 Hz and 80 Hz, were delivered at wave width 0.5 ms and current 50 μA. The high EA frequency of 80 Hz had a better effect to shorten spike-wave discharge duration. EA anti-convulsion was associated with substantia nigra and superior collicullus but not caudate nuclei and cuneiform nuclei of midbrain reticular form, that was evaluated by electro-destruction of the above subcortical nuclei separately (Wu et al. 2000).

Using electroencephalogram and power spectra, different effects of acupunctures performed in different acupoints, different frequencies and different amplitudes were compared further. Acupuncture suppressed seizure when it was applied on acupoints along GV channel like Fengfu (GV-16) and Jinsuo (GV-8) but had no inhibitory effect when it was applied on acupoints in far ends of limbs like Hegu (LI-4) and Waiguan (TE-5) (Fig. 12.3). EA with high frequency and strong amplitude produced better efficacy at rat in penicillin-induced epileptic seizure (Table 12.2).

12.3.2 Effect of Acupuncture on Excitatory and Inhibitory Amino Acids

Excitatory/inhibitory amino acids systems, including amino acids and their receptors, are mediated by acupuncture on its anticonvulsive procedure.

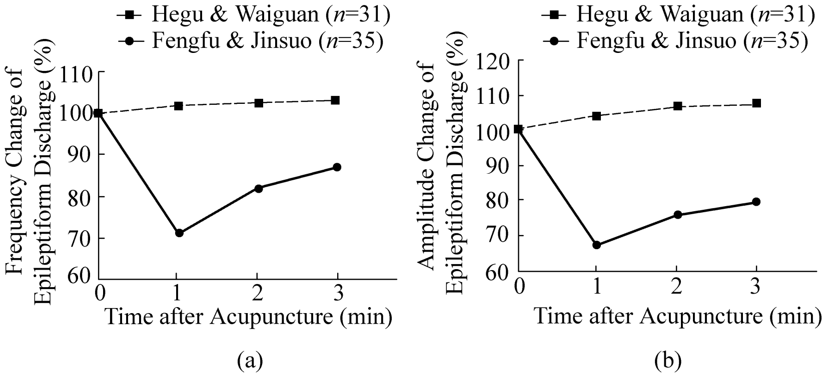

Figure 12.3 Differential effects of acupuncturing different points on frequency and amplitude of epileptiform discharges. EA was delivered to Fengfu (GV 16) Jinsuo (GV 8) and Hegu (LI 4) Waiguan (TE 5). Note that acupuncture at Fengfu (GV 16) Jinsuo (GV 8) reduced frequency (a) and amplitude (b) of epileptic discharges. In contrast, acupuncture at Hegu (LI 4) Waiguan (TE 5) had no appreciable effect on epileptiform discharges.

Table 12.2 Effects of different acupuncture conditions on epilepsy. Acupuncture was applied at different acupoints, different frequencies and different amplitudes. Epileptic discharge was induced by penicillin.

Groups		**Frequency change in epileptiform discharge (%) after acupuncture**			**Amplitude change in epileptiform discharge (%) after acupuncture**		
		1st min	**2nd min**	**3rd min**	**1st min**	**2nd min**	**3rd min**
Acupoint	Fengfu (GV 16) Jinsuo (GV 8)	71.2	81.7	87.3	67.7	75.7	80.0
	Hegu (LI 4) Waiguan (TE 5)	101.9	102.7	103.0	104.2	106.5	107.6
	P value	<0.001	<0.01	<0.05	<0.001	<0.001	<0.001
Frequency	High	62.7	75.6	83.4	53.8	62.9	68.5
	Low	85.5	92.0	93.8	91.3	97.3	99.5
	P value	>0.05	>0.05	>0.05	<0.001	<0.001	<0.001
Amplitude	Strong	62.7	75.6	83.4	53.8	62.9	68.5
	Weak	94.1	96.6	94.2	106.3	108.0	113.3
	P value	<0.01	>0.05	>0.05	<0.001	<0.001	<0.001

Acupuncture was applied at different acupoints with various frequencies and intensities. 100% average value at 3 min before acupuncture.

12.3.2.1 GABA, Glutamate and their receptors

Epileptiform activity can be provoked in hippocampal slices separated from unkindled animals or *in vivo* animals by a variety of manipulation, such as applying glutamate acid, aspartate, kainic acid, $GABA_A$ receptor antagonists or NMDA receptor agonists (Bradford 1995).

Gamma-aminobutyric acid (GABA) is an essential inhibitory amino acid in the mammalian brain. Main active receptors of GABA are $GABA_A$ receptor, a ligand-operated ion channel and $GABA_B$ receptor, a G-protein-coupled metabotropic transmembrane protein. Impairment of GABAergic neuro-transmission by genetic mutations or administration of GABA receptor antagonists leads to epileptic seizures. Pharmaceutic drugs enhancing GABAergic transmission are applied for antiepileptic therapy. Loss in a number of hippocampal GABA neurons is indicated in animal epilepsy models and in tissue from patients with temporal lobe epilepsies. On the other hand, a compensatory increase in GABAergic transmission at certain synapses was detected using electrophysiological and neurochemical investigation. Meanwhile, expression of receptor subunits changed markedly, accompanying neurodegeneration-induced loss in $GABA_A$ receptors, in the dentate gyrus and other parts of the hippocampal formation. It indicated that physiology and pharmacology of $GABA_A$ receptors also altered. Such biological change may be the basis for seizure induction and augmentation of endogenous protective mechanisms. $GABA_B$ receptors are suggested to play a role in absence seizures. Presynaptic $GABA_B$ receptors suppress neurotransmitter release. Anticonvulsant drugs or proconvulsant reagents are created depending on these actions in GABAergic or glutamatergic neurons (Sperk et al. 2004).

GABA transporter is another key protein in GABA neuro-transmission. Two transporters, GABA transporter-1 (GAT-1) and GAT-3, regulate GABA transport by reuptaking GABA in the brain. The transport of GABA limits the overspill from the synaptic cleft and serves to keep a constant extracellular level of GABA. Drugs acting either selectively or nonselectively at GABA transporters have distinct anticonvulsant effects. Tiagabine, an anticonvulsant drug, suppresses epileptic seizure via blocking this reuptake. Recent findings also indicate GABA transporter contributes to GABA release during seizures in response to depolarization. This form of GABA release is induced by extracellular [K^+] and exerts a powerful inhibitory effect on surrounding neurons. Gabapentin and vigabatrin, two anticonvulsants, enhance the transporter-mediated GABA release. The better understanding of dynamic role of GABA transporter will be helpful for new treatment of epilepsy (Richerson and Wu 2004; Dalby 2003).

NMDA receptors are to develop hyperexcitable state and predispose to epilepsy. AMPA receptors initiate individual seizures. NMDA receptors are subsequently activated.

Glutamate metabotropic receptors (mGlu) are likely to be as targets for drug therapy in epilepsy (Moldrich et al. 2003). mGlu, subtypes of AMPA receptors, result in neuronal excitability via activating G-protein-linked enzymes and ion channels. Glutamatergic and GABAergic transmission modified by mGlu presynaptically can contribute to long-term changes in synaptic function. Agonists and antagonists are identified as pro- or anti-convulsant candidates according to these selective actions on subtypes. Agonists acting on mGlu1 and mGlu5 are reported to be convulsant. Antagonists to mGlu1 or mGlu5 receptors are anticonvulsant against 3,5-dihydroxyphenylglycine (DHPG)-induced seizures and in generalized motor seizures mice and absence seizures mice. Although potential anticonvulsant effect of antagonists exists, there is not yet an antagonist of mGlu for clinical usefulness due to their acute and chronic side effects.

Upon Glutamatergic and GABAergic neuro-transmission are highly relevant to epilepsy, the biochemical levels of excitatory and inhibitory amino acid were detected in multiple epileptic animal models and also acupuncture treatment cases. Lots of evidences showed that some amino acids were associated with acupuncture anti-convulsion to certain extent. In the following experiments, multiple acupuncture methods were performed on different acupoints.

In coriamyrtin-induced acute epileptic rat, acupuncture was applied on Baihui (GV-20) and Zhongdu (LR-6). The needle stimulation increased the latency of seizure and reduced the seizure ratio of rats with grade-four epilepsy or more severe (Yan et al. 1999a, 1999b). After acupuncture, Glutamate acid concentration was decreased and the ratio of GABA and glutamate acid was increased in brain stem. The finding indicated that acupuncture may inhibit epileptic seizure through down-regulating excitatory amino acids and up-regulating inhibitory amino acids relatively in the neural-humoral pathway.

In a penicillin-induced epileptic seizure investigation, acupuncture inhibited convulsion through Fengfu (GV-16) and Jinsuo (GV-8) acupoints. Amino acids were calculated with high performance liquid chromatography (HPLC). GABA, taurine, glycine, glutamine levels increased in hippocampus perfusates after acupuncture, which was in comparison with that of epilepsy-only groups. However, the change of glutamate acid showed no statistical significance in this study (Wang and Cheng 1994a).

In other investigation, amino acids were measured in kainic acid-induced epileptic models before and after acupuncture using push-pull perfusion and high performance liquid chromatography with fluorometric detection. Glutamate acid increased in hippocampus during epilepsy and decreased after administration of acupuncture, but the change was not significant. The extra-cellular level of taurine and GABA was elevated after EA (Liu and Cheng 1995), which was compared with that of epilepsy.

Amino-acid automatic analysis in the brain of pentylenetetrazole kindled epilepsy rats gave another data about the changes of glutamic acid, GABA and alanine before and after acupuncture treatment on epilepsy (Yang et al. 2002a). EA was given to rats by puncturing and electrically stimulating Baihui (GV-20) and Fengchi (GB-20) for 30 minutes at 100 Hz and 6 mA, one time a day for seven days. Acupuncture increased the pentylenetetrazole-induced decrease of GABA and alanine whereas it decreased the increase of glutamic acid.

Glutamate, GABA, glycine and taurine were further quantified in the sensory motor area, visual area of the cerebral cortex, reticular nucleus of the thalamus and reticular part of the substantia nigra during EA induced suppression of epileptic petit mal (Zhang et al. 2002). Dazhui (GV-14) and Jizhong (GV-6) were punctured and stimulated electrically for 20 minutes with G6805 EA instrument at electric current of 5 mA and frequency of 80 Hz in epilepsy rat model, which was induced by intraperitoneal injection of pentylenetetrazol plus stimulation of neon light. Collected perfusion fluid from above four brain regions were submitted to high performance liquid chromatography. The resulting data showed that glutamate contents in sensory motor area and visual area of the cerebral cortex decreased slightly after acupuncture treatment but had no statistic changes in comparison with that from pre-treatment. The contents of GABA, glycine and taurine in sensory motor area, visual area and that of GABA in reticular nucleus of the thalamus and reticular part of the substantia nigra were enhanced significantly by acupuncture.

In addition to the change in the levels of excitatory and inhibitory amino acid, the experiments with receptor agonists and antagonists showed that their receptors are also involved in the acupuncture effect. AP5 (2-amino-5-phosphonopentanoic), a competitive antagonist of N-methyl-D-aspartate (NMDA) (Wang and Cheng 1994a), or 6,7-dinitroquinoxaling-2,3-dione (DNQX), a competitive antagonist of non-NMDA receptor (Liu and Cheng 1997), was microinjected into the hippocampus. Analysis of EEG spectrum power showed that both of them partially reduced penicillin-induced epilepsy. Combined with AP5 or DNQX, EA inhibited epilepsy to a large extent, suggesting EA reacting in a synergistic way with AP5, or DNQX. It is proposed that penicillin-induced epilepsy is associated with NMDA receptor and non-NMDA receptor and the inhibitory effect of EA on epilepsy may be related to these receptors.

Bicuculline, an antagonist of GABA receptor's subtype A, microinjected into the hippocampus could partially retard EA antiepileptic effect (Liu and Cheng 1997). (Fig. 12.4). It suggested that the subtype A of GABA receptor might play a pivotal role in EA antiepileptic effect.

Acupuncture attenuated epileptiform discharge induced by microinjection of penicillin in rat amygdala as revealed by reduction of frequency and amplitude. The acupuncture could be reversed by microinjection of 3-mercaptopropionic acid (3-MP), an inhibitor of GABA synthase gultamic acid decarboxylase (GAD), into peritoneal cavity (Zhang et al. 1998a, 1998b).

Two subtypes of GABA receptor play different roles in acupuncture treatment on epilepsy. Muscimol, an agonist of $GABA_A$, either given intrapeneall or microinjected in substania nigra reticular, thalamus reticular nuclei shortened time course of seizure discharge and enhanced improvement of acupuncture. The acupuncture was applied on Dazhui (GV-14) and Jizhong (GV-6) on pentylenetetrazol-induced petit mal epileptic rats. However, Seizure discharge was increased and acupuncture improvement was diminished when given agonists of $GABA_B$ receptor in the same regions, such as baclofen (Wu et al. 2000; Wan et al. 1997, 1999).

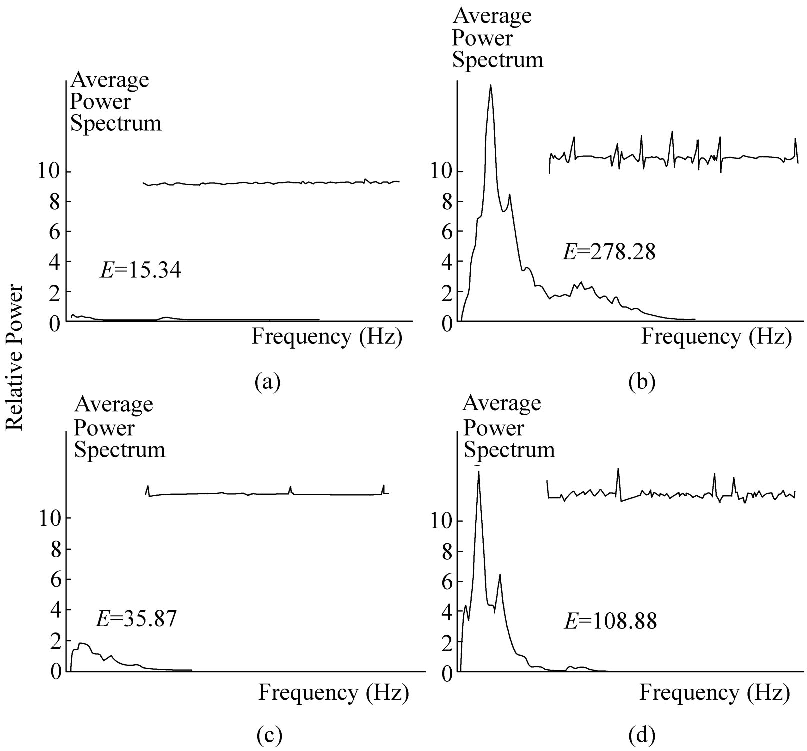

Figure 12.4 Effect of Bicuculline on electro-acupuncture anticonvulsion EEG recordings and related power spectrum in rat. EEG patterns were shown in the upper right sides. *Y* axis referred to average power spectrum. *X* axis referred to frequency (Hz). *E* value referred to relative power. (a) Normal control, $E = 15.34$. (b) Epilepticus, $E = 278.28$. (c) Epilepticus plus EA, $E = 35.87$. (d) Administration of bicuculline on epilepticus plus EA, $E = 108.88$. The recording data showed: (1) Spike waves were evoked and relative power increased dramatically after epilepticus (b) vs (a). (2) Acupuncture suppressed the spike waves and decreased the relative power (c) vs (b). (3) Bicuculline re evoked spike waves and re increased relative power (d) vs (c). The results indicated that subtype A of GABA receptor was involved in the anticonvulsant action of acupuncture.

12.3.2.2 Taurine

Taurine (2-aminoethanesulfonic acid) is one of the most abundant free amino acids in the brain, with similar structure to glycine and GABA. Two distinct Na^+-dependent high-affinity taurine transporters (TAUTl and TAUT2) regulate intracellular taurine levels in glial cells and neurons. During early neocortical development, nonsynaptically released taurine can activate glycine receptors (Alexander and Arnold 1998, Renteria et al. 2004). In adult, taurine can activate $GABA_A$ and glycine receptors to mediate inhibitory synaptic transmission. Actually, taurine has been known to possess some mild anti-convulsive activities in both humans and experimental animal models. Taurine has been used with varying degrees of success in treating patients with epilepsy (Birdsall 1998). Although pooled findings ignited the minds to develop taurine into neuro-protective anti-convulsant, its application is still limited due to blood brain barrier. Taurine lipophilic derivatives like taltrimide (2-phthalimidoethanesulphon-N-isopropylamidc), which was designed against taurine limitations like restricted permeability, is already in the market as an anti-convulsant agent. Many other taurine analogues also have been reported in the literature with partial to marked activity in experimental models and they are undergoing clinical trials.

Taurine suppressed epileptiform discharges induced by removal of Mg^{2+} in combined rat entorhinal cortex- hippocampus slices (Kirehner et al. 2003). *In vivo*, taurine was also found to have a significant anti-epileptic effect in the mouse model of KA-induced limbic seizures (El Idrissi et al. 2003). Taurine level increased after anti-convulsive treatment by ketogenic diet in cerebrospinal fluid of patients with refractory epilepsy and by lamotrigine in rat hippocampus, frontal and parietal cortices. Meanwhile, Taurine release was detected controversial, either with a notable increase in the epileptic hippocampus in a chronic kainate rat model and in a pentylenetetrazol-kindled rat during the seizure period, or with no significant change in plasma and cerebrospinal fluid of patients with acute epilepsy, juvenile myoclonic epilepsy or refractory localization-related epilepsy, or even a marked increase in surviving $SSADH^{-/-}$ mice suffered from lethal tonic-clonic seizures in all brain regions except cerebellum.

One pathway of EA anti-convulsion in recent reports referred to taurine, the essential inhibitory amino acid (Yang et al. 2006). EA inhibited penicillin-induced epileptic activity in a synergistic manner with exogenous taurine at 40 mg/kg while both of them could reduce epileptic events partially in rat behavior and electro-encephalography and exogenous taurine enhanced the anti-convulsive effect of EA (Li et al. 2005). Electrical stimulation on the ear point increased the contents of taurine in hippocampus of penicillin-induced epileptic rat (Shu et al. 2004), and also EA enhanced taurine level on experimental epileptic animals (Wang and Cheng 1994a) when it delivered the anti-epileptic effect. In a taurine depletion rat model, seizure activity, neuronal cell death and taurine transporter expression were investigated during kainic acid-induced epilepsy before and after EA administration on Renzhong (DU-26) and Yongquan (KI-1) (Jin et al. 2005). Taurine levels markedly reduced in cortex, hippocampus, striatum, and cerebellum after beta-alanine supplementation in the taurine deficiency model, which rendered rats more susceptible to kainic acid-induced epileptiform seizures and cell death in CA3 and dentate gyrus area of hippocampus. However, EA suppressed epileptic seizures and cell death partially, and enhanced taurine transporter expression in CA3 and dentate gyrus area.

EA stimulation can generally lower the content of excitatory amino acid to a certain degree and raise that of the inhibitory amino acid significantly in experimental epilepsy models. The collected data mentioned above suggest that the system of excitatory amino acid and inhibitory amino acid in the hippocampus, and their receptors including NMDA, non-NMDA, $GABA_A$ and $GABA_B$ may be involved in the epileptic activity and EA antiepileptic effect.

12.3.3 Effect of Acupuncture on Neuropeptides

The inhibitory effect of electroacupuncture on epilepsy is not only concerned with hippocampal amino acid system but also related to neuropeptides in hippocampus. The level of neuropeptides, including cholecystokinin (CCK), somatostatin, enkephalin, and dynorphin, change in neurons during epilepsy, which suggest that lasting functional changes occur in distinct neuropeptide-containing neurons during epileptogenesis (Mazarati and Wasterlain 2002).

12.3.3.1 Cholecystokinin

Both CCK-immuno-reactivity (CCK-IR) and mRNA were strongly downregulated in the granule cell/mossy fiber system, but CCK-IR appeared increased in the supragranular and molecular layers in seizure-prone GALR1 knockout mice (Fetissov et al. 2003). Cholecystokinin mRNA levels were increased rapidly but transiently in cerebral cortex following amygdaloid-kindled seizures in rat (Burazin and Gundlach 1996). CCK-IR and their mRNAs were highly expressed in basket cells at preconvulsive stage 2 and after three consecutive tonic-clonic seizures of kindling (stage 5). Their signal of immunoreactive was enhanced in the inner molecular layer of the dentate gyrus in the ventral hippocampus. In the hippocampus proper, CCK-IR fibres and its mRNA were particularly expressed in the pyramidal cell layer. The number of CCK-IR neural cells was increased in the subiculum. This change of cholecystokinin may play a pivotal role on synaptic neuro-transmission and contribute to modulate hippocampal excitability (Schwarzer et al. 1996).

The effect of EA on the changes of cholecystokinin (CCK) mRNA levels of the hippocampus was investigated in rat penicillin-induced epilepsy model using Northern Blot and *in situ* hybridization techniques. Epilepsy can significantly increase CCK mRNA levels in dentate gyrus and CA3 areas of hippocampus in diencephalic sections after penicillin-induced seizure, whereas EA not only can attenuate the seizure behaviors and EEG changes, but also can decrease the increase of CCK mRNA contents induced by the seizure. However, in the subiculum, dentate gyrus and CA3 areas of mesencephalic sections of rat hippocampus, EA can further increase the enhancement of CCK mRNA concentration induced by penicillin-induced seizure. The results suggest that EA inhibitory effects on seizure behavior and epileptiform activities may be related to the alteration of CCK gene expression in the different area of hippocampus (Yang et al. 1996).

12.3.3.2 Somatostatin

Somatostatin, a somatotropin release-inhibiting factor, plays a role in controlling partial complex seizures via inhibiting hippocampal circuitries. Brain somatostatin is an inhibitory candidate in seizures and epileptogenesis (Vezzani and Hoyer 1999). Somatostatin neurons in the dentate gyrus participate in down-regulating firing rate of granule cells. Somatostatin in CA3 reduces excitability of pyramidal neurons through interacting with both presynaptic receptors and postsynaptic receptors. In CA1, somatostatin also inhibits the excitatory drive on pyramidal neurons. The alterations of hippocampal somatostatin system were detected in the kindling and in the kainate epileptic models. In the kindled hippocampus, somatostatin level was increased, especially in the dentate gyrus. The change may contribute to control the latent neuron-firing of the kindled brain and prevent excessive discharge and spontaneous seizures. In consistent with somatostain, pharmacological activation of somatostain receptors exerts antiseizure effects (Binaschi et al. 2003). Furthermore, distributions of somatostatin receptors (SSTs) subtypes were different in the hippocampi of seizure-resistant (SR) and seizure-sensitive (SS) gerbils. SST2A and SST3 immunodensity in the hippocampus of SS gerbils was lower than that of SR gerbils. Strong SST4 immunoreactivity existed in the dentate gyrus and in the CA3 region in SR gerbils but not in SS gerbils. Strong SST5 immunoreactivity was detected in the stratum oriens of the CA2-3 regions and the septal area of CA1 region of the hippocampus both in SR and SS gerbils. However, SST5 immunodensity in the stratum radiatum in SS gerbils was lower than in SR gerbils. These changes of SSTs in the hippocampus of these seizure prone animals may be relevant to a regulatory mechanism for epileptic seizure (Kang et al. 2003). Unlike in rats, evidences that somatostain system do not medicate anticonvulsant effects also appeared. Homozygous mice lacking SST2 receptors revealed a 52% reduction in kainic acid-induced EEG ictal activity. The number of tonic-clonic seizures was reduced by 50% in behavior and the onset time of seizures was doubled on average. Agonists of SST2 receptor did not affect kainate seizures in mice while it significantly reduced seizures in rats (Moneta et al. 2002).

The changes of somatostatin messenger RNA (ss mRNA) were investigated on ear acupuncture in rat during penicillin-induced epilepsy using *in situ* hybridization histo-chemistry (Liu et al. 1998). ss mRNA was strongly expressed in piriform cortex, frontal cortex, cingulated gyrus, lateral septal nucleus, basal amygdaloid nucleus, pyramidal layer of CA1 – CA4 area of hippocampus and granule cell layer, polymorphical layer in dentate gyrus 24 hours after penicllin injection. Ear acupuncture decreased the expression of ss mRNA in the frontal corex, basal amygdaloid nucleus, hippocampus dentate gyrus, frontal piriform cortex with inhibiting epilepiform activity.

12.3.3.3 Endogenous opioid peptides and opioid receptors

To elucidate the role of neuropeptides in epileptogenesis, the alterations in Met-enkephalin and dynorphin mRNA were detected with or without phenobarbital treatment. In trimethyltin-induced seizures and aggression, Met-enkephalin mRNA was significantly increased at day 2 to day 6. Meanwhile, dynorphin mRNA was decreased markedly from day 2 to day 16. Met-enkephalin mRNA changes correlate more with seizures and dynorphin mRNA changes are associated more with aggression (Ishikura et al. 2001). The important role of dynorphin in the pathogenesis of seizures was supported by lots of epileptic models. Dynorphin modulates neuronal excitability *in vitro* in hippocampal slices and potentiates endogenous anti-ictal actions in animal models and humans. Recently, an investigation of dynorphin actions in central nervous system viral injury triggered new interest on dynorphin functions in epileptogenesis and epilepsy treatment (Solbrig and Koob 2004).

Acupuncture was reported to suppress seizures through regulating enkephalin (He and Cao 1989). To determine whether the effect of EA on electroconvulsive shock (ECS) was through affecting endogenous opioid peptidergic system in the hippocampus, leu-enkephalin- and beta-endorphin-like immunoreativity (L-E-LI and Beta-E-LI) were measured using radioimmunoassay (RIA) in the hippocampal perfusate after ECS and EA treatments. Wistar rats were given ECS stimulation, which caused convulsion indicated by behavior and elelctroencephalogram. EA suppressed ECS-elicited convulsions, including both behavioral disorders and EEG abnormalities. The results of RIA showed that after repeated ECS treatments, the contents of L-E-LI and Beta-E-LI increased significantly by 136% and 157%, respectively. In contrast, EA treatment depleted alteration of L-E-LI and Beta-E-LI induced by ECS, depleting the former by 32% and the latter by 85%. These observations suggest that EA anticonvulsion is related to the release of L-E and Beta-E in hippocampus and EA may exert its action through decreasing the release of opioid peptide (He and Cao 1989).

An increase in leu-enkephalin immunoreactivity (Wang and Cheng 1994b) and preproenkephalin mRNA level (Wang et al. 1994a) was found in subiculum, CA1 area of hippocampus, hilus, missy fiber, piriform cortex, entorhinal cortex and amygdaloid nucleus in penicillin-induced epileptic rats. The increase was decreased by acupuncture on Fengfu (GV-16) and Jinsuo (GV-8) acupoints.

Acupuncture could enhance dynorphin concentration from 49.3 ± 6.6 pg/ml to 76.7 ± 6.6 pg/ml in hippocampus perfusate during penicillin-induced epilepsy (Wang and Cheng 1992). Penicillin decreased dynorphin concentration in epileptic hippocampus from 97.5 ± 5.8 pg/ml to 56.3 ± 7.8 pg/ml compared to saline control.

The decrease of dynorphin in perfusate during epilepsy and its increase after acupuncture was also confirmed in electroconvulsive shock model (Wang and Cheng 1995). The acupuncture was also detected to enhance dynorphin 1-8 immunoreactivity by its density and distribution in mossy fiber and hilus of rat hippocampus using immunohistochemistry in penicillin-induced epileptic model. (Wang and Cheng 1994b).

Dynorphin A 1-13 antiserum (Gao and Cheng 1998a) or dynorphin blocker could abolish the anticonvulsant effect of acupuncture in rat.

Seizure sensibility is also thought to be mediated by μ-opioid receptor activation partially. μ-opioid receptor immunoreactivity was increased in the inner molecular layer of the dentate gyrus after animal seizures. In kainic acid-induced seizures, these increases are restricted to presynaptic, postsynaptic, or glial profiles. Additionally, some μ-opioid receptor-labeled terminals in kainic acid-treated rats possessed excitatory-type morphology and contained enkephalin or dynorphin. Increased expression of μ-opioid receptor during seizure is associated with terminals originating from several different neuronal populations, including granule cells, surviving GABAergic interneurons, septal cholinergic, and/or supramamillary projection neurons (Skyers et al. 2003). Kainic acid modifies μ-receptor binding in young, adult, and elderly rat brain (Perez-Cruz and Rocha 2002). Agonists for μ-receptor could induce limbic seizures in rats, using intracerebroventricular administration.

Changes in opioid receptors were analyzed in the cerebral areas of rats brain slices using radioreceptor-binding assay combined with autoradiography technique followed electroconvulsive shock (ECS) and EA anticonvulsion. The results from image processing and detection of optic density showed that repeated ECS resulted in an increase of opioid receptor densities in the caudate nucleus, hippocampus, habenular nucleus and amygdala. In the group of EA plus ECS, however, the opioid receptor densities in the hippocampus, habenular nucleus and amygdala decreased as compared with that in ECS group. In addition, the receptor density in the caudate nucleus showed a decrease tendency. The results provided morphological evidence of the involvement of opioid receptors in these cerebral areas in the process of ECS and EA anticonvulsion (He et al. 1990b).

U-50488, an agonist of κ receptor, given by microinjection in hippocampus, reduced the eipleptiform activities and increased the EA anticonvulsion. MR 2266, an antagonist of κ receptor, induced the provocation of the epileptiform activities and resulted in disappearance of reversal of the inhibitory effects of electroacupuncture on seizures. The data was from electro shock epilepsy model. Acupuncture was performed at Jinsuo (GV-8) and Fengfu (GV-16) (Gao and Cheng 1998b). 1,3-di-ortho-tolylguanidine (DTG), an agonist of θ receptor could also reduce the eipleptiform activities and increased the EA anticonvulsion.

Sodium channel mutation has been known to casually link to human epilepsy (Mantegazza et al. 2005; Yamakawa 2006; Xu et al. 2007a, 2007b), and up-regulation of Na^+ channels has been demonstrated to critically lead to epileptic hyper-excitability and seizures (Sashihara et al. 1992; Agrawal et al. 2003; Xia et al. 2003). Interestingly, it was observed that in the mutant brain exhibiting spontaneous epilepsy, Na^+ channel is up-regulated (Xia et al. 2003), while δ opioid receptor (DOR) is down-regulated (Zhao et al. 2005), suggesting a potential role of DOR impairment in the pathophysiology of epilepsy associated with genetic abnormality. Indeed, DOR activation has been shown to inhibit Na influxes (Chao et al. 2008; Chao et al. 2009). Moreover, it has been found with direct evidence that DOR activation inhibits Na^+ channel function (Kang et al. 2008). There is also evidence suggesting that DOR activation is anticonvulsant in animals and human (Lee et al. 1984; Tortella and Long 1985; Koide et al. 1992; Madar et al. 1997). In some experimental models of epilepsy, endogenous enkephalin levels are greatly increased in the brain with epileptic seizures (Tortella and Long 1985; Madar et al. 1997), and opioid receptors are up-regulated following spontaneous epileptic seizure (Hammers et al. 2007), which may represent a compensatory mechanism against epilepsy. Since Na^+ channels play a major role in neuronal excitability including epileptic hyper-excitability and most of anti-epileptic drugs are actually inhibitors of Na^+ channels (Remy et al. 2003; Armijo et al. 2005), the phenomenon may provide novel clues for better solutions of epileptic seizures. Acupuncture has been well documented to activate opioid system in the brain. Therefore, it is likely that acupuncture may inhibit epileptic seizures by inhibiting hyper-excitability due to an up-regulation of Na^+ channel.

However, more studies are needed to clarify this issue because of some controversial observations in the literature. For example, injection of leu-enkephalin induced epileptic seizure (He et al. 1989). Also, Danielsson et al (2006) and Jutkiewicz et al (2006) showed the similar results. In a study to address the relationship between DOR and EA anti-convulsions (He and Cao 1989). The content of leu-enkephalin-like immunoreactive substance (LEK-LIS) in the perfusate from the hippocampus increased after repeated electroconvulsive shock (ECS). EA inhibited epileptiform spikes induced by ECS, and the content of LEK-LIS decreased markedly after EA. Leu-enkephalin (LEK), an agonist of the δ receptors and μ receptors, injected into the hippocampus (10 μg), produced epileptiform spikes. However, ICI 174 864 (4 μg), a specific antagonist of the δ receptors, suppressed convulsions significantly. It is unclear regarding the underlying mechanism in this work because (1) both acupuncture and epilepsy can promote the release of endogenous opioid peptides, leading to a decrease in the content (Ishikura 2001; Wang and Cheng 1992); (2) LEK can activate both δ-opioid receptor and μ-opioid receptor that is not protective against neuronal injury (Zhang et al. 2000); and (3) LEK may inhibit activities of inhibitory inter-neurons in certain regions, leading to a complex effect. A more reliable approach is needed to correctly elucidate the roles of different opioid receptors in acupuncture therapy for epilepsy.

Preliminary reports above indicated multiple neuropeptides participate in anti-convulsive effect of acupuncture on epileptiform seizure, including cholecystokinin (CCK), somatostatin, enkephalin, dynorphin, μ, δ, and κ receptors.

12.3.4 Effect of Acupuncture on Nitric Oxide

Nitric oxide (NO) is documented to play a role in the pathophysiology of epilepsy (Kaneko et al. 2002; Milatovic et al. 2002). Nitric oxide modulates low-Mg^{2+}-induced epileptiform activity in rat hippocampal-entorhinal cortex slices (Schuchmann et al. 2002). Abnormal expression of neuronal nitric oxide synthase triggers limbic seizures and hippocampal damage in rat (Bagetta et al. 2002). NO-mediated events are involved in the anticonvulsant action of some antiepileptic drugs.

Various NO synthase inhibitors (NOSi) have been tested whether they acted on antiseizure activity of antiepileptic drugs in many animal experimental models of epilepsy, including electrically and pharmacologically evoked seizures, sound-induced convulsions and amygdala-kindled seizures. Some NOSi could modify the anticonvulsant properties of antiepileptic drugs, however, L-arginine, a NO precursor, was unable to reverse the effect of NOSi. That indicated NO pathway involved in the action of antiepileptic drugs needs to be further addressed (Wojtal et al. 2003; Huang and Cheng 1998; Wang and Cheng 1997b).

Both nitric oxide and NO synthase, including its three isoforms, were investigated preliminarily in epileptic seizures and acupuncture treatment (Wang and Cheng 1997a; Wang et al. 1994b). Nitric oxide is detected by nitric oxide-sensitive electrode with potentiostat. Nitric oxide concentration in rat hippocampus increased after penicillin-induced epilepsy (Huang et al. 1999). Applied acupuncture decreased nitric oxide concentration with inhibition of total power spectrum of EEG. For nitric oxide synthase, both mRNA and protein were investigated during acupuncture action using Northern Blot, reverse-transcriptional PCR, *in situ* hybridization, immunohistochemistry, and Western Blot (Wang and Cheng 1997a, 1997b). Different isoforms of nitric oxide synthases from different pathways appeared different functions in acupuncture anticonvulsion. Acupuncture decreased neuronal and inducible nitric oxide synthases but had no effect on epithelial nitric oxide synthase (Yang et al. 2000).

12.3.5 Effect of Acupuncture on Other Neurological Factors

Besides excitatory and inhibitory amino acids, neuropeptides and nitric oxide, there are many other neural active substances involved in acupuncture, including c-Fos, c-Jun, glutamate decarboxylase, cAMP, cGMP, actylcholine, serotonin, and melatonin.

12.3.5.1 c-Fos, c-Jun and glutamate decarboxylase

c-Fos proteins were visualized immunohistochemically in the brain of rats after penicillin-induced seizure and EA treatment. An evident expression of c-Fos proteins was presented in the CA1 area of hippocampus, dentate gyrus, piriform cortex, dorsal part of entorhinal cortex, and amygdaloid nucleus. The level of c-Fos proteins was then dramatically increased in CA3 area and the areas mentioned above except CA1 area during seizure whereas c-Fos proteins apparently decreased after EA treatment (Wang and Cheng 1994c, 1994d).

Glutamate decarboxylase (GAD)-67, c-Fos and c-Jun were assayed in another study showing that acupuncture reduced both the incidence of seizures and hippocampal cell death in a mouse model of kainic acid-induced epilepsy. Acupuncture was given every day at acupoint Shaofu (HT-8) bilaterally on 1 and 2 days before and the day after an intracerebroventricular injection of 0.1 ug kainic acid (total 3 times). Acupuncture reduced the severity of the kainic acid-induced epileptic seizure and the rate of neural cell death, and also decreased the expressions of c-Fos and c-Jun induced by kainic acid in the hippocampus. In addition, acupuncture increased GAD-67 expressions in the same areas (Kim et al. 2008).

The elevated expression of GAD(67) by acupuncture was confirmed in dentate gyrus in a rat model of epilepsy induced by injection of lithium-pilocarpine (Guo et al. 2008). Electroacupuncture administered at bilateral acupoints of Zusanli (ST-36) significantly reduced the times of spontaneous recurrent seizure and elevated the expression of GAD(67) mRNA in the granule cell layer of dentate gyrus, but not in the hilus.

12.3.5.2 cAMP and cGMP

There is evidence showing that in the rats with PTZ-induced epileptic seizures, cAMP and cGMP in the hippocampus detected by radioimmunoassay increased during epilepsy, which could be inhibited by acupuncture at Baihui (GV-20), Fengchi (GB 20), and Fengfu (GV-16) (Yang et al. 2002b). In a conscious rabbit model, with experimental epileptic seizures induced by c-AMP, electro-acupuncturing at bilateral Zusanli (ST-36) points inhibited the epileptic waves (Lou 1989). During and after electro-acupuncture treatment, the frequency, amplitude and duration of epileptiform discharges decreased significantly. The seizure waves even disappeared completely. The frequency and amplitude of epileptic waves were significantly different in comparison with that of the non-electroacupuncture group. The duration of epileptic waves was shortened by 58% – 67%. The report suggested that electroacupuncture may attenuate cAMP activity related epilepsy.

12.3.5.3 Actylcholine

The release of brain actylcholine (Ach) increased in experimental seizures caused by different factors. Acupuncture or EA decreased the Ach level. Acupuncture may inhibit neural pathway of cholinergic transmission, enhance activity of cholinesterase in caudate nucleus and thalamus, and inactivate Ach (Zou and Ou 1993). In intraperitoneally pentylenetetrazol-induced petit mal epilepsy in rats, anticonvulsant effect of acupuncture on Dazhui (GV-14) and Jizhong (GV-6) was reduced significantly when hemicholinium-3 (HC-3), an inhibitor of Ach synthesis, was micro-injected into wedge-shape nucleus in midbrain reticular structure (Wu et al. 2000).

Dynamic variation of Ach was observed in the focus of epileptiform discharges induced by topical application of penicillin on rat sensorimotor cortex. Release of Ach in the cortex increased during seizure. Acupuncture decreased the increase of Ach while attenuating epileptiform discharges. Manual acupuncture made Ach concentration lower than EA, which is linked to that manual acupuncture attenuated the epileptiform discharges more effectively than EA in frequency and amplitude. Manual acupuncture was performed at Dazhui (GV-14). EA was applied at Dazhui (GV-14) and Taodao (GV-13) (Zhu et al. 1991a, 1991b).

12.3.5.4 Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) may participate in anticonvulsant effect of acupuncture and EA (Zou and Ou 1993). Electro-activity induced by direct EA at cortex may be suppressed by administration of 5-HT in part regions.

To evaluate the role of 5-HT in the suppression of cortical epileptiform discharges by electro-needling, p-chlorophenylalanine (p-CPA), which blocked the enzymatic synthesis of 5-HT, was injected intraperitoneally into rats. Cortical epileptiform discharges induced by penicillin and surface-negative waves of cortical recurrent inhibition induced by antidromic stimulation of pyramidal tract were detected and recorded. Acupuncture are administrated at Dazhui (GV-14) and right Zusanli (ST-36), Yaoshu (GV-2) and left Zusanli (ST-36). Injection of p-CPA reduced the anticonvulsant effect of electroneedling. Both amplitude and frequency of cortical epileptiform discharges was retarded and recovery of surface-negative waves was delayed. Electric stimulation of dorsal raphe neclei attenuated epileptiform discharges and shortened its duration. When dorsal raphe nuclei were destructed by electrolytic damage, seizure duration prolonged and the antiepileptic effect of electroneedling was reduced. Stimulation of periaqueductor (PAG) also led to suppression of epileptiform discharges, that were also diminished after injection of p-CPA. The finding indicated that 5-HT and dorsal raphe nuclei where a large number of 5-HTergic neurons are located play an important role in antiepileptic action of electroneedling (Ma and Wu 1986).

In intraperitoneally pentylenetetrazol-induced petit mal epilepsy in rats, microinjection of phetamine (PCA), an inhibitor of 5-HT synthase, into dorsal raphe neclei induced more epileptic wave and reduced the anticonvulsant effect of acupuncture (Wu et al. 1999a, 1999b, 2000).

12.3.5.5 Melatonin

The alteration of melatonin levels was explored in pineal, hippocampus and serum during seizure crisis and EA anti-seizures in benzylpenicillin-induced rat seizure model. EA was performed on Fengfu (GV-16) and Jinsuo (GV-8) acupoints in rats. Electroencephalogram of rats was recorded and the relative power of 1 – 30 Hz band of EEG was analyzed. A capillary electrophoresis-electrochemical detection method was used to determine melatonin contents. Melatonin was elevated in pineal and hippocampus. It had no change in serum in the beginning and then significantly enhanced during seizure crisis. The elevation of melatonin level was greatly potentiated with 30 minutes of EA tratment. Meanwhile, the degree of seizures and the increase of EEG relative power induced by seizure were significantly reduced. Because melatonin was considered as an antistressor and a natural downregulator of epileptiform activity, the elevation in melatonin level during seizures was postulated to be possibly one endogenous mechanism that counteracts convulsions and seizure-induced stress. A further elevation of melatonin levels with EA treatment suggests that melatonin might be one of the possible medium of EA anti-seizures (Chao et al. 2000; Chao and Cheng 2001; Chao et al. 2001).

12.3.6 An Anatomical View

Vagal nerve stimulation and electroacupuncture have some promise as neuroprotective therapies for patients with intractable epilepsy, which brought up a hypothesis from anatomical view that electroacpuncture might be targeting the brain through direct and indirect vagal nerve stimulation (Cakmak 2006). Many electroacupuncture types including stimulation of body, facial and auricular point, have anticonvulsant and neuroprotective effects for epilepsy. Stimulation of acupoints on the extremities results in stimulation of the vagus nerve. The nucleus of the solitary tract (nucleus tractus solitarii, NTS) is a primary site when vagal afferents terminate. It may be also the center for afferent pathways of facial, scalp and auricular acupuncture. Body electroacupuncture sends its signal to NTS via indirect vagus nerve stimulation. Scalp and facial acupoints make connection with NTS via trigeminal and cervical nerves. Auricular acupuncture delivers information to NTS via glossopharyngeal, facial, cervical, TG and vagus (Arnold branch) nerves. The neuroprotective pathways of electroacupuncture to hippocampus, thalamus, cortex and amydala may be through the nucleus of the solitary tract via vagus nerve stimulation.

12.4 Concluding Remarks

Acupuncture is documented in literature, experienced in clinic, and researched in bench to exert a very good efficacy to inhibit epilepsy. Clinical reports have been collected starting from two thousand years ago to present in China. However, the biological basis of acupuncture still remains uncertain. What has been detected in the study of acupuncture and epilepsy is still a corner of an ice-berg. From the current evidence, acupuncture modulation may be related to the regulation of excitatory/inhibitory amino acids system, neuropeptides system, nitric oxide system, c-Fos, cAMP, cGMP, actylcholine, serotonin, melatonin and others.

It should be pointed out that the understanding of acupuncture mechanism on epilepsy remains at the very beginning. Experimental data collected above need to be reevaluated by multiple investigators. Lots of different factors could result in the discrepancy of experimental data, including different epilepsy models, different choices of acupoints, different time-windows, frequencies and amplitudes of EA, and different indexes. We should establish a standardized system with stable model, accurate acupoints, time-window, frequency and amptitute of electroacupuncture, to investigate the molecular mechanism of acupuncture at the treatment of epilepsy, including death of neural cells, sprouting, and others. The elucidation of biological basis of acupuncture will help us to further promote acupuncture and develop more effective therapy with or without adjunctive drug.

Could acupuncture control seizures? The question is always addressed in the United States. How could acupuncture be applied better to control seizures? That is the question Chinese acupuncture physician asked themselves.

The question forwarded in the United States is reasonable. Literatures in English gave opposite evidences, which confused people to have a try even they have intractable seizures. Less than 5% Chinese documents were translated into English. Acupoints, channels and meridians are mysterious concepts to people who seldom touched oriental medicine.

The question carried in the mind of Chinese acupuncture physician is also reasonable. Based on Chinese documents, clinical reports and experimental data, they never doubted that patients nonresponsive to antiepileptic drugs should seek for complementary and alternative therapy and acupuncture will be one of the choices.

The cognitive gap exists because the biological basis underlying the therapeutic effect of acupuncture on epilepsy remains uncertain. Very less research was conducted on acupuncture and epilepsy in the world up to date compared to research in epileptic field. On one hand, the traditional Chinese theory that acupuncture balances energy and restores harmony—*Yin* and *Yang*—within the body is not enough to convince neurobiologists. On the other hand, about 30% of all epilepsy patients cannot achieve adequate seizure control with currently available antiepileptic drugs. The only pathway for acupuncture to carry out its potential missions seems to be the elucidation of acupuncture mechanism.

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13 Neuroimmuno-effect of Acupuncture on Immune-mediated Disorders

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Summary This chapter summarizes the clinical practice of acupuncture therapy for immune-mediated disorders and the mechanisms underlying the regulation of neuroimmune function by acupuncture. Numerous data indicate that acupuncture can regulate immune system, tune-up specific and nonspecific cellular and humoral immunity, and modulate leucocytosis, microbicidal activity, antibodies, globulin, complement, and interferon (IFN). The acupuncture-induced output signal has been observed to correct the dysfunction of immune system and induce a homeostatic effect on the body through the accommodation of nervous and immune systems. At the molecular level, the acupuncture-induced neuroimmune regulation is mediated through multiple pathways, and involves various bioactive molecules including steroids, neuropeptides, cytokines, and neurotransmitters, which form the basis for bidirectional-coordinated neuroimmune regulation, in response to homeostasis disturbances. An integrated investigation including the approaches of molecular biology, integrative physiology, and clinical research is considered to further improve the understanding of the acupuncture-mediated regulation of neuroimmune function, and eventually lead to better applications of acupuncture for the treatment of immune-related diseases.

Keywords *immunomodulation, neuro-endocrine-immune network, Rheumatoid arthritis, immunosuppression, hypothalamus-pituitary-adrenal axis*

13.1 Introduction

The human body has an efficient defense system that can recognize and eliminate the invading foreign substances. This defense system is called the “Immune System”. During the normal functioning of our immune system, our bodies will not be afflicted by symptoms such as fever, pain, swelling, or itching. However, when the immunological activity decreases or when too many antigens overpower the defense system, the symptoms described earlier may occur, until the normal condition is restored. The symptoms with the different stages of immunological reactions can be assigned to the defense systems of inflammation and allergy. There are many kinds of immune cells, such as B- and T-lymphocytes, natural killer (NK) cells, and some intriguingly dendritic cells. For over 4000 years, acupuncture has been used to expedite body healing. Acupuncture therapy is thought to rectify a wide variety of disease conditions. Many preclinical and clinical reports have described the effects of acupuncture on cellular and humoral immunity, specifically or nonspecifically, which may have far-reaching implications in the treatment and prevention of many diseases, including immune-mediated disorders (Rogers et al. 1992).

Acupuncture has been found to modulate many immune functions, including modulation of immunoglobulins, enhancement of NK cell activity (NKCA), enhancement of phagocytic and fibrinolytic activity, enhancement of plaque-forming cell concentration in spleen and bone marrow, and stimulation of leukocyte recovery following irradiation. Other studies have demonstrated that acupuncture increases certain T-lymphocyte subsets, enhances E-rosette-forming rate (E-RFR), and increases the interleukin-2 (IL-2) receptor density on the surface of T-helper cells. Furthermore, alterations in the cytokines have also been reported, namely stimulation of IL-2 and IFN-gamma (IFN-γ) production, and suppression of IL-6 and IL-10 in patients with allergic asthma (Rogers et al. 1992).

The growing acceptance and use of acupuncture therapy in Western medical practice have led to increased interest in understanding the mechanisms underlying its claimed benefits. Recent evidence suggests that the effects of acupuncture may be mediated through multiple pathways in the nervous and immune systems. Many substances, such as hormones, neurotransmitters, especially opioid peptides and cytokines, have been reported to be involved in immune response, and could be modulated by acupuncture.

13.2 Acupuncture and Immune-mediated Disorders

Accumulating evidence has shown that acupuncture has been widely used for the treatment of immune-mediated disorders, including inflammation, trauma, tissue healing, burns, ulcers, indolent wounds, ischemia, infections, recurrent urinary infection, candidiasis, post-infection sequel, fever, anaphylaxis and shock, common cold and allergies, Rheumatoid arthritis (RA), osteoarthritis, fibromyositis, side effects of cerebrovascular disease (CVD), coronary heart disease (CHD), general anesthetics, parturition, chronic fatigue syndrome, surgery, cytotoxic chemotherapy, ionizing radiation, hepatitis, and acquired immune deficiency syndrome (AIDS) (Creamer et al. 1999; Kim et al. 2000; Francesco et al. 2002; Sze et al. 2002; Vickers et al. 2004; Wang H. et al. 2005; Berman et al. 2005; Gao et al. 2007; Kent et al. 1988; Ernst 2003).

13.2.1 Immunostimulant Points

Immune tissues are widely distributed throughout the body, and help in recognizing and eliminating foreign stimulus. According to the theory of Traditional Chinese Medicine (TCM), acupuncture is considered to modulate the immune function by strengthening the body resistance and consolidating the constitution. Furthermore, like the immune tissues, twelve primary meridians and eight additional meridians are observed to form a meshwork, and each acupoint is observed to follow a particular directional course along the body. Till date, most of the acupoints are chosen from the Conception Vessel (CV), Governor Vessel (GV), and Yang Ming Meridian. The immunostimulant acupoints include Hegu (LI-4), Quchi (LI-11), Taichong (Liv-3), Tianshu (ST-25), Zusanli (ST-36), Shangjuxu (ST-37), Xuanzhong (GB-39), Sanyinjiao (SP-6), Dazhui (GV-14), Dazhu (BL-11), Pishu (BL-20), Shenshu (BL-23), Qihaishu (BL-24), Dachangshu (BL-25), Guanyuanshu (BL-26), Xiaochangshu (BL-27), Pangguanshu (BL-28), Guanyuan (CV-4), and Zhongwan (CV-12). Besides, the acupoint Zhishi (BL-52) is observed to have immunosuppressive effect, while the acupoints GV-14 and ST-36 are observed to be anti-febrile points.

The clinical practice further demonstrated that acupoints could complement each other. For example, reactive reflex SHU, MU, and Earpoints can be used individually or concurrently, or combined with other points, and are used for treating organic as well as immune-mediated diseases.

However, the mechanism underlying the acupoint-specific function is always an open question. In fact, comparison with the anatomical atlas (Williams et al. 1989) has demonstrated that many of the acupoints correspond to the points at which small nerve bundles penetrate the fascia. Chan (1984) cited two Chinese studies that revealed that 309 acupoints are situated on or very close to the nerves, while 286 acupoints are located on or very close to the blood vessels that are surrounded by small nerve bundles.

Lately, through the patterns of functional magnetic resonance imaging (fMRI), brain images evoked by stimulating Liv-3 and LI-4 acupoints were examined. It has been reported that acupuncture on the acupoint Liv-3 could evoke specific activation at the postcentral gyrus, posterior cingulate, and parahippocampal gyrus, while that on LI-4 could evoke specific activation at the temporal pole (Yan et al. 2005). Thus, the anatomic feature and activation patterns in the human brain by acupuncture may be the reason for acupoint specificity.

13.2.2 Acupoint Specificity and Acupuncture Efficacy

Technologically, acupoint selection is of primary importance. Although no standard guidelines exist for the acupoints selection and combination, published reports are indicative of those that may produce the most promising results. Stimulation of the Hegu (LI-4) acupoint is observed to enhance the recovery of total leukocytes, lymphocytes, and neutrophils in irradiated rats. Clinical studies have demonstrated similar function when this point was concurrently stimulated with Sanyinjiao (SP-6) and Zusanli (ST-36) acupoints. This kind of approach has also yielded increase in the circulating white blood cells and immunoglobulins, and has significantly increased the IL-2 concentrations in patients with RA. In patients with a variety of cancers, acupuncture on acupoint Hegu (LI-4) combined with acupoints Zusanli (ST-36), Neiguan (PC-6), and Guanyuan (CV-4) increased the percentage of certain T-lymphocyte subsets ($CD4^+/CD8^+$ ratio alteration) and the circulation of β-endorphins, while decreased the concentration of soluble IL-2 receptor in the peripheral blood. A recent study in the asthma patients showed that suppression of IL-6 and IL-10, and increase in IL-8 could be obtained by employing an acupuncture regimen comprising 15 points across 8 meridians, some of which were reported previously to have specific diagnostic effects. Therefore, we can assume that the efficacy of acupuncture could be improved by employing combined acupoints, which was observed in rats with immunosuppression induced by cyclophosphamide. Earlier studies also indicated that the stimulation of acupoints Zusanli (ST-36), Dazhui (GV-14), or Shenshu (BL-23) could improve the immune function with different capability; sometimes, the acupoint Zusanli (ST-36) is observed to be better than Dazhui (GV-14), and GV-14 better than Shenshu (BL-23). Thus, acupoint selection as well as the well-matched combination of acupoints are the reasonable way to maximize the acupuncture efficacy, and may have more beneficial effect rather than unexpected side effect (Yang et al. 1994).

13.2.3 Immune Modulation of Acupuncture

A large number of clinical and laboratory data clearly indicate that acupuncture could modulate the immune system by adjusting the immune cells and immune molecules.

13.2.3.1 The modulatory effects of acupuncture on circulating white blood cells

Circulating white blood cells include granulocytes, monocytes, and lymphocytes. Acupuncture could regulate the count of peripheral white blood cells and their phagocytosis function. Acupuncture is also observed to expedite the recovery of red and white blood cell counts (RCC and WCC) to normal or near-normal values in many cases. Furthermore, acupuncture is also observed to enhance WCC, neutrophil phagocytosis, lymphocyte counts, and bactericidal activity in humans (Zhou 1988a). Clinical studies in patients suffering from spastic bronchitis demonstrated that acupuncture could weaken the side effects by long-term cortisone therapy, and restore the granulocyte migration to normalcy (Sliwinski 1987). In addition, acupuncture is also observed to relieve the tissues irradiated by low power laser therapy (LPLT) from degranulation by mast cells (Mayayo 1984). All these effects are considered to be the homeostatic modulation of acupuncture.

13.2.3.2 The modulatory effects of acupuncture on T-lymphocytes

The T-lymphocytes are one of the most important immune cells in the body. Therefore, the quantity and function of T-lymphocytes is reflective of the immune-response condition. The obtained evidences demonstrate that the therapeutic effect of acupuncture on many diseases may partially be owing to the effect exerted on the T-lymphocytes, as acupuncture was observed to increase lymphocyte proliferation, lymphocyte count (Hau 1984; Bianchi et al. 1991), lymphocyte transformation (Ding et al. 1983), T-cell subpopulations (Wu 1995; Yamaguchi 2007), T-cell staining by alpha naphthyl acetate esterase (ANAE) (Lu 1984), and E-rosette formation (Tsibulyak et al. 1988).

13.2.3.3 The modulatory effects of acupuncture on natural killer cells

To date, numerous studies have been carried out to examine the effect of EA on NKCA. We found that acupuncture could increase the NKCA in patients who underwent surgery (Zhang et al. 1996). Acupuncture applied on acupoints Zusanli (ST-36) and Lanwei (Ex-LE-7) was observed to enhance the NKCA in traumatic rats (Du, 1998a). Ten daily acupuncture treatments on the acupoints Zusanli (ST-36), Quchi (LI-11), and Qihai (CV-6) for 30 min elevated the IL-2 level, and thereby, induced the proliferation of thymocytes and increased the NKCA (Wu et al. 1994).

Yamaguchi et al (2007) examined the effect of acupuncture both quantitatively and qualitatively, by measuring the CD-positive cells and cytokine expression levels in the healthy volunteers' blood samples, to determine the activity of T-cells, B-cells, macrophages, and NK cells. They observed a statistically significant increase in the number of CD2+, CD4+, CD8+, CD11b+, CD16+, CD19+, CD56+ cells, as well as IL-4, IL-1β, and IFN-γ levels, after acupuncture stimulation of the meridian points. These data highlight that acupuncture could regulate the immune system and promote the activities of humoral and cellular immunity, as well as the NKCA in healthy volunteers. In addition, other studies also showed similar results, demonstrating that EA stimulation applied on the ST-36 acupoint significantly enhanced the splenic NKCA as well as the endogenous IFN-γ production in rats and mice; however, it did not have any effect on the splenic NK cell population (Yu et al. 1997; Hisamitsu et al. 2002).

13.2.3.4 The modulatory effects of acupuncture on antibody levels

Papers presented at the acupuncture symposium in Beijing (1979) demonstrated the substantial effects of acupuncture in stimulating the immune response in humans and animals (Anonymous 1979). Needling at the acupoints Tianshu (ST-25) and Shangjuxu (ST-37) was observed to increase the immunoglobulins and specific antibody levels in rabbits and monkeys experimentally infected with bacillary dysentery, which was also observed in human cases. In a clinical study on human malaria, acupuncture increased the serum complement levels. The method of injecting specific antigen into the experimental animals (rats, guinea pigs, rabbits, monkeys) and subsequently examining the antibody level, was widely used in the acupuncture-related study. To date, acupoints Hegu (LI-4) and Xuanzhong (GB-39) penetrating into the acupoints Sanyinjiao (SP-6) and Zusanli (ST-36) were found to be the main acupoints that could enhance the antibody production. In these experiments, acupuncture caused a faster increase in the antibody level, a higher plateau, and longer persistence of the antibody, than those observed in the inoculated but non-acupunctured animals. In addition, acupuncture was reported to regulate the immunoglobulin level in the following cases: increased SIgA in the small intestine in mice sensitized against *Vibrio cholerae*; increased specific antibodies and fecal IgA in bacillary dysentery; increased plasma IgM in chronic pelvic inflammation; increased beta and gamma globulins, as well as A/G ratio in dogs with g/i helminthiasis; and improved antibody formation in wounded horses (Rogers et al. 1992). Furthermore, it was found that electroacupuncture (EA) on endocrine points on both the ears and the body points like Hegu (LI-4) and Xiaguan (ST-7), significantly increased the saliva IgA levels in the subjects who previously had lower levels of saliva IgA; however, the levels decreased in those who previously had higher levels (Yang et al. 1989). It was also demonstrated that increased endogenous opioids in the plasma and brain tissues owing to acupuncture application could subsequently affect the levels of serum immunoglobulin (Jin et al. 1996). Thus, it can be presumed that acupuncture has the ability to modulate B-cell function and improve non-specific or hormonal immunity.

13.2.4 Common Practice of Acupuncture on Immune-mediated Disorders

Acupuncture produces many beneficial effects when employed for the treatment of various diseases and painful conditions. Therefore, it is considered to be a useful complementary therapy or the generally accepted substitute for the pharmacological intervention. The attributive effect of acupuncture has been investigated in inflammatory diseases, mainly comprising asthma, rhinitis, inflammatory bowel disease, RA, epicondylitis, complex regional pain syndrome type 1, and vasculitis (Zijlstra et al. 2003).

13.2.4.1 Rheumatoid arthritis

The RA is a chronic systemic inflammatory disease with undetermined etiology, primarily involving the synovial membranes and articular structures of multiple joints. The disease often progressively deteriorates and results in pain, stiffness, and swelling of joints. This illness affects about 1% of the world population. Despite the improvement in the medication for the treatment of RA, the healable component is still very limited, and the quality of life of many patients is observed to deteriorate, with 10% of the patients eventually becoming disabled (Berkow 1992).

Individuals with rheumatic disorders, particularly those with more severe and chronic conditions, are likely to be inclined to the complementary and alternative medical therapies. Although large-scale clinical trials need to be conducted, there is moderately strong evidence indicating that acupuncture is one of the effective ways to treat RA. However, many problems regarding the utility of acupuncture in treating RA still need to be addressed. First, acupuncture must be carried out at the early stage and in a large scale, with randomized controlled trials. Second, physicians who treat the patients suffering from rheumatic disorders should be knowledgeable about the literature on the effectiveness of acupuncture in treating these conditions, as well as the vulnerability of certain patient groups to the side effects.

Table 13.1 summarizes the five relevant studies on the application of acupuncture for the treatment of RA patients (Guan and Zhang 1995; Sun 1995; Changdu et al. 1999; David et al. 1999). The acupuncture therapies studied included a combination of acupoints (different acupoints used in each study) with or without moxibustion (a traditional Chinese therapy that puts the burning dried herbs, known as Artemisia vulgaris, either directly on the skin or indirectly above the skin over specific acupoints). The parameters employed in the studies were clinical evaluations (number of inflamed joints, morning rigidity, and visual analog scale of pain) and laboratory findings (erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF), blood platelet aggregation, IL-2, IL-1, immunoglobulins). All the five studies demonstrated that all the clinical symptoms improved after acupuncture administration. For example, RF became negative, and ESR values, IgM, IgG, IgA titers, and IL-1 contents were reduced. Only one study (David et al. 1999) showed no significant effect of acupuncture treatment when compared with the control group. This may be owing to the fact that only one acupoint was utilized in this study, while the rest of the treatments employed a combination of acupoints. However, it must be noted that all the patients were diagnosed by TCM and treated similarly.

Table 13.1 Studies on Acupuncture and RA (Zan Bar et al. 2004)

Number of patients	Indices	Outcome	Reference(s)
29	Visual analogue scale (VAS) for pain, the number of swollen and tender joints, patient's global assessment, ESR, and C reactive protein (CRP)	Pain score not changed, the number of tender joints decreased significantly	(Tam 2007)
31	Swelling of joints, blood platelet aggregation	Reduction of swelling in joints, reduction in the blood stasis	(Sun 1995)
55	ESR, RF, X ray	ESR: 47.4 ± 6.23 mm/h (before acupuncture); 29.4 ± 5.18 mm/h (after acupuncture) X ray: no change	(Changdu et al. 1999)

(Continued)

Number of patients	Indices	Outcome	Reference(s)
12	ESR, RF, Immunoglobulins, clinical symptoms	Observation of clinical symptoms 25%[a] full recovery of the symptoms, ESR, RF 50%[a] improvement in the symptoms, ESR, RF	(Guan and Zhang 1995)
56	ESR, VAS for pain, questionnaire	No change after acupuncture treatment	(David et al. 1999)

[a] percentage of patients.

Many studies based on the clinical and basic research indicated that acupuncture could improve clinical symptoms, laboratory immune-response evaluation, as well as the drug-induced side effects of RA. However, further studies, especially the normalized approaches, need to be carried out to more thoroughly and more definitely assess the efficacy of acupuncture in the treatment of RA.

The following are some factors that should be kept in mind while investigating acupuncture therapy:

- **Placebo:** The placebo-controlled trials should be utilized in parallel with the acupuncture therapy. Only few studies were conducted following this principle, which make the statistical analysis very complicated.
- **Treatment Duration and Frequency:** Duration of acupuncture therapy should be normalized, as the effect of acupuncture is somehow dependent on the sustaining time period. Observations by Han (2003) indicate that the frequencies of stimulation in EA are of greater importance than the ancient rules for needle placement. High frequency is observed to selectively increase the release of dynorphin, while low frequency is observed to accelerate the release of enkephalin, β-endorphin, and endomorphin (Han 2003). It is important to have a database comprising acupuncture duration parameters, acupuncture treatment effects with various time courses, and the duration in hand, which would make the future work easy to perform and analyze.
- **Choice of Acupoints:** Acupoints-specific functions have been observed by many studies, and the data should be normalized so that specific acupuncture protocol could be used. In addition, atlas based on the acupoints' functions and anatomical locations should be provided to the clinical and basic researchers.
- **Combined Treatments:** Acupuncture is one practice of the TCM, and it can be employed along with Western medicine in some ways. For example, the RA patients can be treated with acupuncture and anti TNF-α agents. By doing so, we can either distinguish the effect of acupuncture from other treatments, or find a good way to make the two therapies complement each other.
- **Assessments:** The acupuncture time course should be recorded, including baseline (0 min), 30 min after treatment, 24 h after treatment, after-treatment.

Furthermore, assessments, 6 months after the treatment, should also be included.

- **Measures:** The study on acupuncture mechanism can be accelerated using conventional and modern life-science techniques. In addition, the quality-of-life questionnaires, medication reduction, visual analog scale of pain, and clinical manifestation are also necessary.

13.2.4.2 Acupuncture and cancer-related immunosuppression

The use of acupuncture in oncology for the management of treatment-related adverse effects and palliative care is widely acceptance in Western medicine. However, the evidence is not extensive and has many limitations such as lack of randomized controlled trials, etc. According to an earlier report, acupuncture appears to play a vital role in managing chemotherapy-induced nausea and vomiting; cancer-related pain; side effects derived from treatment, including fatigue, insomnia, diarrhea, vasomotor symptoms, and anorexia; radiotherapy-induced xerostomia; brachial plexopathy induced by axillary lymphadenectomy for breast cancer treatment; radiotherapy-induced rectitis; dysphagia owing to carcinomatous obstruction; and even the so-called end-of-life symptoms, such as dyspnea. Most importantly, acupuncture is observed to enhance the immune function, and is efficient in alleviating chemotherapy- or radiotherapy-induced myelo-suppression (Conklin, 2001).

Table 13.2 summarizes the function of acupuncture on cell-mediated immunity, especially on the immunosuppression induced by cancer. All the data are based on the clinical study.

Table 13.2 Treatment of Cancer Related Immunosuppression

Technique	Acupoints	Immune function	Reference(s)
Acupuncture	PC 6, LI 4, ST 36, CV 4	Increases $CD3^+$, $CD4^+/CD8^+$ ratio	(Wu 1995; Wu et al. 1996)
Acupuncture	PC 6, LI 4, ST 36, SP 6	Increases $CD3^+$, $CD4^+/CD8^+$ ratio	(Yuan and Zhou 1993)
EA	PC 6, LI 4, ST 36, SP 6	Increases $CD3^+$, $CD4^+/CD8^+$ ratio	(Wang et al. 2004)
Acupuncture	ST 36, LI 11, CV 6	Increases IL 2 levels, NKCA	(Wu et al. 1994)
Acupuncture plus herbal therapy	No specified transformation	Lymphoblast	(Guo et al. 1995)
Acupuncture	ST 36 plus SP 6 or PC 6	Increases leukocyte phagocytosis	(Zhou et al. 1988)
TCM acupuncture	ST 36, SP 6, PC 6, ST 34, LI 4, LI 11, points based on symptoms	Increases E RFR	(Dang and Yang 1998)
TCM acupuncture	PC 6, ST 36, points based on symptoms	Increases E RFR	(Xia et al. 1986)

In a double-blinded random controlled trial (RCT) of 40 patients with malignancies, Wu et al observed significant increases in the $CD3^+$ and $CD4^+$ T-lymphocyte subgroups and an elevated $CD4^+/CD8^+$ ratio after 10 daily acupuncture treatments for 30 min on the acupoints Neiguan (PC-6), Hegu (LI-4), Zusanli (ST-36), and Guanyuan (CV-4) (Wu 1995; Wu et al. 1996). In addition, Yuan and Zhou (1993) also obtained similar results following acupuncture treatments on acupoints PC-6, LI-4, ST-36, and Sanyinjiao (SP-6) (Yuan and Zhou 1993). Furthermore, Wu et al (1994) also reported that 10 daily acupuncture treatments for 30 min on the acupoints ST-36, Quchi (LI-11), and Qihai (CV-6) elevated the IL-2 level, which further induced the proliferation of thymocytes and increased the NKCA (Wu et al. 1994). The immuno-modulatory effect of acupuncture was further supported by Guo et al (1995), who reported that lymphoblast transformation rate was dramatically increased in 50 patients after acupuncture (points not specified) together with an analgesic decoction of herbs used twice daily (Guo et al. 1995). In addition, Zhou et al (1988b) also carried out numerous studies on this field; they carried out a study on 40 patients who got operated for stomach, colon, or breast cancer. To reduce the effects of the surgery and anesthesia on the immune response, they used epidural anesthetics instead of intravenous or inhalational anesthetics. Their results indicated that 30-min acupuncture daily on the acupoints Zusanli (ST-36) and either Neiguan (PC-6) or Sanyinjiao (SP-6), depending on the operation location above or below the diaphragm, respectively, could significantly increase the leukocyte phagocytosis of bacteria, indicating that the acupuncture initiated the immune defense system, which may alleviate the effects of cancer in the patients (Zhou et al. 1988b). In another study by Dang and Yang (1998), TCM acupuncture was concurrently used with acupoint injection on 48 patients who suffered from stomach cancer and received chemotherapy. Cancer as the severe disease itself, along with chemotherapy, could induce immunosuppression, indicated by the decreased E-RFR. Their results suggested that 2 months of TCM acupuncture with acupoint injection could dramatically improve the immune response, and the E-RFR was observed to rise to normal levels (Dang and Yang, 1998). From the systematic investigation on the immunoregulation of TCM acupuncture on the patients suffering from various malignancies, we can concluded that immunosuppression induced by cancer itself or the subsequent chemotherapy or radiotherapy could be improved by acupuncture treatment (Xia et al. 1986).

Thus, we can conclude that acupuncture is gradually becoming the widely accepted approach to cure patients from various diseases, especially cancer or the subsequent therapy-related side effects. In 1997, the National Institute of Health Consensus Development Panel on Acupuncture documented that acupuncture is effective for the treatment of chemotherapy-induced nausea and vomiting, after reviewing the literature published from January 1970 to October 1997, which is considered to be the milestone for the acupuncture study.

13.2.4.3 Acupuncture and surgery-induced immunosuppression

Several studies in humans and animals have shown that surgery is one of the reasons for immunosuppression. The immunosuppression followed by the surgical procedures is widespread throughout the body, and makes the host vulnerable to infections and diseases. It has been shown that surgery depresses several aspects of immune functions, such as decreased splenocyte proliferation to concanavalin A (Con A), depressed antigen presentation, impaired microbial activity, decreased NKCA, and reduced production of a number of cytokines. Clearly, surgery is observed to cause profound changes in the immune system, and acupuncture is believed to awaken the immune function in this realm.

We found that the NKCA changed with different treatment on cholecystectomy, epidural injection of morphine, and with or without acupuncture (Zhang et al. 1996). In this study, 18 patients with cholecystectomy who were undergoing epidural injection of morphine anesthesia were investigated. The NK cell activities were determined immediately after the operation, as well as on the first, third, and seventh postoperative day. The data indicated that 1-h acupuncture on the acupoints Zusanli (ST-36), Sanyinjiao (SP-6), Hegu (LI-4), and Neiguan (PC-6) progressively and temporally improved immunosuppression induced by operation or morphine, that is, it had a little effect on the first and third postoperative days, and greatest effect on the seventh postoperative day. Furthermore, epidural morphine treatment obviously deteriorated the effect of NKCA, although it was used for postoperative pain relief (Fig. 13.1).

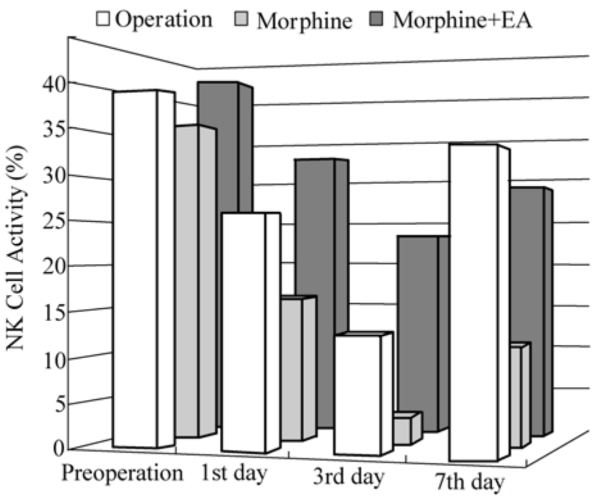

Figure 13.1 Effect of epidural morphine and EA on NKCA in postoperative patients.

In another study, Yang et al (2003) assessed the effect of EA on the immune function of the patients who were undergoing open-heart and cardiopulmonary bypass (CPB) operation. Acupuncture and drug-combined anesthesia was used in the operation, and 30 patients were randomly selected and divided into three groups: drug anesthesia was used in Group A; acupuncture anesthesia was used in Group B; and EA and drug combined anesthesia was used in Group C. The serum NKCA, IFN-γ, and IL-2 levels were measured to evaluate the immune function. The data showed that Group B patients had the highest NKCA level when compared with the other group at the pre-operation stage. However, at 30-min post-operation time point, the NKCA significantly decreased in the three groups of patients, with Group B patients showing the highest amplitude. At 24-h post-operation time point, the NKCA decreased progressively, with Group B patients showing the lowest level. The IFN-γ and IL-2 levels also showed similar change pattern as that of NKCA, with Group B patients demonstrating greater changes than the other two groups. Thus, the result indicate that EA could enhance NKCA; however, acupuncture anesthesia seems to have little effect in this realm. The EA was also observed to modulate IL-2 and IFN-γ levels efficiently. Thus, EA combined with drug anesthesia may apparently be more effective than drug anesthesia and acupuncture anesthesia. However, it somehow could not completely improve the immunosuppression induced by CPB (Yang et al. 2003), and further studies on this subject may be intriguing and tantalizing.

13.3 Mechanism of Acupuncture on Immune-related Diseases

Despite having been practiced for over 3000 years, the scientific research underlying the mechanism of acupuncture started only 50 years ago, first in China and Japan, then gradually in France, Germany, Russia, and other European countries. In the past two decades, since the joining of the USA into the main stream of scientific research of acupuncture, new discoveries and theories on this mechanism have been increasing every year. In spite of the numerous researches on acupuncture worldwide, none could explain the conclusive mechanism of acupuncture. However, there are some theories that are widely accepted to be relatively valid in explaining the many different aspects of acupuncture mechanism.

13.3.1 The General Regulatory Effects of Acupuncture and the Theory of Neuroendocrine-immune Network

Many studies in animals and humans have demonstrated that acupuncture can cause multiple biological responses. These responses can occur locally, that is, at or close to the site of application, or at a distance. This can lead to the activation of pathways affecting various physiological systems in the brain as well as the periphery. In short, local acupuncture is observed to evoke a chain of events. Local tissue stimulation is considered to stir disturbances in the tissue-producing microinflammation. Mediators of the inflammation are observed to convey a message to the center of the autonomic nervous system that decodes the message received and precedes the feedback to the related organs and targets. At this point, the body's interconnected systems come into play. Acupuncture has been observed to produce alteration in the secretion of neurotransmitters, neurohormones, and immune functions-related cytokines, and changes in the regulation of blood flow, both centrally and peripherally (Cabioğlu 2008).

It has been reported that many hormones have their own receptors expressed on the macrophages, T-lymphocytes, and B-lymphocytes. Furthermore, immune cells are observed to secrete various neuropeptides and hormones, known as immune transmitters as a whole. In addition, some neuroendocrine cells are observed to secrete certain substances that can influence the neuroendocrine system and immune system. Nervous, endocrine, and immune systems can communicate and complement each other via these substances and their respective receptors. Basically, immune cells and other immune competent cells function as the body defense system, recognizing foreign antigens and secreting immune transmitters. The immune transmitters can convey the information to the nervous and endocrine systems, by magnifying and initiating the signal. On the other hand, the nervous and endocrine systems can directly or indirectly function on the immune cells through impulses or secreted neurotransmitters and hormones. This is the so-called "neuroendocrine-immune regulatory network" (Fig. 13.2).

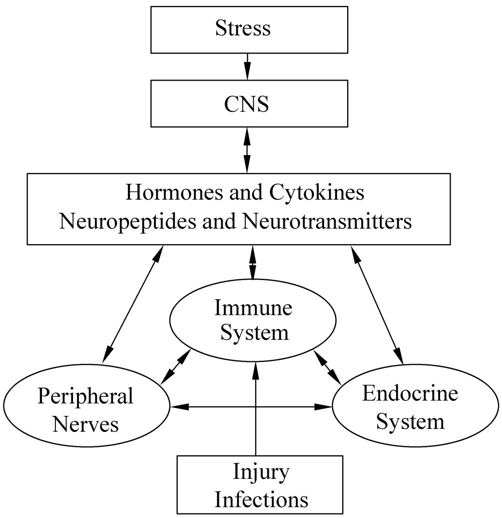

Figure 13.2 Diagram of the neuroendocrine-immune network. Network of bidirectional communication between central nervous system, peripheral nervous system, endocrine system, and immune system.

Clearly, acupuncture is based on the view that the human body must be perceived and treated as a whole and as a part of nature; hence, the regulatory effect of acupuncture on the nervous, endocrine, and immune systems cannot be separated from each other, and are dependent on the neuroendocrine-immune regulatory network. In addition to its direct regulation of these systems, acupuncture is also observed to indirectly act upon the other systems by reopening the normal energy flow, and subsequently affecting the neuroendocrine-immune regulatory network. This is probably the theoretical basis of TCM's general regulatory principle—to create a harmony among the bodily functions, body, and nature. However, this is also a point of conflict between TCM and modern medicine, namely the collision between the holistic divisional medical modes (Wu 1995).

13.3.2 Role of Hypothalamus-pituitary-adrenal Axis in Acupuncture-mediated Effects on Immune System

Hypothalamus-pituitary-adrenal (HPA) axis is involved in the immune function modulation, by releasing neuropeptides including adrenocorticotrophin (ACTH), endorphin, etc. In an earlier study on acupuncture analgesia, the role played by the hypothalamus and the released endorphin in acupuncture analgesia was observed to be most convincing. Acupuncture is observed to exert its function via the peripheral sensory nerves and sympathetic trunks, and finally on the hypothalamus. Hypothalamic activation is subsequently transmitted to the pituitary gland, where ACTH, melanocyte-stimulating hormone (MSH), thyroid-stimulating hormone (TSH), gondatrophins, pancreatic (insulin) trophins, etc., are produced and secreted in response to the respective hypothalamus nuclei stimulation. These hormones expressed in the pituitary gland subsequently reach the adrenal gland, and trigger the release of corticosteroids, adrenalin, thyroid hormones, estrogen, progesterone, oxytocin, prolactin, relaxin, insulin, etc. The effect of acupuncture was well examined at this stage and was reported to show acupoints specificity on substances released in this pathway, but with unknown mechanism (Gong and Wang 1997).

Liu (1996) investigated the interaction between pituitary-adrenal system and EA, as well as the function on the immune modulation. They found that either cellular- or hormonal-mediated immune function was suppressed in the mice receiving cortisol treatment. However, adrenalectomy was observed to overcome this effect, restoring the immune response to almost normal level. The EA exerted the same function on the regulation of IL-2, which was observed by the lymphocyte transformation test (LTT). However, hemolytic anemia and hemagglutination activity were found to be influenced by EA. In the adrenalectomized mice, spleen plaque forming cell (PFC), IL-2, LTT, serum IgG, and thymus lysozyme (LZM) contents were increased, while spleen LZM was decreased. The EA was found to restore the declined spleen LZM, but it could not affect the elevated spleen PFC, IL-2, LTT, serum IgG, and thymus LZM contents. All these results indicate that pituitary-adrenal system might compete with the EA in the modulating the immune responses.

Surgically traumatized rats are the well-defined animal model in our laboratory, which were developed to observe the role of β-endorphin, ACTH, as well as EA on immune function modulation. Using this animal model, we found that pro-opiomelanocortin (POMC) mRNA, endorphin, and ACTH expression levels in the hypothalamus increased after surgical trauma. However, the EA was observed to reverse this effect. Following decreased POMC mRNA, β-endorphin, and ACTH expression level in the hypothalamus, immunosuppression was improved simultaneously. The ACTH and β-endorphin released from the pituitary are observed to reach the lymphocytes through the peripheral blood circulation and then exert the function on the immune function modulation, which is presumed to be the working mechanism of EA. In the same study, Huang et al (2002, 2003) also showed that IL-2 production in the normal rats was markedly decreased when splenocytes were incubated with the culture medium of the pituitary from the traumatized rats. However, the pituitary culture medium from EA-treated traumatized rats failed to change the splenocytes activity. These data suggest that there is a relationship between the immune and the pituitary functions. Thus, these evidences typically indicate that HPA axis plays an important role in the immunoregulation and could be modulated by EA at different levels.

In general, acupuncture signals can regulate the immune function through HPA axis (Fig. 13.3). Acupuncture can regulate the hypothalamus to release CRH and the level of ACTH synthesized from the pituitary, which subsequently causes the adrenal cortex to release corticosteroids. All these mediators alter several aspects of the immune function, including antibody production, cytokine production profiles, and cell trafficking. Thus, acupuncture is observed to regulate the HPA axis accordingly, based on the abovementioned three levels.

13.3.3 Role of Neuropeptides on the Immunoregulatory Effects of Acupuncture

Nervous system could exert its function on the immune system, and the notion that the interaction between them could be modulated by EA is being increasingly accepted by researchers (Ju et al. 1998; Zhang 1998). Brain as the central nervous system is also considered to host immune cells or immune competent cells, thus, becoming involved in the immune response and protecting itself from invasion (Fig. 13.4).

Many studies have demonstrated that bi-directional communication between the nervous and immune systems is through the neuroimmune mediators (neuropeptides, hormones, cytokines, and chemokines) as well as the respective receptors expressed within these two systems. In the last decade, the neuroimmune function of EA was revealed, where EA was found to achieve this function through the modulation of neuroimmune mediators. Besides the hormones described in the last section, neuropeptides such as endogenous opioid-like peptides, substance P, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), etc., are all observed to be involved in the EA function.

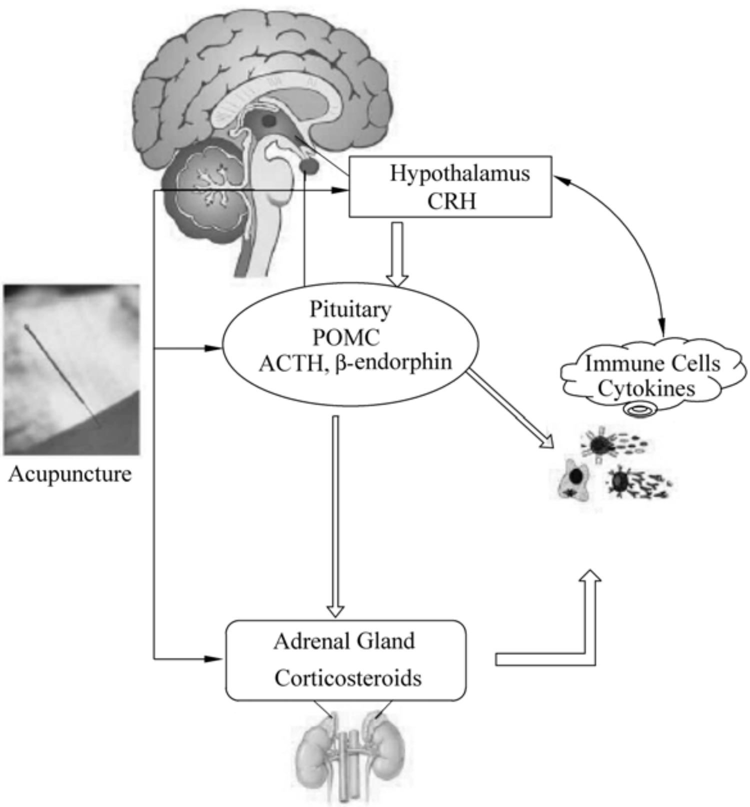

Figure 13.3 Schematic pathways involved in the acupuncture-induced effect on immune system.

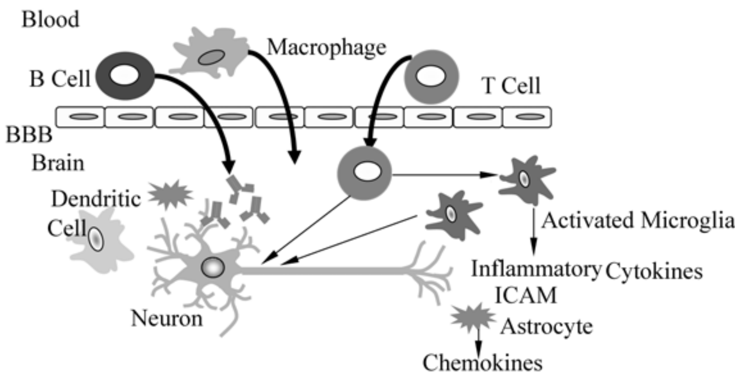

Figure 13.4 Schematic representation of the initiation pathway of immune response within brain. Stimulators like virus, bacteria, dead cells or debris, and toxic central nervous system proteins, could be recognized by the immune competent cells, and subsequently, immune responses are initiated. In this process, proinflammatory cytokines, chemokines, and neurotransmitters are found to be involved.

13.3.3.1 Endogenous opioid-like peptides

Recent evidences suggest that the effects of acupuncture may be mediated through multiple pathways, involving both the nervous and immune systems. Endogenous opioid peptides and their receptors are one of the important molecules.

The fact that endogenous opioid peptides are implicated in the antinociception was established several decades ago. Recently, the coupling between the pain and immune response via the common signaling molecules was reinforced by opioid-related studies. Opioid receptors were demonstrated to be widely distributed in the immune cells. Opioid peptides, such as β-endorphin and met-enkephalin, have been reported to be closely associated with the cellular and humoral immunity, and are considered to work as the mediators between the central nervous system and the immune system. Experimental data on enhanced NKCA and increased T-cell rosette formation, as well as the antagonism of naloxone on the immune response have emphasized their role in this realm. Considering the involvement of EA in pain relief or anesthesia, it is conceivable that opioid peptides and acupuncture may have a dynamic and mutual interaction.

In the past decades, many researches were dedicated to the opioid-related study. For example, Petti et al (1998) examined the endorphin expression, VIP, lymphocyte subsets, NKCA, and monocyte phagocytosis in patients under acupuncture treatment for various nociception disorders. The data showed dramatic increase in β-endorphin by acupuncture treatment, which sustained for more than 24 h; however, VIP level was decreased. Acupuncture also significantly increased $CD3^+$, $CD4^+$, and $CD8^+$ levels. In addition, monocyte phagocytosis was increased in 45% of the cases after 30 min of treatment, and in the rest of the cases, it increased after 24 h of treatment. The NKCA was increased in 40% of cases after 30 min of treatment, and rose to 50% after 24 h of treatment. Furthermore, blockade of opioid receptor by naloxone is also considered to antagonize the effect of acupuncture on the NKCA (Yu et al. 1998). Similarly, systemic pretreatment was observed to dose-dependently inhibit dihydrotestosterone (DTH) suppression evoked by acupuncture treatment (Kasahara et al. 1992). Therefore, it is suggested that the production of opioid peptides and the respective receptors is one of the mechanisms underlying the EA immune response modulation.

Our laboratory examined the EA mechanism for many years. We found that EA had a protective role in immunosuppression induced by trauma. In the traumatized rats, spleen lymphocyte proliferation and IL-2 activity were significantly decreased on the first, second, fifth, and seventh day after operative trauma, with minimum values on the third day (Wang et al. 2003). However, plasma endorphin and corticosterone level was increased. The EA improved the immunosuppression significantly, by reversing the effect of trauma. Further study showed that intracerebroventricular (i.c.v.) injection of naloxone antagonized the depressed NKCA induced by trauma, similar to the action of EA, suggesting that the central endogenous opioid peptides might be involved in the immune modulation of EA (Du et al. 1998a; Cao 2001).

Orphanin FQ (OFQ) is a controversial member in the opioid peptide family; however, its role in the immune modulation and its relationship with EA is still to be understood completely. In the traumatized rats, we found that i.c.v. injection of OFQ attenuated the immune response invoked by trauma. When the synthesis of OFQ receptor was blocked with antisense oligonucleotide (ASO), the effect of OFQ was completely eliminated. However, i.c.v. injection of ASO did not change the effect of EA, suggesting that central OFQ might participate in the immune function modulation; however, its relationship with the EA needs to be further elucidated (Du et al. 1998b).

Another experimental data showed that the central OFQ and its receptor could be downregulated or upregulated by trauma or EA, respectively, and their role in the immune modulation, such as cytokine activity and lymphocyte proliferation had no additive effect. This finding is in agreement with the previous report that observed that OFQ may be the main mediator in the EA immune modulation (Zhao et al. 2002b).

13.3.3.2 Substance P

Substance P (SP) is an important biologically active substance with multiple functions. It has been demonstrated that immune cells can release SP as well as express SP receptors. Accordingly, SP has been proposed to regulate the immune response in the following ways: (1) Stimulate lymphocytes in vivo and in vitro; (2) Enhance the proliferation of the spleen, mesenteric lymph nodes, and intestinal aggregated lymphatic follicles; (3) Induce the production of cytokines, such as IL-1, IL-6, and TNF-α from monocytes at the milli-Molar level; (4) Increase the lipopolysaccharide (LPS)-triggered secretion of IL-10 from monocytes, and conversely, inhibit the effect of INF-γ; and (5) Stimulate the synthesis of prostaglandin E2 (PGE2), which in turn stimulates the generation of cytokines and chemokines. Gao et al (2000) found that after EA at ST-36, ir-SP (immunoreactive SP) in the rats' pituitary gland and peripheral blood increased significantly when compared with the control group, which was also closely correlated with the change in the $CD4^+$ level. However, release of SP invoked by EA on the acupoint ST-36 did not change the red blood cell (RBC) activity. Thus, the data indicate that SP is involved in the EA immune modulation, whose synthesis and release could be modulated by EA. Furthermore, SP may also affect the neuroendocrine-immune regulatory network directly and indirectly by unknown pathways (Gao et al. 2000).

Luo (1996) also reported that there were plastic changes in the releasing rate of spinal SP, CCK-8, and met5-enkephalin (MEK) in the arthritic rats, which could be modulated by repeated acupoint stimulation. Besides, it was observed that EA, SP, and VIP could increase the phagocytosis of polymorphic neutrophils (PMN), and that naloxone could inhibit the enhanced phagocytosis evoked by EA (Li et al. 1994).

13.3.3.3 Role of central IL-1β on the immunoregulatory effects of acupuncture

The IL-1β is synthesized not only in the immune system, but also in the central nervous system. In the immune system, IL-1β and its receptor, IL-1R, are highly expressed in the macrophages and mainly function on the body defense. In the central nervous system, astrocytes and microglia are observed to be the essential hosts of IL-1β and IL-1R. Furthermore, IL-1β and IL-1R are apparently found to be expressed on other types of immune cells, even on the immune competent cells and neurons. This ubiquitous distribution pattern suggests that IL-1β is widely involved in the modulation of body function. Recently, more convincing evidences have been obtained on the distribution of IL-1β in the central nervous system and its involvement in the immune regulation, pain relief, and neuro-generation. Moreover, central administration of IL-1β has been indicated to upregulate the level of corticotrophin releasing hormone (CRH), and subsequently alter the lymphocyte and thymocyte activation state, providing strong evidence on its inarguable role in the neuroimmune regulation.

The mechanism underlying the neuroimmune modulation and the involvement of IL-1β in this process was further reinforced in the traumatized rats. After surgical trauma, IL-1β mRNA expression was dramatically increased in the cortex, hippocampus, and hypothalamus. The i.c.v. injection of IL-1β antibody was observed to reverse the immune depression induced by trauma. Furthermore, acupuncture and i.c.v. injection of OFQ was found to antagonize the increased IL-1β mRNA expression in traumatized rats. The OFQ is also observed to decrease IL-1β mRNA transcripts in the central nervous system. By using confocal microscopy, OFQ immunoreactive cells were found to be co-localized with that of the IL-1β mRNA throughout the central nervous system (Wang et al. 2001; Zhao et al. 2001; Zhao et al. 2002a; Zhao et al. 2002b). Accordingly, it was envisioned that OFQ has a close correlation with IL-1β in the central nervous system. The neuroimmune modulation of EA may be dependent on the collaboration and complementation between OFQ and IL-1β. Furthermore, EA may inhibit central IL-1β expression via OFQ pathway, resulting in the modulation of the immune function (Cao 2001).

13.4 Concluding Remarks

There are nearly 1000 acupuncture points along the body's 14 major meridians. Over the last several years, numerous evidences have been obtained on the underlying pathophysiological mechanism of acupuncture. Stimulation of different acupoints could produce a certain amount of neurotransmitters, neuromodulators, neurohormones, and cytokines. They can either directly affect the components of the immune system, or indirectly, by activating the neuroendocrine axis. Therefore, acupuncture could stimulate the body's ability to resist or overcome illnesses and conditions by correcting the imbalances as well as the communication between nervous system and immune system.

From the modern perspective, the human body has been finally described in terms of cells, biochemicals, and specific structures. Diseases and injuries are found to be resolved by a complex set of responses, including metabolic failures, changes in the DNA structure or signaling, or breakdown of the immune system, and the responses are coordinated by several signaling systems. Modern studies have revealed that acupuncture stimulates one or more of the signaling systems, which can, under certain circumstances, increase the rate of healing process. Also, in the neuroimmune modulation study, it was found that EA was involved in the regulation of immune cell apoptosis (Wang J et al. 2005). Thus, acupuncture and its underlying concepts are gradually being examined and must be evaluated based on the new concepts.

We understand that the Chinese therapeutic principle is to achieve stability by adjusting and harmonizing the internal element/organic environment. We also perceive that the scientific basis of immunomodulatory effects of acupuncture correspond to the modern notion of reestablishing homeostasis by regulating the interactions between the autonomic nervous system, the innate immunity, and several other systems. Furthermore, we can be benefited from the progress in molecular biology, and subsequently, integrative physiology and clinical research, which could reasonably be integrated to gain a complete and clinically relevant understanding of the neuroimmune regulatory function of acupuncture and its relationship with the neuroimmune mediators.

Acknowledgements

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14 Acupuncture Treatment for Female Infertility

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Summary Although the mechanism of acupuncture therapy is not yet well understood, substantial evidence has shown that acupuncture produces prominent therapeutic effects on woman infertility, and acupuncture combined with assisted reproduction technology (ART) is observed to markedly enhance the pregnancy rate of the infertile woman treated with "in vitro fertilization" or "intracytoplasmic sperm injection". In this chapter, we will summarize the clinical and experimental data, and discuss the reproduction-neuroendocrine mechanism of acupuncture for the treatment of woman infertility. Acupuncture is believed to correct the dysfunction of hypothalamic-pituitary-ovarian axis (HPOA) by adjusting the function of the female reproductive system at the levels of the whole body, organs, and cells. However, acupuncture is not observed to change the normal function of HPOA. Various clinical and laboratory studies have proven, with scientific evidence, that acupuncture is a valid, safe, and cost-effective therapy for most woman patients who suffer from infertility.

Keywords *acupuncture, female infertility, hypothalamic-pituitary-ovarian axis (HPOA), ovariectomy, Estradiol (E2)*

14.1 Introduction

Infertility is a disorder in which the patient may not become pregnant even after 1 year of unprotected intercourse. This condition can be further classified into primary infertility, in which no previous pregnancies have occurred, and secondary infertility, in which a prior pregnancy, although not necessarily a live birth, has occurred.

In the late 1980s, the World Health Organization (WHO) organized an investigation on infertile couples using a standardized diagnostic procedure in its 33 centers in 25 countries. The results showed that in the developed countries, about 5% – 8% of the couples are affected by infertility, while in some areas of the developing countries, the prevalence rate of infertility is as high as 30% (Mylene et al. 1994). Infertile patients worldwide comprise about 0.8 – 1.1 billion. Some statistical data showed that infertility may be owing to masculine reasons (approximately 1/3) or feminine reasons (2/3), including about 8% – 17% women of childbearing age with an average incidence of infertility of about 10%. Thus, infertility is a common disease worldwide. The WHO announced infertility, cardiovascular disease, and tumor as the three major diseases that impact human life and health.

Recently in Beijing, at the "National Integrated Treatment of male and female infertility academic meeting", experts stated that in China, the incidence of infertility is 15% – 20%, mainly caused by social factors, working conditions and occupational factors, dietary factors, living habits and lifestyle factors, and genetic factors. These environmental and man-made factors, such as noise, extremely low-frequency electromagnetic fields, chemical exposure (occupational exposure), smoking, alcohol, drug abuse, mental stress, and psychological stress and burden have been identified to affect the human reproductive system, damage and reduce human fertility, as well as affect the initial stage of the embryo to a certain extent.

In some cases, no specific cause could be detected, despite an extensive and complete evaluation. The relative prevalence of different infertility reasons varies widely among the patients (Table 14.1).

Table 14.1 Causes of Infertility

The relative prevalence of the etiologies of infertility	
	Prevalence (%)
Male factor	25 – 40
Both male and female factors	10
Female factor	40 – 55
Unexplained infertility	10
The approximate prevalence of the causes of infertility in females	
	Prevalence (%)
Ovulatory dysfunction	30 – 40
Tubal or peritoneal factor	30 – 40
Unexplained infertility	10 – 15
Miscellaneous cause	10 – 15

Many specific tests have been recommended for the diagnosis of infertility. The diagnostic tests should progress from the simplest (e.g., postcoital test (PCT), endometrial biopsy) to the more complex or the one that implies a major risk to the patient (e.g., laparoscopy). A basic study is usually carried out within one or two menstrual cycles. For women, these diagnostic tests include an analysis of the body temperature and ovulation (by charting the basal body temperature), PCT, X-ray of the fallopian tubes and uterus (hysterosalpinogram [HSG], hysteroscopy), and laparoscopy.

Currently, as a result of progress in the field of medical science, a variety of therapeutic methods, including western medicine, surgical operation, and complementary and alternative medicine such as acupuncture therapy, have been developed for the treatment of infertility. Therefore, men and women with infertility should be aware of all these techniques and have adequate knowledge about the disease and its diagnosis, and actively seek medical attention. Nowadays, most of the infertile couples are being cured by these techniques. In the following section, a brief description is provided about the major infertility therapeutics, including Western Medicine and Traditional Chinese Medicine (TCM) treatments, in particular, acupuncture therapeutic efficacy, on female infertility and its modern scientific mechanism.

14.2 Treatment of Infertility

Infertility is usually treated with medication (clomiphene citrate (CC), human chorionic gonadotropin (hMG)) and/or intrauterine insemination (IUI). Less than 5% of all the infertility cases are treated with assisted reproductive technologies (ART), which include in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT). About half of all the couples who receive these treatments are able to conceive.

14.2.1 Principles of Medication and Reproductive Technologies

The CC is commonly used in patients with oligomenorrhea, especially polycystic ovarian syndrome (PCOS), and slight menstrual irregularities. The hMG and its derivatives are indicated for ovulation induction in patients with primary amenorrhea owing to hypopituitarism, as well as in those with secondary amenorrhea, who do not respond to CC ovulation induction. For the past 20 years, hMG and its derivatives have been the first choice for controlled ovarian hyperstimulation (COH) in ART. The IUI is most commonly used for treating infertility associated with endometriosis, unexplained infertility, anovulatory infertility, very mild degrees of male factor infertility, cervical infertility, and certain immunological abnormalities. However, the most popular ART technique is IVF. Patients with a history of endometriosis who were unsuccessfully treated medically or surgically, those with some malformation of the uterus related to diethylstilbestrol (DES) exposure during pregnancy, those with husbands who have severe oligospermia or a history of obstructive azoospermia, or those with an unknown etiology of infertility (i.e., normal infertile couples, NICs) can be treated using IVF.

14.2.2 Acupuncture Therapeutics

Though there are a number of available treatments for the childless couples, such as drugs, surgery, and assistance to conceive, there also exists alternative medicine, such as Chinese acupuncture, which is promising in infertility treatment. Acupuncture is a traditional, safe, and effective treatment used for curing some diseases in China, and of course, it is a good candidate for the treatment of female infertility. If a woman suffers from infertility induced by the functional, rather than a structural reason, she should be encouraged to try acupuncture treatment.

14.2.2.1 Involved acupoints

In TCM literature, some channels, such as Kidney Channel, Spleen Channel, Liver Channel, Thoroughfare Vessel, Governor Vessel, and Conception Vessel are considered to be closely related to reproduction. According to TCM, the kidney is the foundation of the native (born) constitution which stores the reproductive essence and takes charge of reproduction. A total of 10 out of 27 acupoints on the Kidney Channel are considered to be related to abnormal menstruation and reproduction. The spleen provides the material basis of the acquired constitution and has the function of maintaining the blood flow within the vessels. Among the 21 acupoints on the Spleen Channel, 5 acupoints are considered to be associated with menstrual disorders and reproduction. The liver is a reservoir of blood and also installs and regulates blood. Among the 14 acupoints on the Liver Channel, 7 are observed to be related to menstrual disorders and infertility.

Furthermore, Thoroughfare Vessel is considered to be the reservoir of blood, while Conception Vessel is in charge of the uterus and is the reservoir of Yin meridians. On the other hand, the Governor Vessel is considered to be the reservoir of Yang meridians. Thoroughfare, Governor, and Conception Vessels are all considered to originate from the uterus and subsequently develop into three different vessels. These three vessels can influence each other and play an important role in reproduction. About 1/4 of the acupoints on the Governor and Conception Vessels are considered to be associated with menstrual disorders and infertility. Hence, acupuncture for the treatment of infertility is observed to be closely related to Kidney Channel, Spleen Channel, Liver Channel, Thoroughfare Vessel, Governor Vessel, and Conception Vessel.

The main acupoints used for treatment of infertility are Guanyuan (CV-4), Zhongji (CV-3), Sanyinjiao (SP-6), and Zigong (Ex CA-1). Some acupoints, such as Zusanli (ST-36), Qihai (CV-6), Shenshu (UB-23), Ganshu (UB-8), etc., are selected as adjuvant points according to the signs and symptoms (Jin 1992).

Guanyuan (CV-4) acupoint lies on the anterior midline of the lower abdomen, 3 cun below the center of the umbilicus. Using a needle, the acupoint is perpendicularly punctured to about 2 – 3 cun, and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward the lower abdomen.

Zhongji (CV-3) acupoint lies on the anterior midline of the lower abdomen, 4 cun below the center of the umbilicus. Using a needle, the acupoint is perpendicularly punctured to about 2 – 3 cun, and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward the pudenda.

Sanyinjiao (SP-6) acupoint lies on the medial side of the leg, 3 cun above the tip of the medial malleolus, just posterior to the Tibia. Using a needle, the acupoint is perpendicularly punctured to about 1 – 1.5 cun, and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward vola.

Zigong (Ex-CA-1) acupoint lies on the lower abdomen, 4 cun below the center of the umbilicus and 3 cun lateral to Zhongji (CV-3) acupoint. This acupoint is used bilaterally. Using a needle, the acupoint is perpendicularly punctured to about 1.5 – 3 cun, and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward lower abdomen and pudenda.

14.2.2.2 Acupuncture induction of ovulation

The production of healthy eggs by the woman is one of the essential requirements for pregnancy. Ovulatory dysfunction accounts for 15% – 25% of all female infertility cases. Anovulation is involved in many gynecologic and reproductive conditions, such as oligo/amenorrhoea, PCOS, luteal phase defect, hyperprolactinemia, etc., and acupuncture induction of ovulation is an effective curative method to treat these conditions.

First, the patient’s body basic temperature is recorded. A normal menstrual cycle lasts for 25 – 35 days, with an average of 28 days. From days 12 – 14 of the menstrual cycle, the woman with infertility can be administered with acupuncture treatment once per day, for 3 days. To promote the curative effect, acupuncture may be used every other day from days 8 – 12, and subsequently, every day from days 12 – 14.

Two or three acupoints selected from the acupoints involved, can be used alternatively during every treatment. The long filiform needles are used to perpendicularly puncture the acupoint Zigong to about 3 – 4 cun, where the ovary located, to activate the function of the ovary. For patients with a delayed menstruation, the sessions of acupuncture treatment should be increased according to the patients’ menstrual cycle; usually, three cycles occur during one therapeutic course. During the period of treatment, the needling sensation should be transmitted toward both the sides of the lower abdomen. The *Qi* should be achieved, which helps in promoting the curative effect. Furthermore, based on previous clinical observation, adequate estrogen levels, suppression of the sympathetic nervous system after acupuncture treatment, and low pulsatile frequencies of serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) have been proved to be useful factors related to the induction of ovulation using acupuncture.

In an earlier study, the therapeutic effect of acupuncture was accessed mainly by basic body temperatures (BBT), which can be used as a curative guidance. In addition, other methods of ovulation induction, such as follicular development, demonstrated by ultrasonic B and endocrine hormone examined by radioimmunoassay (RIA), have been combined to conduct systemic observation and to evaluate the therapeutic effect (Yu 2002).

14.2.3 Acupuncture Combined with Assisted Reproduction Technology

Endometrial thickness, morphology, and uterine artery blood flow have been implicated as important parameters for the successful implantation of human embryos. Despite the conflicting results in the utilization of these parameters during various stages of treatment to predict the outcome of IVF, it is generally believed that adequate endometrial thickness is required to optimize pregnancy rate. Endometrial thickness is a function of the uterine artery blood flow, and acupuncture may contribute to reduce the uterine artery impedance and consequently, increase the blood flow to the uterus. Hence, some researchers speculate whether acupuncture accompanying embryo transfer could increase the clinical pregnancy rate.

During the last 6 years, the use of acupuncture as an adjuvant to conventional treatment in ART to treat female infertility has become popular. Some randomized controlled trials (RCTs) have suggested that acupuncture at the time of embryo transfer (ET) improves the clinical pregnancy rate in patients under IVF and ICSI. Acupuncture is observed to significantly improve the IVF/ICSI outcome and might be a complementary option for patients undergoing IVF/ICSI, even though further evidence is needed (Stener-Victorin and Peter 2006).

In general, the above clinical data demonstrate that acupuncture could be an effective remedy for female infertility. However, the scientific mechanism of the therapeutic effect of acupuncture on infertility treatment needs to be elucidated, for which, we have presented a series of our study results along with those of the related published researches.

14.3 Mechanism of Acupuncture Therapy for Infertility

The clinical data presented earlier demonstrate that acupuncture is an effective therapeutics for treating some women's disorders, especially, female infertility. However, many interesting and important questions, such as "why", "how to", and "which", about the mechanism of acupuncture effect still needs to be addressed. One of the possible mechanisms that we presume is that acupuncture might influence the secretion of hypothalamic-pituitary-ovarian axis (HPOA) as well as hormones, neurotransmitters or neuromodulators and their mRNA expression, the activity of enzymes related to the production of hormones, neurotransmitters or neuromodulators, and improve the uterine artery blood flow conditions, which might lead to normalization of the functional status of the body. Thus, consequently, ovulation or pregnancy may occur. We also found certain articles that reported that acupuncture might affect the blood levels of LH, FSH, estradiol (E_2), and prolactin in woman patients, as well as the functional status of sympathetic nervous system. Though these results are significant, they are inadequate to explain the mechanism of infertility treatment using acupuncture. Based on the review of related articles combined with the overview of our studies about acupuncture normalizing the dysfunction of HPOA, we attempted to elucidate the real and scientific mechanism of infertility treatment using acupuncture.

The TCM explains acupuncture based on the ancient medical theory; however, a modern scientific comprehension of acupuncture has developed in the past two decades. In 1977, Mayer first reported that acupuncture analgesia may be involved in the production of brain endorphin and may be antagonized by the narcotic antagonist, naloxone. Similarly, subsequent studies showed that most of the effects of acupuncture are mediated by the nervous system, comprising neurotransmitters, neuropeptides including endogenous opioid peptides and neurohormones, as well as cytokinins. Nevertheless, the mechanisms through acupuncture affects the endocrine system are yet to be elucidated.

14.3.1 Clinical Studies

The clinical study on the mechanism of acupuncture therapy in patients suffering from infertility may have some limitations with respect to some clinical observations and results of the analysis of blood, urine, or cerebrospinal fluid, which may hinder further studies at the level of neuroendocrine regulation.

14.3.1.1 Effects of acupuncture on the levels of blood reproductive hormones

Various investigators have demonstrated that in anovulatory women, acupuncture not only influenced the plasma levels of FSH, LH, E_2, and P, but also the pulsatile secretion of serum FSH and LH (Yu et al. 1989; Chen and Yu 1991; Ku and Chang 2001; Mo et al. 1993). Yu et al (1989) observed the pulsatile secretion of serum FSH and LH as well as the follicular sizes before and after acupuncture in chronic anovulatory cases. Of the 10 cases, 7 cases were diagnosed with PCOS, 2 cases with dysfunctional uterine bleeding, and 1 case with hypogonadotropic amenorrhea. Furthermore, 8 of the 10 cases complained of infertility for 2.7 years on an average. Ovulation resulted in 5 cases (ovulatory group), and 3 of the 5 infertile cases became pregnant in the stimulating cycle. However, 5 cases failed to ovulate after acupuncture treatment (anovulatory group). In the ovulatory group, serum FSH and FSH pulsatile frequency increased after acupuncture treatment. The ovarian follicular size increased dramatically in the ovulatory group, but stopped growing at 14 – 16 mm diameter in 3 out of the 5 cases without ovulation, after acupuncture treatment. Another study showed a significant decrease in the

LH/FSH ratio after electroacupuncture (EA). Furthermore, the testosterone and β-endorphin (β-EP) concentrations were measured in all the anovulatory women before and 3 months after EA, and were compared. Out of the 13 anovulatory cases, 6 responded well to acupuncture treatment and EA on the special acupoints that normalized the HPOA function (Chen 1997). Yang and Yu (2001) examined 14 ovariectomized women with low blood E_2 level and perimenopausal syndrome. All the subjects underwent ear acupressing (EAP) treatment. Consequently, their blood E_2 level elevated significantly; however, no change in the E_2 level was observed in 8 normal controls after acupuncture treatment. These results suggest that acupuncture might normalize the E_2 level when a woman is in the gynecologic status.

Stener-Victorin et al (2002) examined the testosterone/sex hormone-binding globulin (SHBG) ratios and basal insulin concentrations after EA, and observed that the serum concentrations of SHBG became significantly higher after EA treatment, when compared with those who did not exhibit any effect. Furthermore, a significant increase in the prolactin concentrations was observed in all the women examined, 3 months after the EA treatment. These results suggest that ovulation may be induced by acupuncture via a regulation on the function of HPOA, which may play an important role in the induction of ovulation.

14.3.1.2 Acupuncture may modulate the activity of sympathetic nervous system

In humans, acupuncture is believed to change the function of the sympathetic nervous system. After acupuncture treatment, the sympathetic nerve activity was evaluated by examining the norepinephrine level, skin temperature, blood pressure, and pain-tolerance threshold, which were all observed to be decreased (Knardahl et al. 1998). Based on the previous observation, the anovulatory cases were selected with adequate estrogen levels, and changes in the sympathetic nervous system after acupuncture treatment were observed. After acupuncture, ovulation occurred in 83.3% of the patients whose skin temperature was increased, and in 14.3% of the patients whose skin temperature was not increased anovulation was observed (Yu et al. 1986), suggesting that ovulatory induction by acupuncture treatment might be related to the changes in the sympathetic activity.

In TCM, the function of channels was thought to be to control the flow of *Qi* and blood. According to modern medicine, the blood flow requires the dilation of blood vessels, and the velocity of the blood flow is partly controlled by the innervations of the sympathetic nerve on the vascular wall. In an earlier study, the hand temperature and blood β-endorphin-like immunoreactive substances were measured before and after acupuncture to reflect the sympathetic nerve activity. A total of 31 anovulatory women accepted acupuncture treatment in 79 cycles. A total of 22 of the 39 stimulating cycles with increase in hand temperature showed biphasic BBT after acupuncture treatment, while only 10 of the 40 stimulating cycles with decrease in hand temperature after acupuncture showed biphasic BBT (Yu et al. 1995). This result was also observed in another study on 13 cases of PCOS, in whom the blood levels of β-endorphin like substance (β-EPIS) before and after acupuncture treatment were also measured. Blood β-EPIS levels were stable around normal levels (89.56 – 90.74 fmol/ml) in 6 cases (85.81 – 134.65 fmol/ml, $p>0.05$) demonstrating ovulation after acupuncture treatment, while they were significantly high in 7 patients (203.15 – 279.64 fmol/ml, $p>0.05$) who failed ovulate after acupuncture treatment. Furthermore, negative correlation existed between changes in the hand temperature and blood h-EPIS levels ($r = -0.677$, $p<0.01$) (Chen and Yu 1991), suggesting that by suppressing the sympathetic nervous system, the patients can successfully ovulate after acupuncture treatment, and that acupuncture has a normalization effect on the sympathetic activity.

14.3.2 Experimental Studies

For further understand the mechanism of acupuncture therapeutic effect on induction of ovulation, we designed and performed a series of experimental studies in an animal model. The results suggest that acupuncture therapeutics might regulate the hypothalamic gonadotropin-releasing hormone (GnRH) secretion, pituitary LH secretion, and affect the levels of peripheral sexual hormone; in other words, acupuncture may normalize the abnormal function of HPOA, which may be the key factor of acupuncture therapeutic effects on the gynecologic status. The following experimental studies show the effects of acupuncture on the abnormal functions of HPOA.

14.3.2.1 Induced maturation and exfoliation of vaginal epithelium and raise in the blood estradiol

Wistar female rats, weighing 200 – 250 g, were randomly divided into two groups: the ovariectomized rat group (OVX) and intact rat group (animals during proestrous, INT). The experimental acupoints were: Guanyuan (CV-4, location: on the midline of the abdomen, 15 mm below the umbilicus); bilateral Zhongji (CV-3, location: 5 mm below RN-4 acupoint); Sanyinjiao on one-side (SP-6, location: 10 mm directly above the top of the medial malleolus, on the posterior border of medial aspect of the tibia); and bilateral Zigong (EX-CA-1, location: 15 mm below the umbilicus, 7 mm lateral to CV-3) (Fig. 14.1(a)). The control acupoints were bilateral Huatuojieji 3 – 5 (EX-B5 5 – 7, location: 7 mm lateral to the lower part of the spinous process of the 3 – 5 thoracic vertebra) and Waiguan on one-side (SJ-5, 5 mm above the wrist, between the radius and ulna), located at different anatomic sites of the experimental acupoints (Fig. 14.1(b)). The animals received EA for 30 min per day, for 3 days. An EA apparatus produced the electrostimulation and the stimulation parameters were frequency of 3 Hz and intensity about 1 – 2 mA, to produce a slight twitch of the limbs.

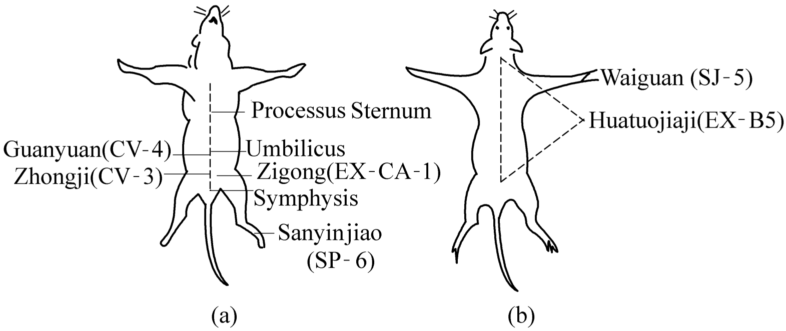

Figure 14.1 Schematic distribution of the acupoints used in our work. (a) ventral view; (b) dorsal view. Panel (a) shows the location of the experimental acupoints, CV 4, CV 3, EX CA 1, and SP 6. Panel (b) shows the location of the contrast acupoints, EX B5 and SJ 5 in the (b) scheme.

The blood level of E_2 in the OVX rats increased significantly, 6 h after the last experiment (Table 14.2). However, no obvious change was observed in INT rats after EA treatment as well as in OVX rats following EA treatment at the control acupoint. The vaginal exfoliative epithelium disappeared in the vaginal smears of the OVX animals 4 weeks after successful ovariectomy, but reappeared after EA treatment (Fig. 14.2).

Table 14.2 Changes in the serum E_2 following EA treatment

	N	Before EA (ng/L)	After EA (ng/L)
Ovariectomized rats	10	$5.47 \pm 0.63^{*}$	$11.58 \pm 0.98^{**}$
Intact rats	10	18.00 ± 3.26	18.34 ± 8.77

Mean ± SE; **p*<0.05 vs. INT rats; ***p*<0.01 vs. before EA.

14.3.2.2 Inhibition of over-compensative release of hypothalamic gonadotropin-releasing hormone and promotion of the release of hypothalamic β-endorphin

It was observed that the high GnRH release from the hypothalamic preoptic area (POA) of OVX rats was inhibited. However, the β-EP secretion in the hypothalamus was raised after EA treatment. Furthermore, no similar effect on the GnRH and β-EP was observed in the INT rats following EA treatment (Table 14.3) (Chen et al. 1994; Lin et al. 1988), suggesting that EA might have an inhibitory effect on the abnormal release of hypothalamic GnRH by promoting the secretion of hypothalamic β-EP.

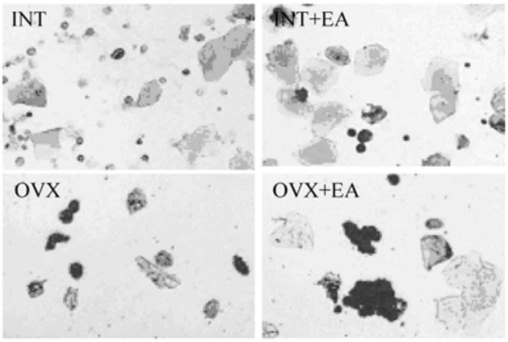

Figure 14.2 Effects of EA on maturation and exfoliation of rat vaginal epithelium × 200. This picture shows the maturation and exfoliation of rat vaginal epithelium with HE staining under optical microscope. Some matured exfoliative epithelium and white blood cells were detected in the vaginal smears of INT rats during preestrus, but no change in the vaginal exfoliative epithelium of INT rats following EA treatment was observed. Some epithelium debris were detected in the vaginal smears of OVX rats 4 weeks after ovariectomy, but the matured, exfoliative epidermic keratinocytes reappeared in the vaginal smears of OVX + EA rats after three successive EA treatments.

Table 14.3 The effects of EA on the release of hypothalamic POA in rats

	GnRH (ng/L)		β endorphin (ng/0.1 L)	
	Before EA	After EA	Before EA	After EA
INT	49.8 ± 12.0	65.7 ± 21.0	137.2 ± 33.7	263.4 ± 47.3
OVX	272.5 ± 77.8$^{\#\#}$	106.5 ± 39.8*	212.5 ± 26.2$^{\#}$	302.7 ± 65.2**

Mean ± S; *p<0.05 and **p<0.01 vs. before EA; $^{\#}p$<0.05 and $^{\#\#}p$<0.01 vs. INT.

14.3.2.3 Effect of acupuncture on the expression of brain prolactin-releasing peptide and orphanin FQ

Prolactin-releasing peptide (PrRP) is a neuropeptide with 31 or 20 amino acid residues, and is regarded as a potent and specific stimulator of pituitary prolactin. The PrRP immunoreactive (PrRP-ir) neurons and mRNA are found in the medulla oblongata and hypothalamus, and the fibers containing PrRP are widely distributed in the rat brains. In 2004, Yao et al were the first to reported that the number of PrRP-ir-positive neurons in the nucleus tractus solitarii (NTS) of the medulla oblongata and the expression level of PrRP mRNA in the medulla oblongata in OVX rat group, were lower when compared with the sham-operation group; however, those in the OVX rats under EA treatment increased when compared with those in the OVX rats without EA treatment (Yao et al. 2004). Similarly, in another study, the expression of GnRH mRNA and the release of GnRH in OVX rats were observed to decrease after EA treatment (Lin 1988), suggesting that PrRP might be involved in the regulation of female HPOA function, and that the brain PrRP might participate in the action of acupuncture in normalizing the deviant function of HPOA, induced by ovariectomy. Subsequently, Feng et al (2006) further studied the actions of brain PrRP in EA normalization of HPOA dysfunction, and showed that PrRP, not only in the nucleus of solitary tract (NTS) and ventrolateral reticular nucleus (VLRN), but also its fibers in the hypothalamic bed nucleus of the stria terminalis (BST), might participate in the EA normalization process in OVX rats. In addition, they also reported that PrRP might be concerned with the regulation of sexual cycle in female rats (Feng et al. 2007).

Orphanin FQ (OFQ) or nociceptin belongs to the endogenous opioid peptide family, which is an endogenous ligand of opioid receptor-like receptor 1 (ORL1) in the mammalian brain. The OFQ and its receptor is presumed to have many effects on the regulation of pain, cardiovascular system, kidney, learning, and memory (Pan et al. 2000). In 2003, Chen et al reported that EA might influence the level of endogenous OFQ synthesis on translation, modification, and enzymolysis of prepronociceptin (PPN), which might provide a great evidence on the notion that EA participates in normalizing the dysfunction of HPOA in OVX rats (Chen et al. 2003). In another study, An et al (2005) showed that EA might affect the expression of OFQ and ORL1 receptor in the POA, ventral medial hypothalamus (VMH), and median eminence (ME), resulting in the normalization of the abnormal secretion of pituitary LH in OVX rats. These results suggest that OFQ might be involved in producing the normalization effect of EA on the abnormal function of HPOA in OVX rats.

14.3.2.4 Acupuncture accelerates the extragonadal aromatization

1. Acupuncture enhances the activity of adrenal argyrophil nucleolar organizer regions and the blood level of corticosterone and androgen

The adrenals of the OVX rats after EA were enlarged and the weight of the adrenals was raised significantly. Using the histochemical method, the adrenal argyrophil nucleolar organizer regions (AgNORs) of the cells in the inner adrenal cortex were examined, which may reflect the activity of cell differentials and transcription of the nucleolar rDNA. The results showed that the activity of AgNORs was enhanced and the level of blood corticosterone was also increased in OVX rats under EA treatment (Table 14.4). However, no similar effects were observed between INT rats and OVX rats after EA treatment on the control acupoints (Chen and He 1992; Gao et al. 1995). These results suggest that EA might promote the activity of adrenal cortex to secrete more corticosteroids, among which androgen, a precursor of estrogen, may be transformed into estrogen by aromatase in the extragonadal tissues, to compensate the lack of estrogen owing to ovariectomy.

2. Acupuncture promotes adrenal expressions of P450CYP mRNA

The more sensitive method of RT-PCR was adopted for further observation of the mRNA expressions of a key androgen synthetic enzyme, P450CYP. The expressions at the adrenal cortexes of the OVX rats under EA treatment increased significantly

Table 14.4 The influences of EA on the blood level of adrenocorticotropin and testosterone

	N	Adrenocorticotropin (pg/ml)	Testosterone (fmol/ml)
OVX + EA	8	$391.0 \pm 43.8^{**}$	$172.0 \pm 9.2^{**}$
OVX	8	$169.5 \pm 10.3^{\#\#}$	139.33 ± 15.4
INT+EA	8	222.7 ± 11.9	199.75 ± 11.3
INT	8	208.2 ± 18.5	177.25 ± 24.8

Mean ± SE; $^{**}p<0.01$ vs. OVX; $^{\#\#}p<0.01$ vs. INT.

when compared with those in the OVX rats without EA treatment. Furthermore, the expressions of P450CYP mRNA at the adrenal cortexes of the OVX rats under EA treatment increased significantly when compared with those in the OVX rats without EA treatment (Zhao et al. 2005), suggesting that EA might influence the transcription of P450CYP, and consequently resulting in more significant synthesis of androgen. As, currently, there are no commercial antibodies against this enzyme, a thorough research on P450CYP could not carried out. Thus, the actual effects and mechanism of this enzyme still needs to be elucidated.

It was reported that corticotropin-releasing horme (CRH) might directly accelerate the expression of P450CYP17 mRNA, and sequentially increase the synthesis of dehydroepiandrosterone-sulfate (DHEA-S). Thus, it can be concluded that EA treatment increases the adrenal P450CYP17 mRNA expression in OVX rats; however, its mechanism is not fully understood.

3. Acupuncture increases the activity and expression of tissue aromatase in subcutaneous abdominal adipose and liver tissues

The RT-PCR technique and radio-enzymological assay were adopted for probing the biochemical and molecular mechanism of EA on the special acupoints to elevate the blood E_2. The results showed the aromatase activity of the subcutaneous abdominal (SA) adipose and liver tissues in OVX rats under EA treatment increased significantly than that in the OVX rats without EA treatment. The results of the RT-PCR and Northern blot showed that the mRNA and protein expression of aromatase in SA adipose and liver tissues also reinforced observably (Cheng and Chen 2001; Zhao et al. 2004).

The results demonstrating increased blood levels of androgen, an estrogen precursor, suggest that the main estrogen origin of the female castrated animal might be other peripheral tissues, such as SA adipose and liver tissues, etc., after EA treatment. Subsequently, the aromatase present in those tissues may convert the blood androgen into estrogen, thus, compensating for the deficiency of estrogen induced by ovariectomy.

Though it has been reported that the splanchnic tissue is a minor site for extraglandular aromatization of androgens (Longcope et al. 1983), a significant conversion of androstenedione to estrone by liver tissues has also been observed

(Feng et al. 2007). In adult liver homogenates, C19 norsteroid (19-nortestosterone; NT) is readily aromatized to estrogens (Frost et al. 1980; Harada et al. 1998). On the other hand, after ovariectomy, the diminution of C19 precursor from ovaries for aromatization may induce the decreased expressions of aromatase in the OVX rats when compared with the gonad-intact rats. However, in our study, the aromatase expressions in the OVX rats did not show consistent changes between the SA adipose and liver tissues, which suggest that the role of SA adipose and splanchnic tissues in the extra-glandular aromatization might be different. Nonetheless, in the final analysis, our results suggest that both the SA adipose and liver tissues contribute to the effects of EA on extragonadal aromatization, to increase the estrogen concentrations in circulation.

14.3.2.5 Acupuncture may improve uterine artery blood flow impedance

Endometrial thickness, morphology, and uterine artery blood flow have been implicated as important parameters for the successful implantation of the human embryos (Yoshiji et al. 1986; Zaidi et al. 1996; Schild et al. 2001). Despite the conflicting results in the utilization of these parameters during various stages of treatment to predict the outcome of IVF, it is generally believed that adequate endometrial thickness is required to optimize pregnancy rate. As endometrial thickness is a function of uterine artery blood flow, Sher and Fisch (2000) reported a novel method of using vaginal sildenafil in an attempt to improve the uterine artery blood flow and endometrial development in patients undergoing IVF (Sher and Fisch, 2000).

With its central sympathoinhibitory effect, acupuncture may contribute to reduce the uterine artery impedance, and thus, increase the blood flow to the uterus. In fact, Sterner-Victorin et al (1996) demonstrated this effect by performing acupuncture on 10 infertile women who were downregulated by GnRH analog to avoid the effect of endogenous hormone on uterine artery blood flow.

14.3.2.6 Acupuncture and stress reduction

It has been well documented that infertility causes stress (Schenker et al. 1992; Domar et al. 1992; Domar et al. 1993), and that stress reduction may, in turn, improve fertility (Domar 1990). However, the relationship between stress and infertility is that of a vicious cycle. Social stigmatization, decreased self-esteem, unmet reproductive potential of sexual relationship, physical and mental burden of treatment, and the lack of control on treatment outcome are some of the factors that can lead to psychological stress in any couple seeking infertility treatment. In turn, stress may lead to the release of stress hormones and influence the mechanisms responsible for a normal ovulatory menstrual cycle through its impact on the HPOA.

The use of acupuncture for reducing anxiety and stress possibly through its sympathoinhibitory property and impact on β-endorphin levels has been reviewed (Chen and Yu 1991; Dong 1993), and the efficacy of acupuncture in treating depression has also been studied (Luo et al. 1998). As the pharmacological side effects of anxiolytic and antidepressant drugs on infertility treatment outcome are largely unknown, acupuncture may provide an excellent alternative for stress reduction in women undergoing infertility treatment.

14.4 Concluding Remarks

Acupuncture therapy is well known and has shown remarkable therapeutic effects on woman infertility. Moreover, acupuncture combined with ART is observed to markedly enhance the successful pregnant ratio among women under IVF/ICSI treatment for infertility. In this chapter, we summarized the data of clinical and experimental studies, and discussed the reproduction-neuroendocrine mechanism of acupuncture treatment for woman infertility. In conclusion, acupuncture is presumed to rectify the dysfunction of HPOA to near normal status by adjusting the function at the levels of the whole body, organs, and cells, in female reproductive system. However, acupuncture is not considered to change the normal HPOA function, and therefore, this adjustment effect of acupuncture has been termed as “acupuncture normalization”. The characteristic of acupuncture normalization is not only observed in the HPOA dysfunction, but also in pain modulation (acupuncture analgesia) as well as hyperthyroidism and autoimmune diseases.

In brief, acupuncture therapy is considered to be the precious heritage of TCM, and its scientific connotation has been validated by modern biomedical researches in the past 40 years. Irrespective of its use in the treatment of diseases or in acupuncture analgesia, certain modern scientific mechanism underlies all its applications. We believe that acupuncture is one of the great treasures of TCM, and will certainly widen its horizon in China as well as all over the world.

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15 Acupuncture Therapy for Menopausal and Perimenopausal Syndrome

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Summary This chapter summarizes the clinical practice and mechanistic exploration of acupuncture therapy for menopausal and perimenopausal syndrome. Accumulating clinic data suggest that acupuncture is an effective and economical therapy for menopausal and perimenopausal syndrome. The mechanistic research has developed the idea that acupuncture signals initiated at the acupoints are transferred to the brain through the nervous pathway, and thus, modulate multiple neurotransmitter systems. Subsequently, the output signaling cascades may correct the dysfunctions of the hypothalamic-pituitary-ovarian axis (HPOA) through neural regulation. On the other hand, acupuncture is observed to activate the endocrine secretion, hormonal, dielectric, and other pathways. There is also evidence showing that the mechanisms of acupuncture are related to the regulation of gene expression and intracellular signal transduction. Taken together, acupuncture is considered to induce an integrated and complex effect on HPOA through the regulation of multiple systems in the body.

Keywords *acupuncture, menopause syndrome, perimenopausal syndrome, Estradiol (E_2), Hypothalamic-pituitary-ovarian axis (HPOA), ovariectomy*

15.1 Introduction

Considered, until recently, as a biological fate, menopause has evolved within a decade into a major public health issue at stake. At present, with many women in the developing and developed countries living at least one-third of their lives after the menopause, it is not surprising to observe the increasing media attention on the health aspects during this crucial period. Topics such as osteoporosis, cardiovascular disease, and the benefits and risks of hormone replacement therapy (HRT) have received markedly increased attention in the last few years.

During perimenopausal period, women commonly report irregular menstrual periods, hot flashes, sleep disturbances, and vaginal dryness. A group of symptoms, including nervousness, anxiety, irritability, and depression, have also been observed to be associated with menopause. However, whether these symptoms are related to the changes in the central nervous system (CNS) as a result of decreased estrogen levels or whether they have a different cause, has not yet been ascertained.

When women reach the menopausal stage, the decision to seek treatment is based on the severity of short-term symptoms, risk of diseases in the later years, and personal attitudes about menopause and medication. Various menopause treatment options are available, including lifestyle changes, nonprescription remedies, prescription therapies, and complementary and alternative medicine (CAM) therapies (Stener et al. 2002).

Many women go through natural menopause with minimal discomfort during the perimenopausal years. For most of them, the disturbances diminish or disappear over time, or are reduced with lifestyle changes, such as exercise and diet modification. Some perimenopausal women find adequate symptom relief from nonprescription remedies, while others may need prescription therapies during this transition. Sometimes, prescription therapies are needed to protect against osteoporosis and other diseases. Prior to beginning any treatment or a combination of treatments, either intended to alleviate the symptoms or prevent the diseases later in life, a woman needs to be assured that the treatment regimen selected is the best for her.

Hormone treatment should always employ the lowest dose for the shortest time needed. The length of the therapy may vary from woman to woman, depending on her individual health profile and risks of developing serious diseases. Furthermore, regular checkups are important throughout the life.

It is well documented that the use of estrogen alone (estrogen therapy, ET) can dramatically increase the risk of developing cancer in the uterus. However, it is also well known that the use of another prescription hormone—progestogen—with estrogen therapy (EPT) reduces that risk to the level of taking no hormones. Many clinical trials have provided evidence regarding the effects of ET/EPT on relieving menopause symptoms and making bones less prone to fracture. A recent, large-scale, high-quality trial—the Women's Health Initiative (WHI)—has given healthcare providers more accurate evidence regarding the various risks of ET/EPT. After 5 years, women undergoing the type of EPT followed in the trial had increased risks for heart diseases, stroke, blood clots, and breast cancer, and decreased risks for colorectal cancer and hip fractures. Owing to these risks, estrogen with or without progestogen should be prescribed at the lowest effective doses and for the shortest duration, keeping in mind the treatment goals and risk for the individual woman.

Acupuncture has been used to treat menopausal symptoms for thousands of years, and has shown excellent results in easing these symptoms without any side effects. It is known to modulate the neurotransmitter function in the CNS, promote homeostasis, and modulate hormonal disturbance. With the onset of menopause, the body experiences a dramatic change. The principle of acupuncture is to strengthen the individual's body and re-establish a harmonious state of the body. Acupuncture treatment regulates the unstable hormone levels during menopause, and the energy flow is regulated in the body by needling techniques.

There is no single way to ensure the best possible quality of life during the period of perimenopause and beyond. Each woman is unique. It is beneficial for a woman to invest time working with her healthcare professionals to create an individual health plan and make therapeutic adjustments that are required over time, not only owing to the fact that new therapies and guidelines are available, but also because a woman's body continues to change in its own individual way.

15.2 Acupuncture Treatment for Menopause and Perimenopausal Syndrome

According to Chinese medical theory, menopause occurs when a woman's body begins to preserve blood and energy to sustain her vitality and provide maximum available nourishment to her body, especially her kidneys. According to Chinese Medicine, kidney is the organ which is the root of life and longevity. Therefore, the body, in its perception, is considered to reserve the flow of a channel in the center of the body, which sends the blood and energy down to the uterus. Instead, blood and essence from the kidneys are conserved and cycled through the body to nourish the woman's spirit and extend her longevity. Thus, in the Chinese Medicine, menopause is presumed to be a true change in the life from a mother to an enlightened and wise being. Accordingly, menopause is classified into three areas: (1) lack of yin leading to hyperactivity of *Yang*; (2) blood stasis as a result of *Qi* (chee) stagnation; and (3) an increasing accumulation of phlegm and dampness in the body.

Acupuncture has been used to treat menopausal symptoms for thousands of years, and has shown excellent results in easing these symptoms without any side effects. With the onset of menopause, the body goes through a dramatic change. The principle of acupuncture is to strengthen the individual's body and re-establish a harmonious state of the body. Acupuncture treatment is considered to regulate the unstable hormone levels during menopause, and the energy flow is regulated in the body by needling techniques.

15.2.1 Commonly Used Acupoints

Many of the acupoints could be used to treat the emotional and physical symptoms of menopause. The acupoints used for menopause treatment are almost the same as those used for the infertility treatment, though the length, number, and frequency of treatments may vary. A single treatment may typically last from 5 to 30 min with the patient being treated once or twice a week. Some symptoms are relieved after the first treatment, while more severe or chronic ailments often require multiple treatments. The style of acupuncture that the acupuncturist follows may influence the length of the treatment, number of points used, and frequency of visits.

In Traditional Chinese Medicine (TCM) literature, some channels, such as kidney channel, spleen channel, liver channel, Thoroughfare Vessel, Governor Vessel, and Conception Vessel are considered to be closely related to reproduction. The kidney is the foundation of the native (born) constitution that stores the reproductive essence and takes charge of reproduction. A total of 10 out of 27 acupoints on the kidney channel are observed to be related to abnormal menstruation and reproduction. The spleen provides the material basis of the acquired constitution and has the function of maintaining the blood flow within the vessels. Among the 21 acupoints on the spleen channel, 5 acupoints are associated with the menstrual disorders and reproduction. Furthermore, the liver is a reservoir of blood and also installs as well as regulates blood, and 7 of the 14 acupoints on the liver channel are related to menstrual disorders.

Thoroughfare Vessel is the reservoir of blood; while Conception Vessel is in charge of the uterus, and is also the reservoir of yin meridians. Furthermore, Governor Vessel is considered to be the reservoir of yang meridians. Thoroughfare, Governor, and Conception Vessels are considered to have originated from the uterus and subsequently developed into three different vessels. These three vessels can influence each other and play an important role in reproduction. About one-fourth of the acupoints on the Governor and Conception Vessels are considered to be associated with menstrual disorders. Hence, acupuncture for the treatment of menstrual disorder is closely related to kidney, spleen, and liver, Thoroughfare, Governor, and Conception Vessels. The main acupoints used for the treatment include Guanyuan (CV-4), Zhongji (CV-3), Sanyinjiao (SP-6), and Zigong (EXTRA-22). However, some acupoints, such as Zusanli (ST-36), Qihai (BL-24), Shenshu (BL-23), Ganshu (BL-18), etc., are selected as adjuvant points according to the signs and symptoms.

Guanyuan (CV-4) acupoint lies on the anterior midline of the lower abdomen, 3 cun below the center of the umbilicus. Using the needle, the acupoint is perpendicularly punctured to 2 – 3 cun and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward the lower abdomen.

Zhongji (CV-3) acupoint lies on the anterior midline of the lower abdomen, 4 cun below the center of the umbilicus. Using the needle, the acupoint is perpendicularly punctured to 2 – 3 cun and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward the pudenda.

Sanyinjiao (SP-6) acupoint lies on the medial side of the leg, 3 cun above the tip of the medial malleolus, just posterior to the Tibia. Using the needle, the acupoint is perpendicularly punctured to 1 – 1.5 cun, and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward the vola.

Zigong (EXTRA-22) acupoint lies on the lower abdomen, 4 cun below the center of the umbilicus and 3 cun lateral to Zhongji (CV-3) acupoint. These acupoints are used bilaterally. The acupoints are perpendicularly punctured to 1.5 – 3 cun using the needle, and the needle is retained for 20 – 30 min. The needling sensation should be transmitted toward the lower abdomen and pudenda.

Zusanli (ST-36) acupoint lies on the anterior lateral side of the leg, 3 cun below the acupoint Dubi (ST-35), and one finger breadth (middle finger) from the anterior crest of the tibia.

Qihai (BL-24) acupoint lies on the lower back, below the spinous process of the third lumbar vertebra, 1.5 cun lateral to the posterior midline.

Shenshu (BL-23) acupoint lies on the lower back, below the spinous process of the second lumbar vertebra, 1.5 cun lateral to the posterior midline.

Ganshu (BL-18) acupoint lies on the back, below the spinous process of the eighth thoracic vertebra, 1.5 cun lateral to the posterior midline.

However, there seems to be little sensitivity to the insertion of the acupuncture needles. These needles are so thin that several acupuncture needles can go into the middle of a hypodermic needle. Occasionally, the patients might experience a brief moment of discomfort when the needle penetrates the skin; however, once the needles are in place, most people become relaxed and even fall asleep during the treatment.

The most common interventions are the traditional manual acupuncture, electroacupuncture (EA), auricular acupuncture, and acupressure.

15.2.2 Therapeutic Effects of Acupuncture on Menopausal Syndrome

Since its dramatic debut in the USA in 1971, acupuncture has been used successfully on millions of women to treat menopausal symptoms, such as hot flashes and depression (Newton et al. 2002). With an origin from the ancient Chinese traditions, acupuncture is rapidly becoming a preferred alternative to traditional health care, and recent studies have demonstrated extremely positive results.

Cohen et al (2003) conducted an early study to explore the effectiveness of acupuncture in alleviating hot flashes, insomnia, and nervousness, and found that during the course of acupuncture treatments, hot flashes decreased by 35% and insomnia decreased by 50%. A follow-up study after 3 months revealed that hot flashes significantly decreased in those receiving acupuncture when compared with those receiving routine care without acupuncture.

These results are promising and the United Nations' World Health Organization has approved acupuncture as a treatment for symptoms associated with menopause. In addition, further clinical trials with larger samples are also currently underway.

Another study (Yael et al. 2007) funded by the National Cancer Institute involved a larger number of participants than the previous studies. The participants were divided into three groups: (1) receiving menopause-specific acupuncture; (2) non-menopause-specific acupuncture, and (3) usual care, respectively.

Recently, researchers from the Stanford Medical Center (Huang et al. 2006) examined whether acupuncture can alleviate hot flashes. During the 1-year, placebo-controlled study at Stanford, the volunteers received 10 treatments over an 8-week period.

Wyon et al (1994) examined 24 menopausal women who received either genuine EA or superficial needling at incorrect points, and were followed-up for 5 months. The scores for flushes by daily diary improved by 50% in both the groups during the 12-week treatment, though the improvement was better only in the acupuncture group and not the control. However, they were not significant. The Kupperman index also improved, but there was no measurable effect on sleep dysfunction. Furthermore, the urinary secretion of calcitonin gene-related peptide, a potent vasodilator, also increased in both the groups during the treatment, but tended to return to normal afterwards.

Another research group (Sandberg et al. 2002) repeated the study on 30 women with vasomotor symptoms. They observed that the acupuncture group showed no greater improvement than the control, with regard to the menopausal symptom scores or psychological well-being throughout the 6-month study. Furthermore, there was a significant increase in the mood-scale scores only during the first 12 weeks. Ten menopausal women with mild hypertension were included in a placebo-controlled, crossover study. The researchers observed that the menopausal complaints and well-being significantly improved during the treatment; however, this effect did not last for more than 2 months. Furthermore, no effect was observed on the hypertension or serum lipids, though there was a reduction in the secretion of noradrenalin in the acupuncture group.

Many acupuncturists in China have reported the treatment of acupuncture on menopausal syndrome. Pu et al (1997) examined 60 menopausal women who received manual acupuncture on the acupoints Guanyuan (CV-4), Zhongji (CV-3), Sanyinjiao (SP-6), Zigong (Ex-CA-1), and Taichong (LR-3), and were followed-up for 6 months. The patients' symptoms were observed to improve at varying degrees. The marked effective rate was 40% and the total effective rate was 100%. Zhang et al (1999) carried out a clinical study on the effect of acupuncture on menopausal syndrome. A total of 62 patients were treated using acupuncture, and 50 women were selected as control. After the treatment, 33 patients recovered well (in a total of 3 months of treatment), with no recrudescence within 3 months. The total effective rate was 96.8%. Furthermore, Mu (1994) also reported over 100 cases of perimenopausal syndrome treated with acupuncture treatment, while Wu and Zhou (1998) reported 300 cases of perimenopausal syndrome treated with acupuncture, thus, claiming the validity of acupuncture on this syndrome.

In addition, other interventions such as auricular acupressure, have been demonstrated to be very effective for the treatment of hot flashes, insomnia, and nervousness symptoms. A total of 89 cases with perimenopausal syndrome were treated by administering pressure on Earpoints, Kidney, Endocrine, and Internal Genitals. Consequently, the subjective symptoms disappeared, menstrual disorder improved, and normal functioning was restored in 82 cases; in 6 cases, the subjective symptoms abated and menstrual disorder improved; and in 1 case, no effect was observed. Thus, the effective rate of this treatment was 99% (Shan et al. 2003).

15.3 How Does Acupuncture Work?

A basic principle of TCM is that there is a life energy flowing through the body, which is termed as *Qi*. This energy flows through the body on channels known as meridians that connect all the major organs. According to the Chinese medical theory, illness arises when the cyclical flow of *Qi* in the meridians becomes unbalanced. Acupuncture is considered to stimulate specific points located near or on the surface of the skin which have the ability to alter various biochemical and physiological conditions, to achieve the desired effect.

The physiology of acupuncture relies on the concepts of changing the flow of energy in the meridians. The needle insertion into the skin and deeper tissues results in a particular pattern of afferent activity in the peripheral nerves. Basic scientific research suggests that manual stimulation of the acupuncture needle activates the muscle afferents (mainly A_δ and possibly C-fibers). Another mode of stimulation is through the application of electrical stimulation, as in EA. Low-frequency (1 – 4 Hz) EA stimulation of the needles may excite a group of receptors found in the muscles, denoted as ergoreceptors, which are physiologically activated during muscle contractions. Both EA and muscle exercise are observed to release endogenous opioids and oxytocin, which seem to be essential for the induction of functional changes in different organ systems (Han 2003).

15.3.1 Electroacupuncture-induced Regulation of Hypothalamic-pituitary-ovarian Axis

Repeated EA on specific acupoints can significantly increase the blood concentrations of estradiol (E_2) in the ovariectomized (OVX) rats, as well as reduce the elevated plasma luteinizing hormone (LH) owing to OVX (Fig. 15.1). In addition, EA is also observed to restored the number of gonadotropin-releasing hormone (GnRH) neurons in the rostral medial septum (MS), Broca diagonal band nucleus (DBB), and medial preoptic nucleus (MPOA) of the OVX rats (Fig. 15.2). These results suggest that EA effectively enhances the function of the hypothalamic-pituitary-ovarian axis (HPOA) (Zhao et al. 2003c). In addition, EA may remarkably

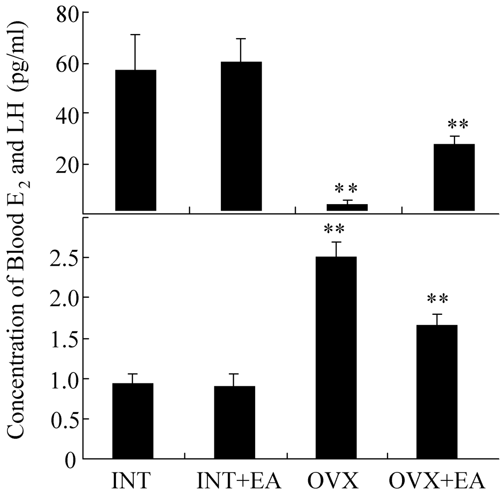

Figure 15.1 Effect of EA on the concentration of blood E_2 and LH in the rats. Female Sprague Dawley rats (180 – 200 g), with regular 4 day estrus cycles were divided into four groups: intact (INT), intact with EA (INT + EA), ovariectomized (OVX), and ovariectomized with EA (OVX + EA). The acupoints employed were Guanyuan (RN 4), Zhongji (RN 3), Zigongxue (EXTRA 22), and Sanyinjiao (SP 6). The stimulation was generated by an EA apparatus and lasted for 30 min (8:00 – 10:00 AM), once a day for 3 days in total. The stimulation parameters were 2 mA of density and a low burst frequency of 3 Hz. The blood E_2 in rats was hardly detected 1 month after ovariectomy, but increased significantly after EA, and reached nearly half of the normal level after three EA treatments. ** $p<0.01$ vs. INT and INT + EA; *$p<0.05$ vs. INT; #$p<0.05$ vs. OVX. Note that the stimulation should be consistent and consecutive, and the acupoints can be adjusted according to the clinical symptoms.

upregulate the decreased protein and mRNA expressions of the estrogen receptor induced by ovariectomy in rats' brain (Chen 1997; Chen et al. 1998).

Aromatase is the key enzyme responsible for estrogen biosynthesis. Considerable emphasis has been placed on the role of extragonadal aromatization in specific brain areas, which includes the medial preoptic/anterior hypothalamus, the medial basal hypothalamus, and amygdala (Lephart 1996). The total amount of estrogen synthesized in these areas may be small, but the local tissue concentrations achieved are high enough to exert significant biological influence locally, and predominantly, in a paracrine or intracrine fashion, on the reproductive function, sexual behaviour, etc. Naftolin et al showed the presence of local aromatization systems in the central neuroendocrine areas and regions, including the anteroventral periventricular nucleus (AVPv), the medial basal hypothalamus, and the suprachiasmatic-preoptic area (Lephart 1996). The AVPv and the MPOA have been widely agreed to be the critical brain regions within which estrogen acts to enable the GnRH surge (Herbison 1998). It has been reported that the EA

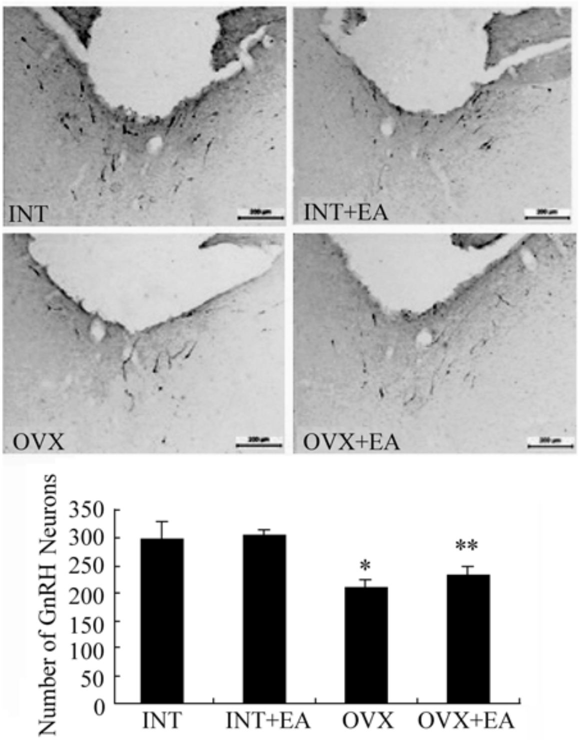

Figure 15.2 The GnRH neurons around organum vasculosum of the lamina terminalis (OVLT) of the INT, INT + EA, OVX, and OVX + EA rats. Female Sprague Dawley rats (180 – 200 g), with regular 4 day estrus cycles were divided into four groups: intact (INT), intact with EA (INT + EA), ovariectomized (OVX), and ovariectomized with EA (OVX + EA). The acupoints employed were Guanyuan (RN 4), Zhongji (RN 3), Zigongxue (EXTRA 22), and Sanyinjiao (SP 6). The stimulation was generated by an EA apparatus and lasted for 30 min (8:00 – 10:00 AM), once a day, total for 3 days. The stimulation parameters were 2 mA of density and a low burst frequency of 3 Hz. The upper picture shows the light micro graphs of the GnRH immunoreactive neurons around OVLT by immunohistochemical method (ABC). The GnRH immunoreactive neurons were detected by the polyclonal antibody. The numbers of GnRH neurons in the all continuous slices was expressed as mean ± SEM ($n = 6$ per group) in each column, indicated in the lower panel. *$p<0.05$ vs. INT and INT + EA; **$p<0.05$ vs. OVX.

Note that EA may modulate the synthesis and release of central GnRH at the molecular level, and also enhance the pituitary GnRH R mRNA level, which may be the central mechanism by which acupuncture regulates the dysfunction of hypothalamic pituitary adrenal axis (HPAA).

may significantly enhance the aromatization in the brain regions of OVX rats, which suggest that EA could enhance the local estrogen synthesis, and that estrogen might influence the functions of GnRH network to facilitate the homeostasis of the HPOA (Zhao et al. 2005a) (Fig. 15.3).

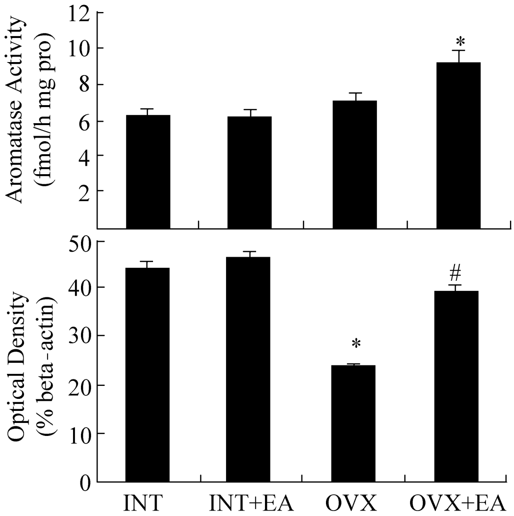

Figure 15.3 Effects of EA on the aromatase activity and expressions in the hypothalamus tissues of the INT, INT + EA, OVX, and OVX + EA rats. Female Sprague Dawley rats (180 – 200 g), with regular 4 day estrus cycles were divided into four groups: intact (INT), intact with EA (INT + EA), ovariectomized (OVX), and ovariectomized with EA (OVX + EA). The acupoints employed were Guanyuan (RN 4), Zhongji (RN 3), Zigongxue (EXTRA 22), and Sanyinjiao (SP 6). The stimulation was generated by an EA apparatus and lasted for 30 min (8:00 – 10:00 AM), once a day for 3 days in total. The stimulation parameters were 2 mA of density and a low burst frequency of 3 Hz. The upper picture shows the aromatase activities in the hypothalamus, and the lower picture shows the aromatase expression in the hypothalamus. *$p<0.05$ vs. INT and INT + EA; #$p<0.05$ vs. OVX.

The expression of the estrogen receptors (ER-α and ER-β) is considered as a problem that should be extensively studied using the same model. The data showed that the expressions of ER-α in the MPOA, ventromedial nucleus of the hypothalamus, and arcuate nucleus, increased apparently in the OVX + EA rats when compared with those in the OVX rats (Chen et al. 1998). Furthermore, the effects of EA on the expressions of ER-β are currently being examined. However, it is still difficult to distinguish the direct effects of EA on GnRH neurons and the indirect regulation role of EA on E_2 and subsequently on GnRH neurons, with respect to estrogen receptors. Thus, it can be concluded that the EA could stimulate the hypothalamic aromatization, and that the locally synthesized estrogens might influence the function of GnRH network.

There has been limited literature on gonadotropin releasing hormone immune reactive cells (GnRH-ir) expression in Paraventricular thalamic nucleus (PVN), and we believe that GnRH-ir elements exist in the corticotropin releasing hormone (CRH) cells of PVN (Zhao et al. 2003a). It is presumed that EA may promote the expression of GnRH whose immunoreactivity can be easily observed in OVX rats. Thus, further studies based on these observations may provide a new scientific mechanism for the clinical acupuncture therapeutics. In addition, further studies are also needed to determine the exact neuroanatomical organization and physiological significance of the GnRH-ir, which is still unclear. Some neurotransmitters and neuromodulators, traditionally thought to function only through synaptic contacts, are now considered to act in a paracrine fashion as well. The GnRH as a hormone might also act in the paracrine fashion in several non-brain tissues; however, whether we can conclude that the synaptic contact is essential for GnRH to exert neuromodulatory influence in the brain tissues, is still an open question.

15.3.2 Role of β-endorphin

In the recent years, researches have indicated that β-endorphin[β-EP], an endogenous opioid with s high affinity for the μ-receptor, is involved in regulating GnRH secretion and menstrual cycle. Hence, there has been a particular interest to examine the role of β-endorphin in acupuncture therapy.

It has been reported that acupuncture may alter plasma β-endorphin levels, and thereby produce an effect on the release of hypothalamic GnRH and pituitary gonadotropin secretion.

Chen et al (1994) found that EA treatment in OVX rats might significantly decrease the GnRH release from the preoptic area, increase the β-endorphin release from the preoptic area, and elevate the plasma β-endorphin level. The results suggest that the negative feedback of estrogen may be a major regulative factor for GnRH release under normal conditions, and that after the elimination of estrogen feedback induced by ovariectomy, the central opioid peptide might be the main regulative factor for GnRH release.

Zhang (2006) examined a total of 65 female patients with menopausal symptoms from Shandong Hospital of TCM from June 1998 to April 1999, who either received acupuncture treatment ($n = 33$) or were administered oryzanol ($n = 32$), randomly. When compared with those receiving oryzanol, patients undergoing acupuncture treatment exhibited higher effective rates with respect to hot flush, desudation, sensory disorder, insomnia, apt-excitement, urinary infection, depression and suspiciousness, dizziness, headache, arthralgia, palpitation, tendency to become tired, and formication of skin. In addition, the plasma β-endorphin level of the patients was observed to significantly increase after acupuncture treatment ((136.1452 ± 54.6915), (94.3486 ± 30.8609) mg/L, $t = 3.632$, $p < 0.05$).

Shan et al (2003) reported that the blood concentration of follicular stimulating hormone (FSH) was significantly decreased, and E_2 and β-EP were markedly elevated after auricular point-pressing treatment in 31 patients with menopausal syndrome.

Acupuncture demonstrated good effects on the treatment of menopausal symptoms in females. Furthermore, acupuncture is observed to improve many clinical symptoms efficiently. For example, the β-EP level in the patients decreased significantly before treatment, but increased significantly after acupuncture treatment. There has been evidence showing that this hypothalamic β-endorphin system has a central role in mediating the changes observed in the autonomic functions after acupuncture, which are probably caused by an inhibition of the vasomotor center (VMC). This can result in a sustained decrease in the general sympathetic tone with vasodilatation, increase the skin temperature, and decrease the blood pressure, indicating that acupuncture can influence the entire regulatory function of the neuroendocrine-immunological network's internal environment by promoting the release of β-EP and elevating the level of peripheral β-EP.

15.3.3 Role of Corticotrophin-releasing Factor and Hypothalamus-pituitary-adrenal Axis

The release of β-endorphin is regulated by Corticotrophin-releasing factor (CRF), which is produced and released from the paraventricular nucleus of the hypothalamus. The CRF promotes the release of β-endorphin, adrenocorticotrophic hormone (ACTH), and melanocyte-stimulating hormone in equimolar amounts through the stimulation of the synthesis of their precursor, pro-opiomelanocortin. These hormones exert their effects in different target organs via the bloodstream (Rivest and Rivier 1995).

Stress increases the activity of the hypothalamic-pituitary-adrenal axis (HPAA) and decreases the reproductive functions (George et al. 1998). This suggests a close relationship between the hormones of the HPAA and those of the hypothalamic-pituitary-gonadal (HPG) axis. The CRF, ACTH, β-endorphin, and adrenal corticosteroids are observed to play an important role in modulating the effect of stress on reproductive functions. Through this route, acupuncture may exert an effect on both the HPAA and the HPG axis (Mastorakos et al. 1997).

The CRH is a potential mediator of stress-induced alteration in the GnRH neurons (Viau 2002). In addition, CRH may also mediate the seasonal or circadian effects on the reproductive axis. The EA treatment resulted in a significantly higher number of CRF immune reactive cells (CRF-ir) neurons in the OVX rats (Zhao et al. 2003a). The data obtained by Zhao et al (2003b) on the release of CRH from PVN by push-pull perfusion suggest that the level of CRH release in the OVX rats was higher than that in INT rats. Thus, EA may enhance both the release and synthesis of CRH in OVX rats (Zhao et al. 2004b) (Fig. 15.4).

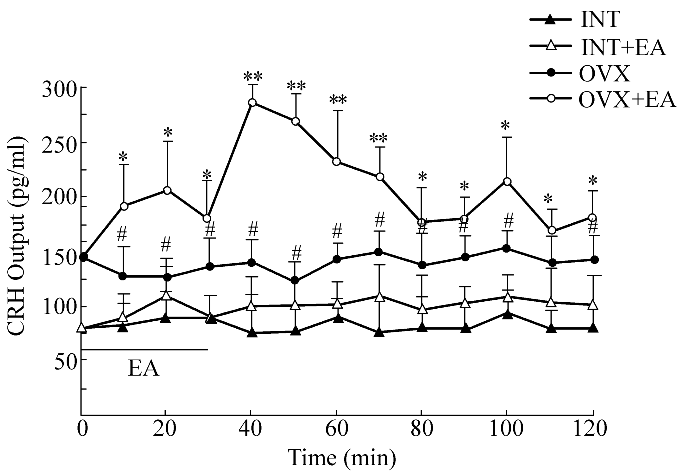

Figure 15.4 Temporal patterns of CRH release in push-pull cannulae implanted in the hypothalamic paraventricular nucleus of INT, INT + EA, OVX, and OVX + EA rats. Female Sprague Dawley rats (180 – 200 g), with regular 4 day estrus cycles were divided into four groups: intact (INT), intact with EA (INT + EA), ovariectomized (OVX), and ovariectomized with EA (OVX + EA). The acupoints used were Guanyuan (RN 4), Zhongji (RN 3), Zigongxue (EXTRA 22), and Sanyinjiao (SP 6). The stimulation was generated by an EA apparatus and lasted for 30 min (8:00 10:00 AM), once a day, total for 3 days. The stimulation parameters were 2 mA of density and a low burst frequency of 3 Hz.
One week after implantations, measurements were taken in free moving INT and OVX animals, as well as INT + EA and OVX + EA groups, 1 h before the beginning of the third EA treatment. Perfusion was collected at 0 h time point and at 10 min interval. The black line indicates the EA procedure for the third time. #$p<0.05$ vs. INT and INT + EA at the same time point, *$p<0.05$ vs. OVX at the same time point, **$p<0.05$ vs. OVX + EA at the time point of 30 min.

In our previous research, we observed the effects of EA on the adrenals of the experimental rats, which showed that the mean weight of the adrenals in the OVX + EA rats increased significantly than that in the OVX and intact (INT) rats, and that the level of argyrophilia of NOR proteins (AgNORs) in the reticulate zone of the OVX + EA rats was considerable more than that of the OVX and INT rats. This observation suggests that the adrenal function might be activated by EA (Chen and He 1992). In addition, the contents of blood corticosterone in the OVX + EA rats markedly increased, but showed no statistical difference when compared with those in the OVX and INT rats, providing further evidence that the adrenal cortex cells were activated in the OVX + EA rats (Gao et al. 1995). All these results suggest that EA may activate the adrenal compensatory mechanism in OVX rats.

15.3.4 Role of Extragonadal Aromatization

Aromatase is the key enzyme responsible for estrogen biosynthesis (Simpson

2003). Extragonadal aromatization has been generally recognized, although only recently, its significance is being appreciated. It has been reported that aromatization in the adipose tissue is not negligible under normal and pathological conditions. Hemsell et al first addressed the significance of adipose tissue as a major source of estrogen production, showing that there is a progressive increase in the conversion efficiency with advancing age, and that the increase of estrogen production is a function of obesity (Frost et al. 1980). In our study, increased aromatase protein expression was observed in the OVX and OVX + EA rats' subcutaneous abdominal (SA) adipose tissue. However, only in OVX + EA rats, an associated increase in the aromatase activity of the SA adipose tissue was observed (Fig. 15.5). Though it has been reported that the splanchnic tissue is a minor site for the extraglandular aromatization of androgens, a significant conversion of androstenedione to estrone by the liver tissues has been observed (Frost et al. 1980). In adult liver homogenates, C19 norsteroid (19-nortestosterone; NT) is observed to be readily aromatized to estrogens. We also observed that the aromatase activity of the liver tissues was higher in the OVX+EA rats than that in the INT and OVX rats, which is closely related to the elevated aromatase mRNA and protein expressions. In the final analysis, both the SA adipose and the liver tissues were observed to contribute to the effects of EA on extragonadal aromatization, to promote the concentrations of the circulating estrogen (Zhao et al. 2004a).

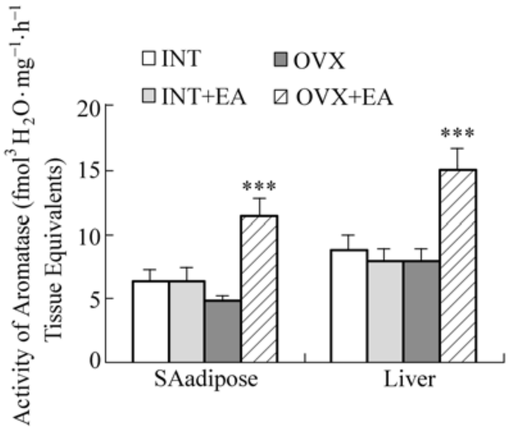

Figure 15.5 The aromatase activities in SA adipose and liver tissues of the INT, INT + EA, OVX, and OVX + EA rats. Female Sprague Dawley rats (180 – 200 g), with regular 4 day estrus cycles were divided into four groups: intact (INT), intact with EA (INT + EA), ovariectomized (OVX), and ovariectomized with EA (OVX + EA). The acupoints used were Guanyuan (RN 4), Zhongji (RN 3), Zigongxue (EXTRA 22), and Sanyinjiao (SP 6). The stimulation was generated by an EA apparatus and lasted for 30 min (8:00 – 10:00 AM), once a day, total for 3 days. The stimulation parameters were 2 mA of density and a low burst frequency of 3 Hz. ***p<0.01 vs. INT, INT + EA, and OVX.

It is well known that adrenal gland is the principle organ to secrete sexual hormones except ovarian hormones in females (Grodin et al. 1973; Meikle et al. 1991). Microsomal enzyme cytochrome, P450C17, is an important regulator of steroidogenesis. Its activity is abundant in the testis, lesser in the ovary, and low in the adrenal gland. The EA was observed to significantly enhance the mRNA expression of the enzyme in the adrenal cortex of the OVX rats. These results suggest that the androgen synthesis from the adrenal gland might be enhanced, and that subsequently more androgens might be aromatized into estrogen at the extragonadal sites, such as adipose and liver tissues.

The results including the changes in the blood steroids contents, the tissue aromatase activity, and our previous reports suggest that the effects of acupuncture in the regulation of HPOA may be exerted by enhancing the extraglandular aromatization and promoting the function of HPAA, thereby resetting the negative feedback of estrogen to HPOA.

Disruption of reproductive function in mammals is a well-known consequence of stress. However, given the potential effects exerted by a stressor, one can realize that each description of the response of the HPOA to the stimuli must be accompanied by the precise characterization of these stimuli. Sometimes, EA can be considered as a stressor for a conscious rat, owing to its strong electrical stimulation. However, in the clinical studies, the blood levels of corticosterone, which are considered to be the most reliable indicator of stress, detected in the same experimental animals, did not show any changes in the INT + EA model. It is known that stress increases the release and production of steroids from fat tissues. Glucocorticoids are known to increase aromatase expression in fat. However, the use of acupuncture to reduce anxiety and stress, possibly through its sympathinhibitory property and impact on the β-endorphin levels has been well reviewed, and is presumed to be an excellent alternative therapy for stress reduction in women undergoing infertility treatment.

15.3.5 Electroacupuncture Promotes the Homeostasis in Ovariectomized Rats

Acupuncture has long been known to promote natural functional homeostasis, and is observed to produce effects such as modulating the neurotransmitter function in the CNS (Clement et al. 1979; Kim et al. 2001) as well as adjusting the hormonal disturbance (Stener et al. 2002). We observed that the circulating E_2 levels (Zhao et al. 2005b), the liver and adipose aromatization (Zhao et al. 2005c), as well as the total content (ng/g tissue) of the hypothalamic CRH and the CRH mRNA expressions (Zhao et al. 2005b) increased gradually with time after ovariectomy in rats. All these results suggest that the EA stimulation might enhance the intrinsic compensational function for abnormal hypofunction of the HPOA in the ovariectomized rats (Zhao et al. 2003d).

15.3.6 Psychological Impact of Acupuncture

It is important to keep in mind that neurophysiological and humoral events are related to the psychological factors. Undoubtedly, sensory stimulation—particularly, acupuncture—has the potential to produce strong placebo effects. Acupuncture is probably one of the most effective nonpharmacological methods in terms of activation of the placebo effects. Indeed, acupuncture works by stimulating the endogenous opioids, thus, producing the placebo effects. To achieve optimal acupuncture therapy, physiological and psychological factors must synergistically interact and utilize their respective endogenous mechanisms efficiently (Sandberg et al. 2002).

Reports from China have stressed the importance of psychologically preparing the patients before surgery, when acupuncture analgesia is employed. The purpose of this preparation is to increase the effectiveness of the procedure and possibly to enhance the magnitude of the analgesia.

The importance of psychological factors before and during acupuncture treatment is further supported by the findings of increased concentrations of cholecystokinin (CCK) in both animals and humans during anxiety and panic attacks (Sandberg et al. 2002). As CCK is an antagonist of endogenous opioid, its increased concentrations may reduce or completely negate the positive effects of acupuncture treatment. Recently, it was reported that anxiety decreased pain thresholds. Thus, the therapeutic response depends on the complicated interaction between the factors and expectations of the patients, therapists, as well as treatment factors, including the specific and non-specific effects of the treatment. Therefore, it can be concluded that the treatment outcome depends on the patient's responsiveness to the entire therapeutic encounter.

15.4 Concluding Remarks

This chapter presented the experimental data on the effects of EA on OVX rats, which was obtained in the recent years in our laboratory, to provide the preliminary scientific background of acupuncture therapy. The experimental results suggest that the effects of acupuncture on the regulation of the hypofunction of HPOA in the OVX rats might be exerted by enhancing the extraglandular aromatization and by promoting the function of HPAA.

Till date, the use of acupuncture in reproductive medicine has not been well investigated. It has been observed that more than 40% of the people in the USA use some form of alternative treatment. Irrespective of whether there exists a true effect or not, it is necessary for the scientific community to investigate the effects of this method, as no other organization is better qualified to carry out this task. Furthermore, acupuncture is a very safe intervention if it is carried out by competent practitioners. The dangers of many traditional procedures are certainly greater, though no easy comparisons can be made. On the other hand, it must be pointed out that unless substantiated by research, the therapeutic use and acceptance of acupuncture cannot be extended in the future with confidence. It is obviously unethical to promise cure and recovery when the method used lacks evidence of an effect. Furthermore, it is also unscrupulous to disallow a method that demonstrably works.

We do agree that there are few well-designed papers on the effectiveness of the treatment methods that have not been generally established in the Western Medicine; however, we do not agree that they can best be summarized as “much ado about nothing”. We need to stick to the basics and have open scientific minds to determine the effectiveness and the underlying mechanisms of acupuncture.

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16 Acupuncture for Smoking Cessation

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Summary This chapter will introduce the research progress on the clinical application of acupuncture for smoking cessation and the underlying mechanism. The commonly used acupoints, acupuncture methods, and combination with other therapies will be briefly summarized with comments on their efficacy. Several lines of evidence show that acupuncture significantly improve the withdrawal symptoms. The mechanistic investigation suggests that acupuncture can change the gustatory sensation and mouth environment, regulate neuroendocrinology, and improve cardiorespiratory function. Lastly, we will comment on several unsolved issues concerning acupuncture treatment for smoking cessation.

Keywords *acupuncture, smoking cessation, addiction symptoms, withdrawal symptoms*

16.1 Introduction

It is well known that smoking is harmful to health. The objectionable constituents of cigarette, especially nicotine, tar, benzopyrene, and nitrogen monoxidum may cause or worsen hypertension, coronary heart disease, chronic bronchitis, pulmonary emphysema, and even induce cancers and congenital malformations of fetus. However, once the smokers try to give up or reduce smoking, a series of addiction symptoms arises, such as craving for tobacco, dysphoria, irritability, anxiety, difficulty in concentrating, restlessness, nausea, drooling, tiredness, increased hunger, etc. Nicotine-dependence disorder is a form of substance abuse that leads to clinically important impairment or distress. As a result of persuasion and education by government and society, more attention and methods are being adopted to help smokers quit. Till date, psychotherapy, behavioral therapy, and pharmacotherapy have been employed for smoking cessation, but the effect is far from satisfaction (Yang 2006).

Acupuncture is a convenient and cost-effective therapy with relatively less side-effects. Acupuncture treatment for smoking cessation began in the 1970s in the USA. Soon after, both clinic treatment and mechanism research on acupuncture treatment for smoking cessation began in China as well as many other countries. It has been reported that acupuncture has a role in reducing the desire for cigarettes, easing the nervous and tensed mood, and improving the immunity and sensory function (vision, sense of smell, taste, touch, and intuition), thus, improving the health condition of the smokers on the whole.

16.2 Researches on Smoking Cessation

In 1996, the American Agency for Health Care Policy and Research developed recommendations for the physicians to treat smokers. This recommended approach is often referred to as "the 5 As", and its five steps are presented in Table 16.1.

Table 16.1 The five steps (5 As) for smoking cessation*

Step 1	*Ask* *Systematically identify all patients who smoke* ("vital sign" stamp that includes smoking status)
Step 2	*Advise* *Strongly advise all who smoke to quit* (Tailor the advice towards the patients' clinical situation)
Step 3	*Assess* *Assess the patient's willingness to quit* (Ask every patient if he or she is willing to attempt to quit. If the patient is not ready, then provide motivational intervention to promote future attempts)
Step 4	*Assist* *Assist patients in their efforts to quit* (Pharmacotherapy and counseling)
Step 5	*Arrange* *Schedule a close follow up* (Follow ups should occur around the date when the patient stops smoking)

* Adapted from the Agency for Health Care Policy and Research (13), with permission from JAMA. 1996; 275: 1270 1280. Copyright 1996, American Medical Association.

The nonpharmacologic methods for smoking cessation mainly include counseling and tobacco withdrawal. Physician's communication about the benefits of smoking cessation and encouragement to quit has been proved to be very successful. A study by Pederson et al (1991) showed that among the hospitalized patients with chronic obstructive pulmonary disease, the counseled group exhibited higher cessation rates, observed at the 6-month follow-up. All the patients were advised to quit smoking, and half of the patients were provided with a self-help manual and brief 15 – 20 min counseling sessions. The cessation rates at 6 months were 33% in the counseled group, and only 21% in the control group (Pederson et al. 1991). Another nonpharmacologic method is tobacco withdrawal. In a study on 554 patients who were attempting to quit smoking without assistance, 87% (482/554) of the subjects reported withdrawal symptoms during the first week of follow-up (Gritz et al. 1991).

Pharmacologic methods of smoking cessation include nicotine polacrilex gum, transdermal patch, nicotine nasal spray, and nicotine inhaler (Table 16.2) (Karnath 2002). In a study examining whether the preference for a nicotine replacement product is correlated with the abstinence rates, no difference was observed at 15 weeks of follow-up. Furthermore, the subjects were allowed to rank their preference for a nicotine replacement product (gum, patch, nasal spray, or inhaler). Those who smoked heavily preferred the spray or inhaler, but overall, the patch was the most preferred product (Hajek et al. 1999). Though persons who have been trying to quit smoking are recommended to receive pharmacotherapy for smoking cessation, the subsequent side-effects and the costs are major problems. In addition, some people like pregnant women, adolescents, and breast-feeding mother should not use pharmacologic treatments.

Table 16.2 Pharmacotherapy for Smoking Cessation

Pharmacotherapy	Side-effects	Dose	Pharmacokinetics	Duration
Nicotine gum	Dyspepsia, jaw ache	2 mg gum if <25 cigarettes smoked daily; 4 mg gum if >25 cigarettes smoked daily	30 min	Up to 12 weeks
Nicotine inhaler	Throat irritation, coughing	6 – 16 cartridges daily	30 min	Up to 6 months
Nicotine nasal spray	Nasal irritation, rhinorrhea, coughing	8 – 40 doses daily	10 min	3 – 6 months
Nicotine patch	Local skin reaction	21 mg/24 h 14 mg/24 h 7 mg/24 h 15 mg/16 h	6 h	4 weeks 2 weeks 2 weeks 8 weeks
Sustained release of bupropion hydrochloride	Dry mouth, insomnia, contraindicated in seizure disorder	150 mg daily for 3 days, then 150 mg twice daily		7 – 12 weeks

Adapted from Karnath B. (2002). Smoking cessation. The American Journal of Medicine 112: 401.

16.3 Clinical Application of Acupuncture for Smoking Cessation

A variety of acupuncture approaches, including electroacupuncture, auriculo-acupuncture, nasal-acupuncture, and a combination of acupuncture and medicine, have been used in acupuncture therapy for smoking cessation (Han and Li 2006). The commonly selected acupoints are located at Yangming Lung Meridian of the hand, Shaoyin Heart Meridian of the hand, and Yangming Stomach Meridian of the foot. The concrete body acupoints include Yinxiang (LI-20), Hegu (LI-4), Zhusanli (ST-6), Shenmen (HT-7), Neiguan (PC-6), Lieque (LU-7), Sanyinjiao (SP-6), Baihui (GV-20), Taiyuan (LU-9), Yintang (Ex-HN3), Feishu (BL-13), and Xinshu (BL-15); and the common auriculo-acupoints are Ear-Shenmen, Lung, Stomach, Heart, Sympathetic Nerve, Mouth, Nose, and Hungry spot (Cui 1996).

16.3.1 Body Acupuncture

Tianmei is a new extra-meridian acupoint, which was named by an American doctor, Olms, in the 1970s (Olms 1981). It is a magical acupoint, and Dr. Olms himself quitted his 40 years of smoking after only a single acupuncture treatment on this acupoint. It is located at the wrist, at the line joining the acupoint Lieque (LU-7) of the Taiyin Lung Meridian of the hand and acupoint Yangxi (LI-5) of the Yangming Large-Intestine Meridian of the hand, a depressed spot between the tendons of the musculus extensor pollicis brevis and radial styloid (Fig. 16.1). A 1-cun needle is straightly punctured about 3 – 4 mm like a key inserted into a lock. Thereafter, the needle is rotated moderately and retained for 15 min. After acupuncture treatment, the smokers may feel numbness in the hand and heaviness, as well as the taste of tobacco may become bitter, tasteless, abnormal, or sweet. Moreover, some patients even reported dizziness and nausea when they smoked again. In 1981, Olms treated 5000 cases using only the acupoint Tianmei, and the effect rate was 80% (Olms 1981). In another study, a total of 19 American cases were treated using the acupoint Tianmei, out of which 15 cases quitted smoking completely, and the total effect rate was 84.2% (Tan 1996). Therefore, acupuncture on the acupoint Tianmei is considered to help smokers to relieve the desire for cigarette and quit smoking completely (Wang 2001).

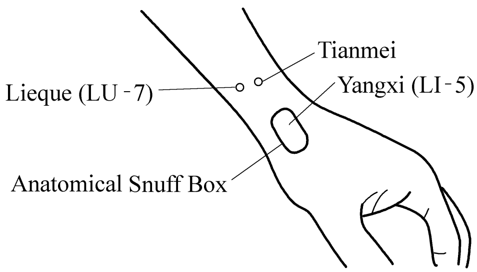


Figure 16.1 The location of Tianmei. Tianmei is a new extra meridian acupoint, which was named by an American doctor, Olms, in the 1970s (Olms 1981). It is located at the wrist, at the line joining the acupoints Lieque (LU 7) of the Taiyin Lung Meridian of the hand and the acupoint Yangxi (LI 5) of the Yangming Large Intestine Meridian of the hand, and is a depressed spot between the tendons of musculus extensor pollicis brevis and radial styloid.

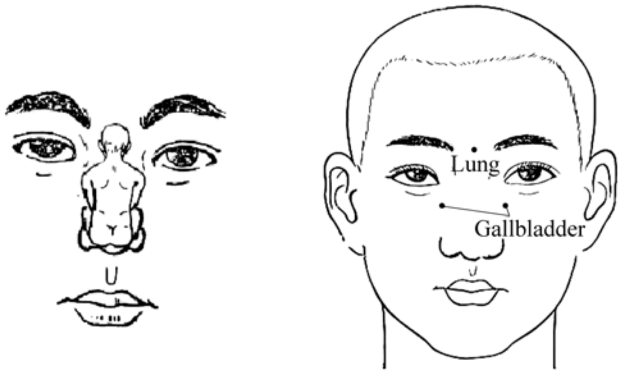
In another study, the acupoints Chuanzhu (BL-2), Sibai (ST-2), Yinxiang (LI-20), Zhongfu (LU-1), Quchi (LI-11), Shousanli (LI-10), Qiyangguan (GB-33), Sanyinjiao (SP-6), Taicong (LR-3), Yifeng (SJ-17), and Fengchi (GB-20) were used for the first treatment, with intermittent stimulation, and retaining of the needles for 20 – 25 min. For the second treatment, the acupoints Quhuan (SI-13), Tianzhong (SI-11), Fengmen (BL-12), Feishu (BL-13), Jueyinshu (BL-14), Xinshu (BL-15), Dushu (BL-16), Geshu (BL-17), Ganshu (BL-18), Zhishi (BL-52), Huantiao (GB-30), Weiyang (BL-39), and Chengshan (BL-57) were used, and subsequently, the first treatment was repeated. Appropriate needles were selected for different acupoints, with intermittent stimulation and retaining of the needles for 30 min. Electric stimulation was provided from the acupoint Fengmen (BL-12) to the acupoint Ganshu (BL-18), and the treatment was given every 2 or 3 days. The effect rate of the 639 cases treated reached 98.28% after 1 or 4 treatments (Dung 1984).

16.3.2 Auriculo-acupuncture

Xu and Li (1990) adopted the Ear-Shenmen, Lung, and Mouth acupoints as the key acupoints, along with Ear Airway, Endocrine, and Adrenal Gland for treating serious symptoms. A 0.5-cun needle was inserted with the needle body at an angle of 45° to the surface of the skin, until the needle tip reached the ear cartilage, and the needle was retaining for 15 – 20 min. Subsequently, the Cowherb seeds (sometimes, special magnetic beads of about 1 mm) were embedded into the acupoints of the other ear after acupuncture treatment. Once a day, both the ears were alternatively treated for 10 times, which made up one treatment course (Xu and Li 1990). The needles were inserted quickly and slightly on the Ear- Shengmen, Sympathetic Nerve, Lung, Heart, Stomach, Airway, Liver, Spleen, and Mouth acupoints after sterilization by perpendicular or oblique needling. Needles were generally left in the acupoints for 30 min, and were rotated for every 5 min in both the ears alternatively. However, attention must be paid to avoid puncturing the cartilage of the helix, and it is recommended to press expertly. The treatment course was once a day for 7 days. The effective rate was about 80% when the treatments ended (Yang and Yang 2000). In another study, Choy et al embedded a wheat-seed-like intradermal needle at the Ear-Hungry acupoint in the two ears alternatively, and subsequently fixed it with rubberized cloth, once a week for 4 weeks, until the smokers quitted smoking completely. About 87.6% of the 339 cases treated quitted smoking completely, and 152 cases among the 220 cases did not smoke again in the 2-year follow-up (Choy et al. 1983).

16.3.3 Nasal Acupuncture

In nasal acupuncture therapy, the acupoints on the nose are selected and provided acupuncture treatment. The distribution of the nasal acupoints is similar to a person sitting down with his back towards the readers (Fig. 16.2(a)). Though the nasal acupoints were seldom used in smoking cessation by acupuncture, the use of Nasal-Gallbladder (the crossing point of the highest point of the bridge of the nose and the line of the inner canthus) or Lung (the midpoint of the two eyebrows) acupoints were reported (Fig. 16.2(b)). In an earlier study, 14 patients were exposed to a 3-mW helium-neon laser for 1 min, once a day for 3 days with an interval of 4 days, for 2 weeks. After 2 weeks, 8 (57.1%) out of the 14 cases quitted smoking completely or significantly reduced the number of cigarettes smoked (Tan et al. 1987).



(a) (b)

Figure 16.2 The conceptual diagram of nasal acupoints and the location of Nasal-Gallbladder and Lung acupoints. (a) The distribution of nasal acupoints is like a person sitting down with his back towards the readers; (b) Nasal Gallbladder acupoint is located at the crossing point of the highest point of the nose bridge and the line of the inner canthus, and Nasal Lung acupoint is located at the midpoint of the two eyebrows.

16.3.4 Combination Therapy

In combination therapy, more than one techniques such as acupuncture, auricular-acupuncture, nasal acupuncture, electroacupuncture, helium-neon laser, cupping, and herbs are selected and provided to the patients according to their needs. Different treatments are observed to supplement each other and enhance the outcome.

In an earlier study, the Ear-Lung acupoint was chosen as the key acupoint along with the acupoints Hegu (LI-4), Tongli (LI-7), Neiguan (PC-6), Taicong (LR-3), Zhusanli (ST-6), Chibian (BL-54), Feishu (BL-13), Xinshu (BL-15), Fengchi (GB-20), Tianzhong (CV-17), and Qihai (CV-6). The U-type needles were embedded at each acupoint once every other day in the first week, twice in the second week, and once a week from the third to the sixth week. About 389 cases quitted smoking over 6 months, and 102 cases reduced the number of cigarettes smoked from 20 to 4 or 5 in 6 months. The quit rate was 60.59% and the effect rate was 76.48% (Sacks 1975). In another study, the Ear-Shenmen, Lung, Sympathetic, and Subcortex acupoints were used along with Hegu (LI-4) acupoint. The needles were inserted into the auricular-points at the depth of 2 mm, and into the body acupoints at the depth of 10 mm. All the acupoints were activated (*De-Qi*). The needles were left in place for 45 min, for 5 days a week (from Monday to Friday), a total of 6 weeks (Avants et al. 1995). Furthermore, Li et al (2000) inserted the needles at the body acupoints quickly and rotated them until the *De-Qi* was achieved. The G6805 electroacupuncture apparatus was used on the acupoints Lieque (LU-7) and Kongzui (LU-6) with continuous wave of 200 Hz. Cuppings were used on the acupoints Feishu (BL-13) and Weishu (BL-21), and the needles were embedded in the cups. The needles were left in the acupoints for 30 min, with the cupping for 15 min, once a day. A total of five acupuncture treatments made up one treatment course (Li et al. 2000). In another study, Olms (1981) adopted the acupoint Tianmei along with the Nasal-Gallbladder and Ear-Attack acupoints for smoking cessation. He applied silver needles on Tianmei and Ear-Attack acupoints, and subsequently exposed them to helium–neon laser for 10 min. The apparent effect appeared immediately after one treatment, and the effect of 2822 cases was as high as 90% (Olms 1981).

16.4 Mechanisms of Acupuncture Therapy for Smoking Cessation

Till date, the mechanism of acupuncture for smoking cessation is still unclear. It is also difficult to carry out studies on this issue, owing to the lack of general standard for animal models and evaluation of the effect. Most mechanisms of acupuncture therapy for smoking cessation are hypotheses based on clinical observations. The possible mechanisms are presumed to be related to gustatory sensation and mouth environment, neuroendocrinology, and cardiorespiratory function.

16.4.1 Gustatory Sensation and Mouth Environment

Some researchers found that acupuncture treatment for smoking cessation is related to change in the gustatory sensation. The long-term smokers were examined for the threshold of bitterness, saltiness, sweetness, and sourness. It was found that the threshold of bitterness increased by 8%, as the long chain organics and alkaloid (including nicotine) is presumed to produce the bitter taste as well as because of the fact that the root of tongue is sensitive to bitterness. Owing to the use of nicotine and being non-sensitive to bitter taste for a long time, the threshold of bitterness was observed to increase. However, after acupuncture treatment, the smokers' taste of cigarette changed into bitter, tasteless, abnormal, or sweet, and resulted in the loss of the desire to smoke (Fang 1999). Zhang (1990) tested the pH values of the saliva in the mouth of the smokers and showed that the pH value was higher than normal. However, after acupuncture treatment, the pH value was found to decrease. Therefore, it is believed that smoking might change the internal environment of the mouth, gullet, as well as stomach. Moreover, acupuncture treatment is considered to lead the smokers to feel bitterness, experience paralysis, cough, and dizziness symptoms when they smoked again, by regulating the internal environment of the mouth and whole body (Zhang 1990).

16.4.2 Neuroendocrinology

Pituitary ACTH (adrenocorticotrophic hormone) and blood endorphin were observed to increase in smokers. The plasma amidocaproic acid increased rapidly from 106.4 ± 8.9 pg/ml to 187.3 ± 16.5 pg/ml after inhaling only one cigarette, but decreased to 166.0 ± 8.8 pg/ml after acupuncture, which suggests that acupuncture may play a key role through the regulation of meridian and nervous system, as well as the blood leucine-endorphin balance. In addition, the contents of adrenaline, noradrenalin, dopamine, and dioxyphenylalanine (DOPA) were tested before and after acupuncture treatment. The results showed that the contents increased in long-term smokers, but decreased after auriculo-acupuncture treatment (Fang and Li 1985).

16.4.3 Cardiorespiratory Function

Another paper reported that pulmonary perfusion of the adult smokers obviously increased, but tended to become normal after acupuncture treatment on the acupoint Kongzui (LU-6), suggesting that this acupoint could improve the blood flow, and supply enough blood and oxygen to the lung tissues (Wu et al. 1996). Furthermore, the blood carbonylhemoglobin was observed to be higher in smokers; the inner and outer environment of the erythrocytes changed and affected the fluidity of the membrane lipid zone. This might be the direct action of nicotine or a series of responses to nicotinic derivants. However, acupuncture is believed to reverse the effect of nicotine on the fluidity of membrane lipid zone, suggesting the role of acupuncture treatment for smoking cessation (Li 1984).

16.5 Theory of Traditional Chinese Medicine in Smoking Cessation

According to the theory of TCM, the nose and mouth are the openings of lung and spleen, respectively, on the exterior part of the body. According to the theory of *Zang-fu* organs, the lung and the large intestine, as well as the spleen and the stomach, are the exterior-interior organs for each other. During smoking, smoke is inhaled through the mouth and released through the nose. Hence, the smokers usually exhibit the heat-evil symptoms of the lung and stomach, such as cough with yellow sticky sputum, pain in the chest, xeromycteria, constipation, anorexia, xerostomia, halitosis, etc. Furthermore, smokers generally have a red tongue with yellow coating, and rapid pulse. Therefore, the principle of acupuncture treatment for smoking cessation is to clear away the heat-evil of the lung and stomach (Fig. 16.3). The commonly used acupoints for the treatment of smoking cessation are the Yinxiang (LI-20), Hegu (LI-4), Zhusanli (ST-6), Lieque (LU-7), Feishu (BL-13), and Weishu (BL-21).

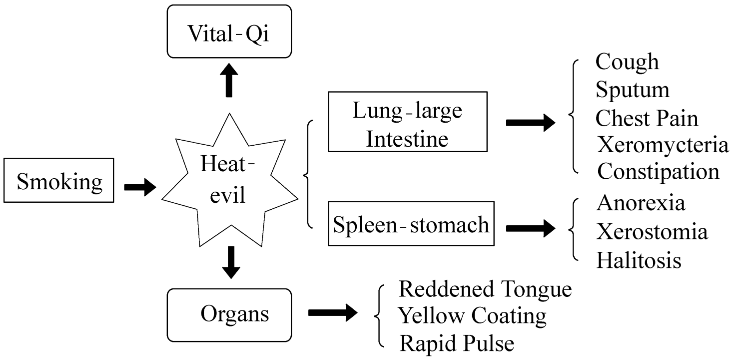


Figure 16.3 The pathogenesis of smoking according to TCM theory. Smokers usually present the heat evil symptoms of the lung and stomach, such as cough with yellow sticky sputum, pain in the chest, xeromycteria, constipation, anorexia, xerostomia, halitosis, etc. They generally have red tongue with yellow coating, and rapid pulse. Therefore, the principle of acupuncture treatment for smoking cessation is to clear away the heat evil of lung and stomach.

16.6 Concluding Remarks

As evidenced by many researches, the desire of the smokers to smoke is very important for the long-term effect of acupuncture treatment. However, it has been proved that acupuncture does not produce immediate effects. Researchers also found that the psychological factor of acupuncture treatment was principally from the support of therapists, but not the smokers themselves. Therefore, it is hard to regard acupuncture only as a placebo therapy. When combined with the psychological and behavioral therapies, the effect of acupuncture treatment is observed to be better (Cui and Jiang 1992). Sun (2000) randomly divided 60 patients into two groups: auriculo-acupoints group and auriculo-acupoints with psychological treatment group. The patients of the latter group were given a professional introduction, transference, teaching, and rising morale. The results showed that there was obvious differences between the two groups, and the withdrawal symptoms of the auriculo-acupoints group, when compared with the auriculo-acupoints with psychological treatment group, were less and statistically insignificant.

In summary, as a nature therapy, acupuncture is considered to be effective for smoking cessation, as it is presumed to regulate the whole body. However, there are still many problems that need to be addressed in the future, such as high recurrence rate, unstable immediate effects, etc.

When compared with the pharmacologic or psychological methods, acupuncture therapy is observed to be unique and effective. However, owing to limited mechanistic researches, its use and development in the clinic environment is still not widespread. As the study on the effects of acupuncture treatment for smoking cessation has been carried out since the past 30 years, more work on the clinical study or basic research is believed to provide greater insight and offer great help to patients who are attempting to quit smoking.

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17 Beneficial Effect of Acupuncture on Depression

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Summary This chapter presents the clinical and laboratory evidence regarding the effect of acupuncture on depression and its potential mechanisms. Most of the clinical studies have demonstrated that either acupuncture alone or acupuncture combined with other therapies has a therapeutic effect on subjects with depression. There were significant differences in the scores of Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Depression (HAMA) before and after treatment with acupuncture in patients suffering from depression. The adverse effects were less and milder in the group under acupuncture treatment than in those under regular medication. Studies on the mechanisms of acupuncture suggest that acupuncture or electroacupuncture (EA) could change the concentrations of monoamine neurotransmitters and their metabolites in the brain, which was determined by high-performance liquid chromatography-electrochemical detection (HPLC-ECD). Acupuncture signals were also observed to modulate the immune system and improve the function of neuroendocrine system, especially the hypothalamus-pituitary-adrenal (HPA) axis. There are also evidences implying that the regulation of intracellular signal transduction is involved in the antidepressant-like effect of EA treatment. Lastly, the hippocampus, an important brain structure that plays a key role in the etiology of depression, has been observed to be involved in the mechanism of acupuncture. In an earlier study, the neuropeptide Y-immunoreactive cells in area CA1 and the dentate gyrus (DG) of the hippocampus were observed to decrease in the depressed animals, but significantly increase in the acupuncture-treated animals. In addition, acupuncture was observed to attenuate the decrease in the hippocampal progenitor cell proliferation, and increase the number of the neurons containing the brain-derived neurotrophic factor (BDNF) in the hippocampus of the depressed animals.

Keywords *depression, acupuncture, hippocampus, neurogenesis, BDNF*

17.1 Introduction

Depression is a common and serious psychological disorder, affecting people of all ages, backgrounds, and ethnic groups. Psychologist Martin Seligman addressed depression as the "common cold" of psychological problems, because nearly everyone suffers from it at some time point. In the USA, depression is extremely common and is one of the ten most-frequently reported medical conditions (Eisenberg et al. 1993). It is estimated that 9.5% of the population, or about 20.9 million American adults suffer from a depressive illness each year (Robins and Regier 1990), and that approximately 16% of the population suffer from depression at least once in their lives (Bland 1997). Furthermore, according to the World Health Organization (WHO), depression is currently the leading cause of disability in the USA as well as other countries, and is expected to become the second leading cause of disability worldwide (after heart disease) by the year 2020 (Murray and Lopez 1997).

Clinical depression is a real medical condition and is different from the term "being depressed" that is used frequently. It is a "whole-body" illness, involving the body, mood, and thoughts, which presents with depressed mood, loss of interest or pleasure, feeling of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These symptoms linger, intensify, and lead to substantial impairments in an individual's social functioning and/or activities of daily living. In other words, depression can interfere with a person's normal functioning, and frequently disrupt the work, social, and family adjustment. It makes a person feel sad or hopeless most of the time and lose interest in things that were once enjoyed. It affects the way a person eats and sleeps, the way one feels about oneself, and the way one thinks about things. People who suffer from depression usually struggle to do even the simplest things. Depressive episodes can last for weeks, months, or years if left untreated. The economic cost for this disorder is high, but the cost of human suffering cannot be estimated. It causes pain and suffering not only to those who have the disorder, but also to those who care about them. Serious depression can destroy family life as well as the life of the depressed person.

There are a variety of antidepressant medications and psychotherapies that can be used to treat depressive disorders. Psychological treatment of depression (psychotherapy) assists the depressed individual in several ways, which include supportive counseling, cognitive therapy, and problem-solving therapy. Some people with milder forms of depression may respond well to psychotherapy alone, while those with moderate to severe depression most often benefit from antidepressants. Most of the patients respond best to combined treatment: Medication—to gain relatively quick symptom relief, and psychotherapy—to learn more effective ways to deal with life's problems, including depression. Electroconvulsive therapy (ECT) is useful, particularly for individuals who suffer from severe or life threatening depression or who cannot take antidepressant medication (Sackeim et al. 1990). However, conventional treatments like psychotherapy and medication can alleviate the symptoms in a whopping 50% – 70% of patients who complete the regimen; however, about one-third of the patients who begin therapy never complete it, because they may not observe any improvement or may experience debilitating side effects. Even among people who recover from depression, more than one-third revert back within 18 months. In addition, most empirically supported psychotherapies are also not readily available or affordable. Hence, there is a need for safe, effective, and affordable alternative treatments for depression. Traditional Chinese Medicine (TCM) is the major form of healthcare for more than 20% of the population worldwide, and according to the 2002 National Health Interview Survey, an estimated 2.1 million American adults had used acupuncture in the previous year (Barnes et al. 2004). Acupuncture originated in China at least 3000 years ago, and moved to the west in the 1970s. It is a type of therapy that involves inserting needles into the acupoints along the body's meridians. Electroacupuncture (EA) uses needles that are electrically stimulated. Initially, its availability was limited owing to the scarcity of practitioners, however, currently, there are an estimated 20,000 certified acupuncturists in the USA, and one-third of them are medical doctors. According to the Food and Drug Administration (FDA) figures of 1993, Americans make 9 – 12 million visits a year and spend as much as $500 million to have the needles strategically placed along the invisible latitude and longitude lines of their skins. However, does acupuncture work for depression? This chapter summarizes the therapeutic practice and mechanistic research on acupuncture treatment for depression.

17.2 Clinical Trials

The clinical practice of acupuncture as a sole therapy or in combination with other therapies to treat depression based on TCM identification and treatment pattern is already in use. Some examples of typical clinical cases will be discussed in the following sections. Simultaneously, we will also list some of the commonly used acupoints for the treatment of depression.

17.2.1 Acupuncture as a Sole Therapy

Increasing clinical studies in China have started to examine the effect of acupuncture on depression. In these studies, either the primary or secondary depression has been addressed, although there are some studies without double-blinded control. These clinical data give us some indications that acupuncture can be utilized as a therapy for depression.

The latest remarkable report on *Chinese Acupuncture and Moxibustion* (*Zhongguo Zhen Jiu*) in 2008, described a multi-centered randomized controlled double-blinded clinical study carried out in China from 2004 (Fu et al. 2008). A total of 440 patients with depressive neurosis, a subtype of depression, were employed in this study, and were divided into three groups: an acupuncture group, a non-acupoint needling group, a Prozac group. In the acupuncture group, the patients were treated with standardized acupuncture manually, on acupoints, such as Hegu (LI-4), Taichong (LR-3), Baihui (GV-20), Yintang (EX-HN-3), and some auricular acupoints. On the other hand, needling the points that deviate from the acupoints was prescribed for the non-acupoint group, as a control treatment. The other medication group was administered with 20 mg/d of fluoxetine. The therapeutic effect was evaluated by Hamilton Rating Scale for Depression (HAMD) score reduction rate. Asberg's antidepressant side effect rating scale (SERS) and severe adverse reaction were used for safety evaluation. Subsequently, the data were analyzed with Intention-To-Treat (ITT) by blinded assessors. After 12 weeks of treatment, no significant difference was observed in the HAMD score between the acupuncture and fluoxetine group, and the total effective rates were 86.4% (acupuncture), 59.1% (non-acupoint needling), and 72.7% (fluoxetine). The SERS scores of the acupuncture and non-acupoint needling groups were significantly lower than that of the fluoxetine group. These results demonstrate more positive clues that acupuncture is an effective and safe therapy for depressive neurosis. The therapeutic effect of acupuncture on depressive neurosis is observed to be possibly better than or similar to fluoxetine, but with less side effects. Thus, the well-designed clinical trials carried out in multi-centers with strict control provided further evidence on the clinical applications of acupuncture.

In 2007, another pilot study was published on *the Chinese Journal of Integrated Traditional and Western Medicine* (*Zhongguo Zhong Xi Yi Jie He Za Zhi*) (Li and Liu 2007). A total of 56 depressed patients (from mild to severe) were randomized into two groups: acupuncture group and medication group. The researchers selected the dominant acupoints, such as Fengchi (GB-20), Anmian (EX-HN-22), Sishencong (EX-HN-1), Yintang (EX-HN-3), Baihui (GV-20), Shenmen (HT-7), Jianshi (PC-5), Hegu (LI-4), Taichong (LR-3), Sanyinjiao (SP-6), Qiuxu (GB-40), Shuaigu (GB-8), Zusanli (ST-36), and other auxiliary acupoints, to relieve the patient from depression and regulating the mentality. Manual acupuncture and EA were combined to treat the patients, and fluoxetine (20 mg/d) and paroxetine (20 mg/d) were prescribed as control medications. The therapeutic effect was also evaluated using HAMD score reduction rate. The total effective rates were 87.5% (acupuncture) and 79.1% (medication). Furthermore, the therapeutic effect appeared earlier and lasted longer in the acupuncture group than in the medication group. However, this study did not monitor the side effects of acupuncture and did not set up the sham-acupuncture control and double-blinded assessment systems. Nevertheless, this study further suggests that acupuncture could be a promising therapy for depression.

Another research on the effect of EA on depression was performed by Han et al in the early twenty-first century. To compare the efficacy of EA and maprotiline in the treatment for depression, 30 patients suffering from depression were administered with EA and 31 patients with maprotiline, orally. The EA was administrated at the dominant acupoints, such as Baihui (GV-20), Yintang (EX-HN-3), and the auxiliary acupoints. The therapeutic efficacy and side effect were evaluated with the scores of HAMD, Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), Clinical Global Impression (CGI), and Asberg's SERS, before treatment and on the day 14, 28, and 42 of the therapeutic course. The results exhibited that the scores of HAMD and SDS significantly decreased after the treatment, but no significant difference was observed between the groups. With regard to the patients with somatic syndrome, the HAMD score rate was obviously lower in the EA group than that in the maprotiline group. Among the patients with anxiety/somatic syndrome, the scores of SAS and SERS in the EA group were significantly lower than those in the maprotiline group. Moreover, the efficacy index was higher in the EA group. These results suggest that both EA and maprotiline are effective remedies for depression. The EA as a sole therapy is presumed to produce the same clinical therapeutic effect as that produced by the tetracyclic drug, maprotiline, with less side effects and better symptomatic improvement (Han et al. 2002a, 2004a).

Furthermore, a randomized controlled study focused on the female patients with climacteric depression, a subtype of secondary depression was carried out (Zhou and Wu 2007). A total of 60 cases were examined and randomly assigned to acupuncture group and medication group. Manual acupuncture was administered individually on the acupoints Ganshu (BL-18), Shenshu (BL-23), Xinshu (BL-15), Zusanli (ST-36), Sanyinjiao (SP-6), Shenting (GV-24), Benshen (GB-13), Sishencong (EX-HN-1), and other auxiliary acupoints. As a control therapy, 20 mg/d of fluoxetine was administered to the medication group. The therapeutic effect was also evaluated by HMAD score reduction rate. Though the side effects were not monitored, the levels of dopamine (DA), norepinephrine (NE), and 5-hydroxyindoleacetic acid (5-HIAA) in the blood were detected before and after the therapeutic course. The total effective rates were 86.7% (acupuncture) and 92.9% (fluoxetine), with no significant differences between the groups. However, HAMD scores reduced faster and were lower in the fluoxetine group than the acupuncture group. These two therapies were observed to elevate the blood DA, NE, and 5-HIAA concentrations in patients. Although the results imply that acupuncture can improve the climacteric depression, the clinical implications of acupuncture on this condition must be investigated further.

Three clinical studies on the efficacy of acupuncture in the treatment of post-stroke depression (PSD), another subtype of secondary depression, were carried out (Dong et al. 2007; Liu et al. 2006; Zhang 2005). Dong et al (2007) randomly allocated 108 PSD patients to three groups: a point-through-point EA group; a nonpoint-through-point EA group (traditional EA group); and a medication group.

Fluoxetine (20 – 80 mg/d) was also administered as the control medication. The HAMD score reduction rate and the SDS self-rating scores were employed to evaluate the therapeutic effect. After a 30-day therapeutic course, the point-through-point EA group demonstrated a total effective rate of 86.84%, which was better than that obtained by the nonpoint-through-point group (63.89%) and the fluoxetine group (67.65%). Liu et al (2006) employed 560 cases and rated them using HAMD scale. Furthermore, the lesion parts, gender, age, and property of the stroke between the PSD and non-PSD patients were compared using analysis of variance and χ^2 test. Subsequently, the PSD patients were randomly divided into two groups and treated respectively, with Prozac-20 and acupuncture-moxibustion on the acupoints Sishencong (EX-HN-1), Anmian (EX-HN-22), Neiguan (PC-6), Shenmen (HT-7), Zusanli (ST-36), Sanyinjiao (SP-6), Taichong (LR-3), Zhaohai (KI-6), and Shenmai (BL-62). The total incidence rate of PSD was 43.9%, with no relation to the lesion parts, gender, age, and property of the stroke. However, between the two groups, obvious significant differences were observed in the HAMD scores before and after treatment, and no significant difference was found in the effective rate. The results show that PSD has a high incidence and influences the recovery of nervous function, and should be treated at an early stage. Acupuncture-moxibustion and Prozac-20 were observed to have similar therapeutic effect on PSD. In the clinical trial performed by Zhang (2005) in another city of China, 90 PSD patients were randomly divided into two groups, each comprising 45 cases. In the acupuncture group, Neiguan (PC-6), Renzhong (GV-26), Sanyinjiao (SP-6), Baihui (GV-20), and Shenmen (HT-7) were selected as the dominant acupoints. On the other hand, the oral medication of fluoxetine (20 mg/d) was prescribed for the control group. Only the HAMD scores were used to evaluate the therapeutic effect. The total effective rate in the treatment group was 77.7% and that in the control group was 75.1%, showing no significant difference between the two groups. Although different acupoints and different forms of acupuncture were used, both the results provided more evidences supporting the beneficial effects of acupuncture on PSD.

In China, numerous clinical researches have focused on the antidepressant-like effect of acupuncture or EA on depression, in the last century. In one study, 68 participants who did not take any mood-altering drugs (11 with anxiety, 8 with depression, and 49 with both anxiety and depression) were recruited to assess the impacts of acupuncture on anxiety and depression symptoms in patients with chronic disease (Tao 1993). A TCM practitioner evaluated and diagnosed each individual’s condition and determined the appropriate acupoints to be used in treatment. The results showed a statistically significant reduction in both anxiety and depression, 1 month after acupuncture treatment. Luo et al (1998) performed two consecutive clinical trials on the treatment of depression using EA. The first study was double-blinded placebo-controlled, in which 29 depressed inpatients were included. The patients were randomly divided into three groups: EA + placebo, amitriptyline, and EA + amitriptyline groups. The patients received EA and/or amitriptyline treatment for 6 weeks. The HAMD, CGI, and SERS scores of the patients were used to evaluate the therapeutic efficacy and side effects. In addition, based on the results and research protocol of the previous study, a multi-centered collaborative study was conducted, in which 241 inpatients with depression were included. The patients were randomly divided into two treatment groups: the EA + placebo and the amitriptyline groups. The results from both the studies showed that the therapeutic efficacy of EA was similar to that of amitriptyline for the treatment of depressive disorders. However, EA demonstrated a better therapeutic effect on anxiety somatization and cognitive process disturbance of the depressed patients than amitriptyline. Moreover, the side effects of EA were much lesser than those of amitriptyline. These results suggest that EA treatment could be an effective therapeutic approach for depressive disorders. Particularly, it can be a beneficial choice for depressed patients who could not comply with the classic tricyclic antidepressants owing to their anticholinergic side effects.

To further scientifically confirm the efficacy of acupuncture on depression and improve the clinical application, it is very important to carry out well-designed clinical trials of randomized controlled double-blinded protocol. Accordingly, in the USA, a randomized controlled clinical trial was performed (Manber et al. 2004). The aim of this pilot study was to determine whether acupuncture holds promise as a treatment for depression during pregnancy. A total of 61 pregnant women with major depressive disorder (MDD) and a HRSD17 (17-item Hamilton Rating Scale for Depression) score $\geqslant 14$ were randomly assigned to one of the three treatments delivered over 8 weeks: an active acupuncture (SPEC = special acupuncture, $N = 20$); an active control acupuncture (NSPEC = non-special acupuncture, $N = 21$); and massage (MSSG, $N = 20$). Standardized acupuncture treatments were individually tailored and provided in a double-blind fashion. Responders to acute-phase treatment (HRSD17 score <14, and $\geqslant 50\%$ reduction from baseline) were allowed to continue the treatment to which they were initially randomized, until 10 weeks postpartum. The response rates at the end of the acute phase were statistically as well as significantly higher in the SPEC group (69%) than that in the MSSG group (32%), with the NSPEC group demonstrating an intermediate response rate (47%). The SPEC group also exhibited a significantly higher average rate of reduction in Beck Depression Inventory (BDI) scores from baseline to the end of the first month of treatment, than the MSSG group. All the responders to the acute phase of all the treatments had significantly lower depression scores at 10 weeks postpartum, than the non-responders. Thus, this study demonstrated that acupuncture is a promising technique for the treatment of depression during pregnancy.

Another remarkable clinical trial was performed by John Allen and his team at University of Arizona, to assess the efficacy of acupuncture as an intervention for MDD. This clinical trial was carried out for almost 10 years. In the initial trial, only 38 patients with MDD were examined. The specific intervention involved TCM-style acupuncture with manual stimulation for depression; the control conditions comprised: (1) A nonspecific intervention using a comparable number of legitimate acupuncture points, not specifically targeted to depressive symptoms, and (2) A waitlist condition, which involved waiting without intervention for 8 weeks. After 8 weeks, all the patients received the depression-specific acupuncture. Each 8-week intervention regimen consisted of 12 acupuncture sessions at an acupuncturist's clinic in the community. The preliminary outcome measure was the HRSD17. According to their preliminary data published in 1998 (Allen et al. 1998), about two-thirds of the MDD patients were cured of the depressive conditions, a rate similar to that achieved with antidepressants and psychotherapy, after they underwent treatments aimed at relieving depression. This study is the first randomized, controlled, double-blinded study on the efficiency of acupuncture treatment for depression, reported in the western scientific literature. Furthermore, 151 patients with MDD were randomly assigned to one of the three groups in the subsequent study conducted from February 1998 to April 2002 (Allen et al. 2006). However, 20 patients opted out themselves (they were not excluded by the study group) from the treatment before the completion of the 8-week intervention (13%). Random regression models of the intent-to-treat sample revealed that although patients receiving acupuncture improved better than those awaiting intervention, no evidence of differential efficacy of the depression-specific over the nonspecific intervention was found. Furthermore, the response rates in the acupuncture-treated patients were relatively low after 8 weeks (22% and 39% for specific and nonspecific intervention groups, respectively), with the response rate after the entire 16-week trial reaching 50%. Although TCM manual acupuncture is a well-tolerated intervention, the results obtained failed to support its efficacy as a mono-therapy for MDD. It is possible that the factors that are unique with respect to the implementation of acupuncture in this research study may have limited the efficacy of the interventions, when compared with those provided in the naturalistic settings.

Apart from the abovementioned researches, a few studies on acupuncture as a treatment for depression or depression-like syndromes had been published in Eastern Europe, Germany, and the former Soviet Union (Cherkezova and Toteva 1991; Dudaeva et al. 1990; Frydrychowski et al. 1984; Poliakov 1987). As the diagnostic criteria used in these studies differ from those of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-Ⅳ), and as most of these studies (other than their abstracts) have not been translated into English, it is difficult to completely evaluate them. However, collectively, these studies suggest that acupuncture can be an effective treatment for depression and depressive symptoms, and that in some cases, it may be as effective as the antidepressant medications. These findings encouraged us to carry out a well-controlled double-blinded large multi-centered study to examine the efficacy of acupuncture on depression.

In many clinical trails, various acupoints have been used for the treatment of depression, based on the TCM rules. The most frequently used dominant acupoints for the treatment of depression are listed in Table 17.1 (Lv and Fan 2003).

Table 17.1 Acupoints most frequently used for the treatment of depression

Acupoints	Location	Meridian	Efficacy and indication
Baihui (GV 20)	5 cun posterior to the AHL	Governing Vessel Meridian	Headache, dizziness, eye pain and redness, irritability, hypertension, visual dizziness, tinnitus, vertex pain, windstroke, seizures, prolapse, anal, uterine, and vaginal hemorrhoids
Yintang (EX HN3)	Midway between the medial ends of the eyebrows		Calms the spirit insomnia, anxiety, stress, frontal headache, congestion, sinusitis
Neiguan (PC 6)	2 cun up to the wrist crease between the tendons of palmaris longus and flexor carpi radialis, 0.5 – 1.0 deep	Pericardium Meridian	Chest pain, palpitation, stomach ache, vomiting, insomnia, epilepsy, dizziness from depression, stroke, wheezing, paralysis, migraine, fever, pain in arm or elbow, etc.
Sanyinjiao (SP 6)	On the medial side of the leg, 3 cun above the tip of the medial malleolus, posterior to the medial border of the tibia	Lung Meridian	Abdominal pain, borborygmus, distention of the abdomen, diarrhea, dysmenorrheal, irregular menstruation, metrostaxis and metrorrhagia, abnormal vaginal discharge, prolapse of uterus, infertility, dystocia, emission, impotency, enuresis, dysuria, edema, hernia, pain in the vulva, flaccidity of the lower extremities, headache, dizziness, insomnia
Shenmen (HT 7)	At the wrist crease, on the radial side of the flexor carpi ulnaris tendon, between the ulna and the pisiform bones	Heart Meridian	Insomnia, muddled thinking, anxiety, mania, anxiety with palpitations, nausea with panic and/or fear, irregular heart beat, pounding heart, angina
Sishencong (EX HN 1)	Four points on the vertex of the head, 1 cun anterior, posterior, and lateral to the acupoint Baihui (GV 20)		Headache, dizziness, insomnia, amnesia, epilepsy
Fengchi (GB 20)	On the nape, below the occipital bone, on the level of acupoint Fengfu (DU16), in the depression between the upper ends of the sternocleidomastoid and trapezius muscles	Du Meridian	Headache, dizziness, insomnia, stiffness of the neck and nape, blurring of vision, optic atrophy, conjunctivitis, tinnitus, convulsion, infantile convulsion, epilepsy, fever, common cold, stuffy nose, rhinorrhea with turbid discharge
Taichong (LR 3)	On the dorsum of the foot in a depression distal to the junctions of the 1^{st} and 2^{nd} metatarsal bones	Liver Meridian	Anger, irritability, insomnia, anxiety, headaches, dizziness, canker sores, blurred vision, red, swollen, painful eyes, dysmennorrhea, amenorrhea, premenstrual syndrome (PMS), breast tenderness, pain/swelling, hernia, impotence, seminal emission, subcostal tension, chest/flank pain, swellings in the axillary region, nausea, vomiting, constipation, diarrhea with undigested food

(Continued)

Acupoints	Location	Meridian	Efficacy and indication
Zusanli (ST 36)	3 cun below the acupoint ST 35, one finger width lateral from the anterior border of the tibia, in tibialis anterior	Stomach Meridian	PMS, depression, nervousness, asthma, wheezing, dyspnea, breast problems, lower leg pain

17.2.2 Acupuncture Combined with Other Therapies

Acupuncture as a sole therapy might be a better therapy for the treatment of mild to moderate depression. However, acupuncture combined with medicine may be the best choice for the treatment of severe depression, according to the clinical experiences of the Chinese Traditional Medical Society. Nevertheless, further critical clinical trial is required to examine the clinical efficacy and safety of acupuncture on depression. Several clinical trials have been carried out in China, which have focused on the therapeutic effects and adverse reactions of acupuncture combined with medication (TCM or Western Medicine).

In an earlier study, a total of 61 cases with mental depression were randomly divided into a treatment group of 30 cases and a control group of 31 cases (He et al. 2007). The former group was treated using acupuncture (the main acupoints: Baihui (GV-20), Shenting (GV-24), Yintang (EX-HN-3), Renzhong (GV-26), Anmian (EXTRA), Shanzhong (CV-17), Neiguan (PC-6), Daling (PC-7), Shenmen (HT-7), and Taichong (LR-3)) along with TCM medication (Chinese herb decoction), and the latter with TCM medication alone. The HAMD scoring system was adopted to evaluate the therapeutic effects, and the Treatment Emergent Symptom Scale (TESS) was used to evaluate the adverse reactions. The treatment group showed better results than the control group with respect to the total effective rate, with significant differences between the two groups with regard to the reducing rate of HAMD score at the end of the second, fourth, and sixth week of treatment. However, no remarkable difference was observed between the two groups in terms of adverse reactions. These results indicate that acupuncture along with TCM medication may produce satisfactory effects on mental depression, indicating that a synergic action may exist between acupuncture and TCM medication.

Another clinical study carried out in China examined 42 patients with depression (Zhang et al. 2007), who were randomly assigned to the observation group (22 patients) treated with EA (dominant acupoints: Baihui (GV-20) and yintang (EX-HN-3); auxiliary acupoints: Neiguan (PC-6), Waiguan (SJ-5), Shenmen (HT-7), Hegu (LI-4), Taichong (LR-3), Zusanli (ST-36), Fenglong (ST-40), Sanyinjiao (SP-6), Taiyuan (LU-9), etc., all bilateral) combined with paroxetine, and the control group (20 patients) treated with paroxetine alone. The therapeutic courses for both the groups were 6 weeks. The therapeutic efficacy and adverse reactions were evaluated using HAMD and TESS scores, respectively. The HAMD scores were determined at the end of the first, second, fourth, and sixth week of the treatment course, which were significantly lower in the observation group than those in the control group. However, the significant improvement rate evaluated at the end of the 6-week treatment was remarkably higher in the observation group than that in the control group (72.7% vs. 40.0%). No significant difference in the TESS scores was observed between the two groups. These results also imply that EA combined with paroxetine has better clinical efficacy than that with paroxetine alone, with milder adverse reaction and quicker initiation of the effect.

To assess the clinical therapeutic effect and safety of acupuncture combined with fluoxetine on depression, Lin et al (2005) divided 53 patients with depression into an observation group ($n = 30$) treated with acupuncture combined with fluoxetine, and a control group treated with fluoxetine alone. The clinical therapeutic efficacy and adverse effects were assessed by HAMD, Hamilton Rating Scale for Depression (HAMA), CGI, and TESS scores. After 6-week treatment, the total effective rate was 80.0% in the observation group, and 69.6% in the control group with no significant difference between the two groups. However, there were significant differences in the scores of HAMD and HAMA before and after treatment in the two groups, with no significant difference between the two groups. Furthermore, the adverse effect in the observation group was less and milder than that in the control group. These results show that acupuncture combined fluoxetine has a good therapeutic effect on depression with less and mild adverse effects (Lin et al. 2005).

Another clinical research performed by Qian et al (2001) examined the therapeutic effect of EA combined with the Chinese medicine, Shu Xue Ning (extract of Ginkgo leaf), on depression. The patients were divided randomly into two groups. One group received treatment of EA and Shu Xue Ning, and the other group received treatment of EA and placebo. The effects of the treatment were evaluated using the HAMD, SDS, and SAS scores. The results demonstrated that all the 21 patients treated in the two groups responded to the treatment very effectively. To compare the two groups, the HAMD, SDS, and SAS scores were employed. The HAMD and SDS scores did not show any significant differences, while the SAS scores reached significant difference with SAS's T value close to the significant difference value. Thus, this study demonstrated that the combination of EA with Shu Xue Ning was more effective than simple EA for the treatment of depression (Qian et al. 2001).

Another clinical study was carried out to determine the effect of acupuncture combined with antidepressants on dyssomnia in patients with depression (Wang et al. 2006). Patients suffering from depression with dyssomnia were randomly divided into a treatment group ($n = 23$) and a control group ($n = 22$). The treatment group was treated with Governor Vessel Daoqi needling method and oral administration of antidepressants, with Shenting (GV-24), Baihui (GV-20), Dazhui (GV-14), Shendao (GV-11), and Zhiyang (GV-9) selected as main acupoints. On the other hand, the control group was treated with simple antidepressants. The total therapeutic course was for 4 weeks. Changes in the scores of HAMD and

PSQI (Pittsburgh Sleep Quality Index) were investigated in the two groups. After treatment, there were significant differences in the scores of HAMD in both the groups and a significant difference in the PSQI score only in the treatment group, when compared with the scores before treatment. There were also significant differences between the two groups in the scores of HAMD and PSQI after treatment. These results suggest that the combined therapy of Governor Vessel Daoqi needling method and antidepressants can significantly improve dyssomnia in patients with depression.

Another clinical report (Shi 2004) studied the combination treatment of acupuncture and psychotherapy for depression. Among the 36 cases with a major depressive episode, the curative rate was 27.7% (10/36), and improvement rate was 52.8% (19/36) after the combination treatment.

Although these trials are pilot, small, and incomplete, with some researchers failing to establish a complete control group such as placebo or sham-acupuncture control, they provide more evidences to validate the clinical efficacy and safety of acupuncture treatment for depression.

There are also some psychiatrists and acupuncturists outside China who have carried out studies on the clinical efficacy of acupuncture combined with the medication, even before their Chinese counterparts. In 2000, a single-blinded, placebo-controlled study examined the efficacy of acupuncture combined with the tetracyclic antidepressant, mianserin, in 70 inpatients with a major depressive episode. The patients were administered with a valid acupuncture treatment combined with mianserin for depression (verum acupuncture group); a placebo acupuncture treatment (placebo acupuncture group); or simply continued medication with no additional acupuncture (control group). The verum group received acupuncture on specific acupoints considered effective on depression. The placebo group was treated with acupuncture on non-specific locations, and the control group received pharmacological treatment along with clinical management. Acupuncture was applied thrice a week over a period of 4 weeks. The results showed that all the patients who received the combination of mianserin and acupuncture improved slightly more with respect to the overall function and symptomatology, than those treated with mianserin alone (Roschke et al. 2000). Although the studies outside China are limited, they are well-designed and well-conducted clinical trials. However, to address the clinical efficacy and safety of the combination of acupuncture and medication, further large-scale multi-centered clinical trials are necessary.

17.3 Mechanism Studies

There have been some evidence indicating that the scientific basis for acupuncture is the stimulation of the small-diameter nerves in the muscles using needles, which is considered to send impulses to the spinal cord, midbrain, pituitary, and hippocampus, and signal the release of some neurotransmitters and endorphins.

Increasing mechanism studies have been carried out on depression, with respect to some central neurotransmitters, Hypothalamus-pituitary-adrenal (HPA) axis, immune system, limbic system including the hippocampus and amygdala as well as the anterior thalamic nuclei and a limbic cortex, and the signal transduction system in the nerve cell. All these studies attempted to illuminate the mechanisms by which acupuncture might be effective in treating depression and anxiety; however, understanding of the complete mechanism needs further investigation.

17.3.1 Effect of Electroacupuncture on the Neurotransmitters

Early in 1992, Fan measured the lymphocyte β-adrenergic receptor function in 20 depressed patients and 18 healthy volunteers, using radioligand binding technique. They found that the affinity and sensitivity of this receptor were significantly higher in the endogenous depressed patients than those in the normal control. However, after EA treatment, lymphocyte β-adrenergic receptor function decreased in patients who responded well to EA treatment, but still failed to reach the normal level (Fan 1992). This clinical research suggests the involvement of β-adrenergic receptor in EA treatment for depression.

Numerous studies about the effect of EA on the animal depression models have been carried out by researchers at Beijing University of Chinese Medicine. Jin et al (1999) investigated the treatment mechanism of EA for depression by employing EA on Baihui (GV-20) and Yintang (EX-HN3) acupoints. Male Sprague-Dawley rats were randomly allocated into four groups: control, depression model, depression model along with EA, and depression model along with amitriptyline. The concentrations of monoamine neurotransmitters and their metabolites in rat brain were determined by HPLC-ECD. The 5-Hydroxytryptamine (5-HT)/5-HIAA in the cortex and DA/3,4-dihydroxyphenylacetic acid (DOPAC) in the striatum of the depression model rats were observed to be significantly lower than those of the control group; and the NE/5-HT in the cortex of this group was significantly higher than that in the control group. After EA treatment, 5-HT/5-HIAA and NE/5-HT in the cortex returned to normal level, and the decrease in the DA/DOPAC in the striatum was not affected by EA. These results suggest that stimulation of the acupoints by EA could increase the activity of 5-HT-type neuron, by decreasing the 5-HT metabolism in the cortex, which could rebuild the balance of NE and 5-HT and produce a potential antidepressant effect (Jin et al. 1999). Furthermore, Qiu and Shi (2002) also showed that the mechanism of the regulative effects of EA on depression model might be related to the changes in the metabolism of 5-HT and 5-HIAA.

Another recent research also demonstrated that EA could modulate the level of central and peripheral monoamine neurotransmitters. The results showed that levels of NE and 5-HT in the serum of depression model rats were significantly higher than those in the control group. The levels of NE, 5-HT, and DOPAC in the prefrontal cortex, and those of 5-HT and 5-HIAA in the hippocampus and DA in the hypothalamus of the depression model rats were significantly lower than those in the control group. Furthermore, after EA treatment, the increased levels of NE and 5-HT in the serum declined significantly. At the same time, the level of monoamine neurotransmitters in the brain was enhanced by EA (Han et al. 2004b). Another research carried out by Sun et al (2003) demonstrated that the imbalance in the function of 5-HT receptors might also be an important cause for depression, and EA is presumed to play a regulatory role to rectify this imbalance.

17.3.2 Effect of Electroacupuncture on the Hypothalamus-pituitary-adrenal Axis

Some clinical research groups in China carried out some studies on the neuroendocrine mechanism of acupuncture treatment for depression. In a study, 60 patients with depression were randomly divided into acupuncture group and medication group. They were treated using acupuncture and oral antidepressant, fluoxetine, respectively, for 4 weeks. Before and after the treatment, dexamethasone suppression test (DST) was carried out, and subsequently, the plasma cortisone and adrenocorticotropic hormone (ACTH) were determined. The results showed that the marked effective rate was 73% in the acupuncture group with a less reverse effect. Furthermore, there were significant differences in the plasma cortisone and ACTH levels in the treatment group before and after treatment, which reached the normal level with the alleviation of clinical symptoms (Xu et al. 2004). Other researches on the neuroendocrine mechanism of acupuncture treatment for depression were carried out on the animal depression models. Han et al (2001a) detected the levels of plasmatic cortisol and ACTH using radioimmunoassay in rats with chronic stress-induced depression or under EA treatment. The quantitative comparison of the arginine vasopressin-positive neurons (AVN) of the paraventricular nucleus of the hypothalamus was carried out in each group of rats, using immunohistochemical method and computer image pattern analysis. The results showed that the plasmatic cortisol and ACTH levels as well as the number of AVN of the paraventricular nucleus of the hypothalamus were obviously higher in the depression model group than those in the normal control group, and were significantly lower in the EA treatment group than those in the depression model group, which were near to the normal levels (Han et al. 2001a). These results suggest that the regulating effects on the hyperactivity of the function of HPA axis could be one of the mechanisms of EA treatment for depression.

17.3.3 Effect of Electroacupuncture on the Immune System

Han et al (2002b) investigated the effect of EA on serum cytokines in depressed patients. The serum levels of interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) of 30 patients in the EA treatment group, 31 patients in the maprotiline group, and 10 normal controls were detected by radioimmunoassay. The serum levels of IL-1β, IL-6, and TNF-α were significantly elevated in depressed patients when compared with the normal controls. Furthermore, in depressed subjects, the serum levels of IL-1β and TNF-α correlated positively and significantly with the total HAMD scores. There were additional positive and significant correlations between IL-1β and the scores of cognitive disorder, TNF-α and desperation, IL-6 and anxiety/somatization. However, after antidepressant treatment using EA or maprotiline, the levels of cytokines declined along with the alleviation of depressive symptoms. Furthermore, no significant differences were found between these groups. These results indicate that the alteration of cytokine levels in the blood may be associated with the mechanism of depression (Song 2000), and demonstrate that the treatment of EA for depression might be related to the regulation of serum cytokines. Another study conducted on the depression model rats also showed that the regulation of serum cytokines might play an important role in the antidepressant-like effect of EA treatment (Li et al. 2006).

17.3.4 Effect of Electroacupuncture on Signal Transduction System

To investigate the changes in the signal transduction system of MDD patients and the effect of EA treatment for depression on the signal transduction system, patients who met the DSM-Ⅳ criteria for MDD were examined. Under a double-blinded, placebo-controlled randomized trial, these patients were divided into three groups treated with different remedies for 6 weeks: EA ($N = 20$); fluoxetine ($N = 21$); and needle punching ($N = 21$). Furthermore, the blood samples of the 30 normal controls matched with age and sex were collected before and after the treatment. After separation of the platelet membrane from the plasma, the concentrations of various protein kinase C (PKC) subtypes were detected using Western blot and radioactive self-imaging. The results showed that the patients with MDD had lower total PKC concentrations. After treatment with fluoxetine, the classic PKC concentration was observed to decrease, while the novel and atypical PKC concentrations increased. Surprisingly, after treatment with EA or needle punching, classic PKC concentration was upregulated, but novel and atypical PKC concentrations were downregulated. The study demonstrated that the decreased concentration of PKC indicates the dysfunction of PI signal pathway in patients with MDD, and that EA is different from fluoxetine in influencing the concentrations of various PKC subtypes, suggesting that EA might have a different effect on the signal transduction system when compared with fluoxetine (Li et al. 2004).

Recent study investigated the therapeutic effect of EA on GTP-binding protein (G protein) in platelet membrane, using fluoxetine for comparison (Song et al. 2007). A randomized controlled trial was performed on 90 depressed patients, who were divided into three groups treated with fluoxetine, EA, and sham EA, respectively. Several antibodies were utilized to quantify the levels of G protein-α subtypes in the platelet membrane, before and after 6-week antidepressive treatment. Thirty age- and sex-matched normal individuals were used as control. The results exhibited that all the treatments had the same therapeutic effects in treating moderate depression. Furthermore, both the levels of Gαi and Gαq in the depressed patients were significantly higher than those in the control group, and were not reduced by treatments, although the severity was considerably relieved. The study concluded that EA might serve as an alternative treatment for moderate depression, and also demonstrated that the abnormal levels of Gα protein in the platelet membrane might be a potential risk factor for depression.

17.3.5 Effect of Electroacupuncture on Hippocampus

The hippocampus is one of the two large limbic-system structures involved in motion, motivation, and memory. The hippocampus could contribute to increased anxiety, and indirectly influence mood and cognition via connections with the amygdala and the prefrontal cortex. In addition, dysfunction of the hippocampus is observed to induce loss of feedback inhibition of the HPA axis, and also directly contribute to the cognitive deficits observed in depression. Based on these observations, many studies on the mechanism of acupuncture have focused on the role of hippocampus.

Maternal Separation (MS) is a risk factor for the development of mood-related disorders such as depression. Human and animal studies support the involvement of neuropeptide Y (NPY) in the pathology of depression (Pohl and Nordin 2002). To investigate the antidepressant effect of acupuncture and the changes in NPY expression associated with MS, Lim et al (2003) not only observed the body weight and locomotory activity, but also performed NPY immunohistochemistry in the hippocampus. MS for 7 days, beginning from the postnatal day 14, induced a significant decrease in the body weight and locomotion, while acupuncture treatment resulted in a significant increase in both. The NPY-immunoreactive cells in area CA1 and the DG were decreased in the MS group, but significantly increased in the acupuncture group. These findings suggest that acupuncture could have an effect on the depression-like disorder caused by MS, possibly by modulating the NPY expression in the hippocampus (Lim et al. 2003). In the same animal model, Park et al (2002) investigated the effect of acupuncture on cell proliferation in the DG of hippocampus. The BrdU (5-bromo-2-deoxyuridine) immunohistochemistry was performed on MS rat pups. MS for 7 days, from postnatal day 14, induced a significant decrease in the BrdU-positive cells in DG, while acupuncture treatment, at the end of the transverse crease of the ulnar wrist, resulted in a significant increase in the number of BrdU-positive cells in DG. These findings demonstrate that acupuncture may stimulate cell proliferation in the DG of hippocampus during the treatment of diseases related to MS (Park et al. 2002). Our study also showed that EA treatment on CUS (chronic unpredictable stress)-induced depression model rats attenuated the decrease in the hippocampal progenitor cell proliferation (Liu et al. 2007). The EA was performed on the acupoints Baihui (GV-20) and unilateral Anmian (EX-17) once daily for 3 consecutive weeks, 2 weeks post-CUS procedure. Open field test and forced swimming test were employed to evaluate the behavioral activity during a stress period or EA treatment. The results revealed that exposure to CUS caused a decrease in the behavioral activity, whilst a daily session of EA treatment significantly reversed the behavioral deficit of these depression model rats. Moreover, through BrdU immunohistochemistry, hippocampal progenitor cell proliferation was found to decrease in the DG of the depression model rats. Intriguingly, EA treatment effectively blocked this event. Thus, the study demonstrated the potential antidepressant-like effect of EA treatment on CUS-induced depression model rats, which is presumed to be mediated by the upregulation of the hippocampal progenitor cell proliferation. The number of BrdU-positive cells in the DG of adult hippocampus among different groups is shown in Fig. 17.1. A study carried out at the Beijing University of TCM demonstrated the effects of EA on BDNF neurons in the hippocampus in the animal model of chronic-stress depression. The immunohistochemistry results showed that the number of infected neurons of the depressed animals was much lesser than those of the normal animals, while EA was observed to increase the number of BDNF neurons in the hippocampus in the depressed animal. The study demonstrated that EA might cure depression by protecting the BDNF neurons in the hippocampus (Han et al. 2001b). The possible mechanisms responsible for the antidepressant-like effect of acupuncture treatment on depression are shown in Fig. 17.2.

17.4 Concluding Remarks

This chapter presented a summary of the evidences on the effectiveness of acupuncture treatment for depression and its possible mechanism. The available sources provide some evidences on the notion that acupuncture or acupuncture combined with other therapies is an efficacious remedy for depression. However, the mechanisms of acupuncture are not completely understood. Nevertheless, owing to the efforts of many scientists, it has been recently understood that the levels of neurotransmitters, such as NE and 5-HT, increase in the plasma and brain tissues as a result of acupuncture application. Furthermore, acupuncture or EA can also modulate the immune system and the neuroendocrine system, especially the HPA axis. Moreover, the signal transduction system is also observed to be involved in

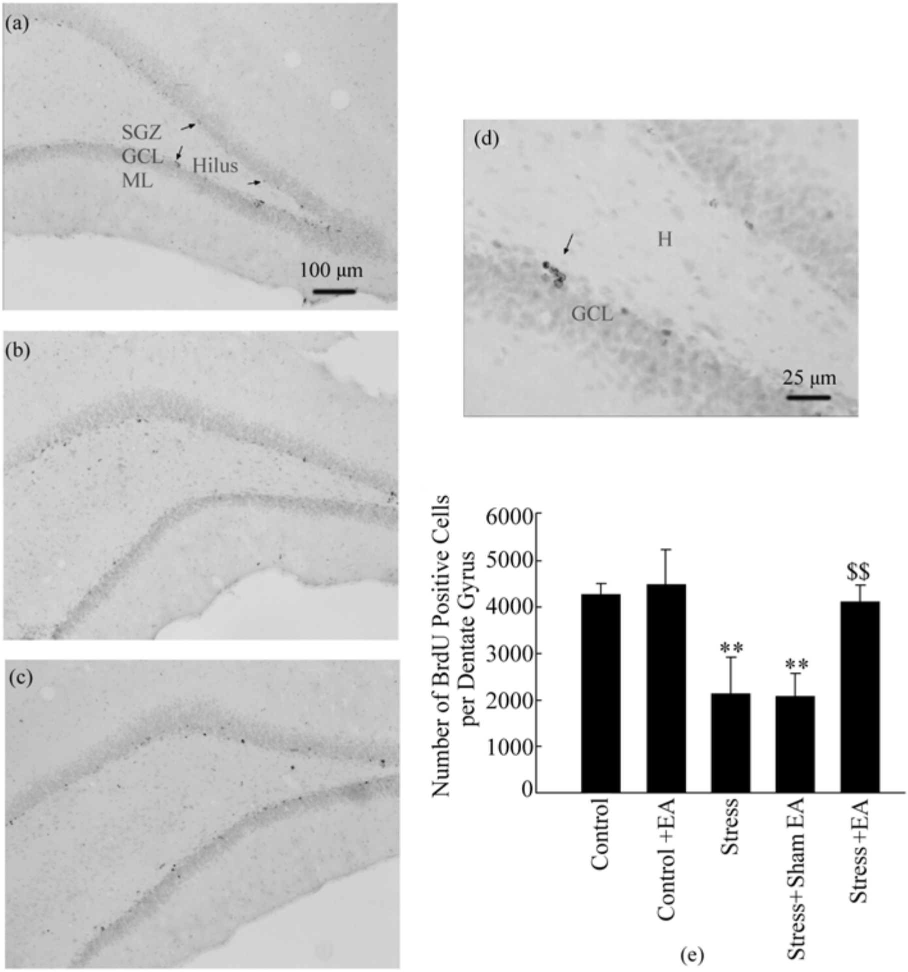

Figure 17.1 EA attenuates the decrease in the hippocampal progenitor cell proliferation in the adult rats exposed to CUS. Panels (a) (b), and (c) are representative photographs showing the distribution of BrdU labeled cells in the hippocampus from the groups of Control (a), Stress (b), and Stress + EA (c). The BrdU labeled cells, as indicated by arrows, appear in pairs or clusters in the subgranular zone (SGZ) of the DG. Under a 40 × with a 100 × zoom magnification, individual cells in the clusters are clearly visualized (d). The BrdU labeled cells in the SGZ were counted under high magnification. Panel (e) shows the number of BrdU labeled cells in the SGZ of rats. The results are expressed as the estimated mean total number (± SEM). **$p<0.01$ for the stress group vs. the control group; $$$p<0.01$ for the Stress + EA group vs. the Stress + sham EA group.

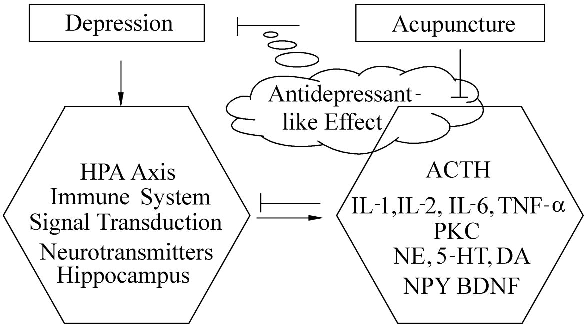

Figure 17.2 Possible mechanisms of acupuncture treatment for depression. The etiology of depression may be attributed to the dysfunction of some central neuro transmitters, the immune system, the HPA axis, the signal transduction system, and certain brain regions, especially the hippocampus. On the contrary, acupuncture may regulate the production of 5 HT, NE, DA, IL 1β, IL 2, IL 6, TNF α, ACTH, PKC subtypes, NPY, and BDNF, thus relieving depression.

the antidepressant-like effect of EA on depression. In addition, the hippocampus, one of the important brain structures which play a key role in the etiology of depression, has been observed to be involved in the mechanism of acupuncture or EA treatment for depression. Owing to these studies and observations, the use of acupuncture for the treatment of depression is gradually increasing worldwide.

Chinese Medicine is perhaps one of the foremost therapeutic avenues which use nature's assistance to rebalance the human body. As humans function at so many levels, from spiritual to physical, emotional, etc., each of these strata must be addressed separately. The somewhat magical art of TCM works beautifully in uniting the body-mind-spirit, to restore the harmony again. As one of the predominant techniques of TCM, acupuncture has a history of over 3000 years (Han 1986; Ulett et al. 1998). The term "Acupuncture" consists of two words from the Latin—acus: needle and puncture: insertion. It is a treatment procedure in which, generally, steel, silver, or gold needles are inserted into specific acupuncture points. Although the history of acupuncture dates back to ancient times, it has not lost its popularity. On the contrary, it has gained popularity recently. In a large- scale study by Harvard Medical School, which has been published in the New England Journal of Medicine, depression was observed to be among the most frequently-reported conditions, and one of the top five conditions for which people were more likely to seek alternative treatments, with or without established treatments, than established treatments alone; and acupuncture was one of the alternative treatments listed in the study (Eisenberg et al. 1993). The studies presented in this chapter suggest that the use of acupuncture or acupuncture combined with other therapy could be as effective as other types of treatments typically used in the Western Medicine, such as psychotherapy and drugs, in relieving depression symptoms. These results are promising and the United Nations' WHO has approved acupuncture as a treatment for depression. However, further clinical trials with larger samples are necessary to endorse this treatment for relief from depression.

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18 Effect of Acupuncture on Drug Addiction

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Summary This chapter summarizes the advancement of clinical acupuncture for drug addiction and the basic research on its mechanisms. The applications of auriculo-acupuncture, body acupuncture, electroacupuncture (EA), acupuncture with Han's acupoint nerve stimulator (HANS), and combination therapy will be briefly introduced with comments on their efficacy. Although, the mechanisms underlying the acupuncture treatment are not well understood, evidence has shown that acupuncture can regulate the function of endogenous opioids and other neurotransmitter systems, and can modulate immunity, endocrinology, and psychology, to achieve the therapeutic effect on drug addiction.

Keywords *acupucture, drug addiction, β-endorphin, hypothalamus-pituitary-adrenal axis, withdrawal syndrome*

18.1 Introduction

Drug abuse and addiction develops into a critical social and medical problem. Various drugs, such as cocaine, heroin, ice (the popular name for methamphetamine hydrochloride, a deadly addictive stimulant drug), and dancing outreach, can induce severe addiction, serious withdrawal syndromes, and have extremely high recurrence rate after quitting. Both psychological problems and somatic disorders may appear in opioid-dependent patients, such as myoendocarditis, hepatitis, stomach ulcer, duodenal ulcer, constipation, convulsion, paralysis agitans, peripheral neuritis， and even have a close relationship with AIDS. In addition, in pregnant women, drugs may also have an impact on their unborn children.

Acupuncture treatment for opioid dependence was employed in 1972 by a Hong Kong surgeon, Wen (Wen and Cheung 1973). Inspired by the principle of acupuncture anesthesia, he tried to use acupuncture for treating drug users. Subsequently, some experimental researches on acupuncture treatment for drug addiction were carried out in the USA, and the technique has been widely employed all over the world. Nowadays, many doctors and researchers in different countries use acupuncture to treat drug addiction. Various acupoints are chosen based on different symptoms of the patients, such as Shenting (GV-24), Baihui (GV-20), and Fengchi (GB-20) for head symptoms; Dazhui (GV-14), Zhiyang (GV-9), and Huatuojiaji (EX-B5) for somatic symptoms; Neiguan (PC-6), Shenmen (HT-7), Hegu (LI-4), Taichong (LR-3), Zusanli (ST-36), Sanyinjiao (SP-6), and related Back-Shu acupoints for limbs symptoms.

18.2 Clinical Application of Acupuncture for Drug Addiction

Auricular-acupoints were first adopted in acupuncture therapy for drug addiction, which became the most popular technique in terms of clinical application. The common auricular-acupoints include Ear-Lung, Sympathetic Nerve, Shenmen, Liver, Kidney, Heart, Endocrine, Stomach, Attack point, and Frustration point (Cui 1996). The concrete body acupoints include Baihui (GV-20), Yintang (Ex-HN3), Hegu (LI-4), Zhusanli (ST-6), Yinxiang (LI-20), Tianshu (ST-25), Shenshu (BL-23), Dachangshu (BL-25), Shenmen (HT-7), Zhubing (KI-9), Fuliu (KI-7), Weizhong (BL-40), Huantiao (GB-30), Neiguan (PC-6), Sanyinjiao (SP-6), Tongli (HT-5), Lieque (LU-7), Taichong (LR-3), Heyang (BL-54), Feishu (BL-13), Xinshu (BL-15), Fengchi (GB-20), and Qihai (CV-6).

18.2.1 Auriculo-acupuncture

Dr. Wen, a surgeon in Hong Kong, studied acupuncture anesthesia in China in 1972, and adopted bilateral auricular-acupoints to treat drug addiction in Tung Wah Group Hospital. He and his colleague punctured the auricular-acupoint, Ear-Lung, 2 – 3 times per day for 3 – 5 days during acute phase, followed by subsequent daily treatment for another 4 – 5 days. In the 40 cases treated, 39 quitted the drug completely (Wen and Cheung 1973). Furthermore, when electroacupuncture (EA) was employed, the effect was observed to be even better. Subsequently, an American psychiatrist, Michael O. Smith, studied acupuncture treatment for drug addiction for 20 years, supported by the National Drug Abastain Committee, where people and doctors learnt the procedures of acupuncture treatment. Since the 1970s, auriculo-acupuncture for drug addiction has been used in the Lincoln Hospital, New York. The clinical data confirmed that auriculo-acupuncture could alleviate the withdrawal symptoms and reduce craving; furthermore, the drug users were willing to undergo treatments (Smith and Khan 1988; Smith, 1992).

The Ear-Lung, Shen, Shenmen, and Pizhixia acupoints on both the ears have been associated with hypnosis therapy. In an earlier study, 20 cases were followed-up for 2 years. The withdrawal rate reached 80% in the first 3 months, and 70%, 65%, and 55% by the end of sixth month, first year, and second year, respectively (Cetin 1996). Furthermore, in another study, Russell et al (2000) employed auriculo-acupuncture on 37 patients, with 49 non-acupuncture cases as the control. The results showed that in the group of auriculo-acupuncture, shorter period was needed for the urine of the subjects to turn negative, when compared with that of other groups. More importantly, more subjects completed the treatment and the rate of relapse was lower in the auriculo-group (Russell et al. 2000).

18.2.2 Body Acupuncture

Hegu (LI-4), Zusanli (ST-36), Neiguan (PC-6), and Waiguan (SJ-5) acupoints are considered to be the key points for opioid dependence. Along with these acupoints, Xingjian (LR-2) and Xiaxi (GB-43) acupoints are employed for patients with stagnation of liver-qi; Pishu (BL-20) and Weishu (BL-21) acupoints are used for patients with asthenia-cold in spleen and stomach; and Sheshu (BL-23) and Zhishi (BL-52) acupoints are employed for patients with deficiency of kidney yang. Generally, through mild supplementing and reducing manipulation of the needle, these acupoints are stimulated, and usually, the treatment is provided for 10 times (Wen 1997; Song et al. 2005). Neiguan (PC-6) or Dazhui (GV-14) acupoints have been adopted as the key acupoints, along with Shaochong (HT-9) and Shenmen (HT-7) acupoints in the first day; Shangyang (LI-1) and Zulingqi (GB-41) acupoints in the second day; and other acupoints according to personal conditions in the third day. For example, Hegu (LI-4), Zusanli (ST-36), Gongsun (SP-4), or Zhigou (SJ-6) acupoints are employed for treating digestive-organ disorders; Shenmen (HT-7), Sanyinjiao (SP-6), Baihui (GV-20), or Yongquan (KI-1) acupoints are used for treating insomnia; Shuigou (GV-26) and Yongquan (KI-1) acupoints are employed for curing vague mind; and Zhongchong (PC-9), Laogong (PC-8), Shixuan (EX-UE11), or Dazhui (GV-14) are used for treating dysphoria, by rotating the needle fiercely for 2 – 5 min, with blood flow at Shixuan (EX-UE11) and Dazhui (GV-14) acupoints. After a 10-day acupuncture treatment, 7 out of the 20 cases treated exhibited obviously effective outcome, and the morphine content was found to be negative in the urine samples of all the 20 cases (Fan 1998).

18.2.3 Electroacupuncture

Han Jisheng, a Chinese academician, devoted his life to study the effects of acupuncture anesthesia and acupuncture treatment for drug addiction. He and his research group found that different frequencies of EA could inhibit the withdrawal symptoms in opioid-dependent rats. Based on the results of EA experiments in animal models, EA is currently being widely used in the clinic. The EA is employed by perpendicularly puncturing the Neiguan (PC-6) acupoint to about 1 cun, using a needle, and rotating it up and down for 1 min. Low frequency of EA was provided for 20 min on the acupoints Quchi (LI-11), Hegu (LI-4), and Yinlingquan (SP-9). Acupuncture has been reported to produce orphan-like substance in the brain and relieve pain through re-balance effect (Tong et al. 1995).

In an earlier study, the EA was applied on the acupoints Baihui (GV-20) and Yintang (EX-HN3) with continuous wave of highest tolerance for the patients. The treatment lasted for about 50 min, once a day. With the addition of some acupoints according to the different symptoms, the doctors reduced the Methadone dose gradually to complete cessation. After 14 treatment sessions, the withdrawal symptoms were evidently reduced (Quan et al. 1986; He and Li 2005).

Liu et al (1997) used different electric waves on bilateral acupoints Neiguan (PC-6), Laogong (PC-8), and Zusanli (ST-36), and subsequently undertook physical examination, blood, urine, and stool test, as well as heart, liver, and kidney function. In addition, the measuring scales of withdrawal symptoms obtained, and the urine morphine test and naloxone-induce test were carried out. The result showed that both continuous electric wave and sparse-dense electric wave were effective. However, the amelioration rate of withdrawal symptoms and the effect rate in continuous electric-wave group were better (Liu et al. 1997).

18.2.4 Han's Acupoints Nerve Stimulator

Han demonstrated that naloxone-induced morphine abstinence syndrome in rats can be suppressed by EA of 2 Hz or 100 Hz. The 2 Hz EA or transcutaneous electrical nerve stimulation (TENS), which is an application of electrical current through the skin for pain control, is known to induce the release of central endorphins and enkephalin, and that of 100 Hz is found to release dynorphin in the spinal cord (Han and Wang 1992). This effectiveness of the 100 Hz stimulation might suggest the involvement of dynorphin in this event. Thereafter, in the 1990s, Han invented the **Han's acupoints nerve stimulator** (HANS)—an acupoint nerve stimulator that stimulates the nerves through the skin, which is found to help the drug addicts to quit the drugs by themselves—based on his previous researches. The HANS is a special TENS device, and was used to treat 212 heroin addicts (161 males and 51 females, 15 – 38 years old) subjected to abrupt abstinence. The HANS was used for 30 min per day from day 1 to 10. Two pairs of skin electrodes (4 cm × 4 cm) were placed on the acupoint Hegu (LI-4) on one hand, and the acupoint Neiguan (PC-6) on the other forearm (Fig. 18.1). The frequency of HANS was set at one of the following values: 2100 or 2/100 (2 Hz alternating with 100 Hz, each lasting for 3 s). Comparison between two groups was made by sequential analysis or by ANOVA among multiple groups. Among the objective indices, the decrease in the heart rate was the most obvious, which returned to normal level within 4 – 5 days of HANS treatment, whereas, in the control group receiving placebo electrodes, the tachycardia remained for at least 10 days.

Comparison of different frequencies revealed: (1) Overall clinical effect, 2/100 > 2 = 100 Hz; (2) Suppression of tachycardia, 2/100 > 2 = 100 Hz; (3) Euphoria-like effect, 2/100 > 100 = 2 Hz; (4) Warm feeling, 2/100 > 2 > 100 Hz; (5) Hypnotic effect, 2/100 > 100 = 2 Hz; and (6) Increase in body weight, 2 = 100 = 2/100 Hz >> control group. Thus, it is obvious that HANS was effective in relieving the opiate withdrawal syndrome, and that 2/100 Hz seemed to be the most favorable frequency. Interestingly, 2/100 Hz was also observed to be the most effective frequency to induce analgesia in rats and humans. This interesting clinical finding may be owing to a synergistic effect between enkephalin and dynorphin (in the case of 2/100 Hz stimulation). It has been anticipated that HANS may also be useful to prevent recurrence of drug use after abstinence (Wu et al. 1995).

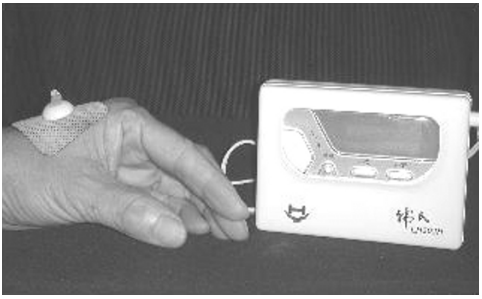

Figure 18.1 HANS. HANS is a TENS device designed in the 1990s, which is used for the treatment of drug addiction. Patients can use it by themselves. Human and animal researches demonstrated that HANS can improve additional symptoms and prevent recurrence after abstinence.

18.2.5 Combination Therapy

Zhuang et al (1995) selected the acupoints Neiguan (PC-6, bilateral), Shuigou (GV-26), and Suliao (GV-25) as the key acupoints, along with the acupoints Shenmen (HT-7, bilateral) for treating palpitation, and Zusanli (ST-36, bilateral) for treating chest or abdominal pain, with fierce or electric stimulation. Furthermore, they combined Jiedu Decoction (including Chinese thorowax root, pinellia tuber, liquorice root, baikal skullcap root, bamboo shavings, immature bitter orange, aromatic turmeric root-tuber, tangshen, rhubarb, plantago seed, white couch grass, etc.) is to combine with acupuncture treatment.

Jing (2002) punctured the auricular-acupoints with gradually decreased methadone administration on 32 drug users in Malta. Ear Shenmen, Lung, Liver, Heart, Kidney, and Spleen acupoints were punctured perpendicularly about 0.1 – 0.3 cun by 0.5 cun needles, and were rotated twice and left for 30 min. When pulling up the needles, the acupoints were pressed with sterilized tampon. Acupuncture was administered on the two ears alternatively, twice a week. The methadone was reduced gradually according to the condition of the patients. The effect rate of the 32 cases was 90.6%, which was better than the control (70%, 30 cases).

18.3 Mechanisms of Acupuncture Therapy for Drug Addiction

The mechanisms of acupuncture treatment for drug addiction are related to many important systems, such as nervous, immune, and endocrine systems. Endorphin is regarded as the key factor of the whole mechanism. In addition, the psychology and the will of the patients are also vital to the final outcome.

18.3.1 The Role of Endorphin in Acupuncture Treatment for Opioid Dependence

Exogenous opioid drugs, such as morphine and diamorphine are the antagonists of endorphin in the brain, which can bind with the opioid receptors easily, and produce a feeling of joy and happiness immediately. These feelings feedback to the brain and enhance positive sensation, resulting in the abuse of these drugs. Chronic abuse may interfere with the function of the receptors and decrease the endorphin release through negative feedback. Hence, the body needs to fill up more endogenous opioid once exogenous opioid drugs are consumed.

It has been presumed that acupuncture could induce the increased release of endogenous opioid in the central nervous system (CNS) during the process of acupuncture analgesia (AA) (Han and Terenius 1982), which may be a physiological mechanism of acupuncture treatment for opioid dependence. Some studies revealed that EA of low frequency (2 Hz) could accelerate the release of β-endorphin and enkephalin in the CNS, while EA of high frequency (100 Hz) could accelerate the release of dynorphin (Fei et al. 1986, 1988; Han and Wang 1992). Furthermore, these studies also tested the effect of low- or high-frequency EA stimulation on naloxone-precipitated abstinence syndrome in morphine-dependent rats (Luo et al. 1999). The naloxone-precipitated morphine withdrawal syndrome in rats includes a series of signs, including wet shakes, penile licking (or self-stimulation), escape attempt (or jumping), teeth chattering, and weight loss (Way et al. 1969). The results showed that 2 Hz EA stimulation for 15 min attenuated the number of wet shakes and escape attempts (ANOVA, $p<0.05$), and these signs were reduced by 50% and 75%, respectively, in the 15 – 30 min period in rats dependent on morphine. However, 100 Hz EA stimulation significantly suppressed wet shakes (– 73%), teeth chattering (– 69%), penile licking ($p<0.05$), and escape attempts ($p<0.05$) (Fig. 18.2). Thus, the 100-Hz EA stimulation was observed to be more effective than the 2 Hz EA, which may be owing to two possible reasons: (1) The naloxone was administered immediately after EA; therefore, the effect of EA could have been blocked by naloxone. However, the effect of 100 Hz EA mediated by dynorphin was not affected by naloxone, because dynorphin is a κ-opioid agonist and is relatively resistant to naloxone blockade; and (2) 100 Hz stimulation demonstrated the release of dynorphin in the CNS (Han 1991). Furthermore, dynorphin has been reported to suppress the withdrawal syndrome in heroin addicts (Wen and Ho 1982), and hence, it is expected to suppress morphine withdrawal in rodents (Han and Zhang 1998).

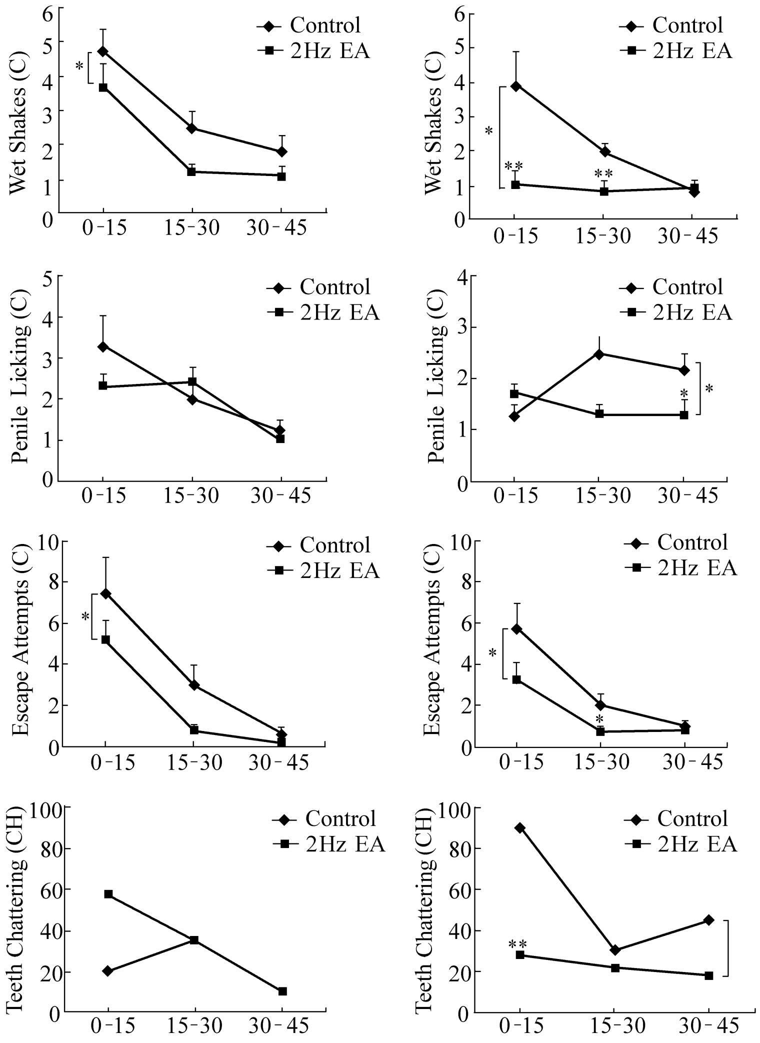

Figure 18.2 Effect of 2 Hz or 100 Hz EA stimulation on naloxone-induced withdrawal signs in rats without morphine for 5 days. The withdrawal signs are expressed as scores, either counted (C) or checked (CH), over 3 × 15 min period (naloxone 0.5 mg/kg, i.p.) *p<0.05, paired t test; p<0.05, ANOVA.

It has been observed that HANS has a similar effect and mechanism as that of EA. The effects of HANS include the change in the heart rate (HR), body weight (BW), and emotion.

(1) Effect of HANS on HR: A total of 60 cases were divided into four groups randomly: control, 2 Hz, 100 Hz, and DD mode (2/100 Hz). The average HR was 100/min before the treatment, and 2 Hz, 100 Hz, and DD HANS stimulation decreased the HR to an average of 91/min (2 Hz), 86/min (100 Hz), and 80/min (DD) immediately after treatment, which lasted for at least 2 h. A stable normalization of the HR was obtained by day 4 (DD) and day 5 (2 Hz or 100 Hz) of HANS treatment.

(2) Effect of HANS on BW: The average BW of the 4 groups was 49 – 51 kg during their admission (day 1). In the HANS-treated groups, there was a steady increase in the BW, which started to demonstrate a significant difference with the control group on day 5 (2 Hz and 100 Hz) and day 8 (DD), reaching 54 kg on day 11 ($p<0.01$, compared with the control group).

(3) Effect of HANS on emotion: In contrast to the changes in the HR and BW, which can be measured objectively, some of the effects of HANS's treatment were subjective. The latter included relief from anxiety, reduction of chilling sensation, appearance of a warm sensation in both the hands, up to the elbow joint, and a sense of euphoria immediately after treatment. To eliminate the placebo effects, the sequential analysis method was used for comparing the effects induced by HANS of different frequencies.

(4) Effect of HANS on palpitation: A visual analog scale (VAS) was used to quantify the degree of palpitation. In the control group, the score went up from 76 (day 1) to 94 (day 3 and day 4), and subsequently subsided to 64 on day 10. However, in the group receiving DD mode HANS treatment, the scores were $\leqslant 81$ in the first 4 days, and dropped sharply to 50 on day 5, the further decreased to 10 on day 10, and the difference between the two groups was very obvious (ANOVA, $p<0.01$). Apart from the abovementioned issues, craving, lacrimation, yawning, nausea, and vomiting were also alleviated by HANS treatment (Han et al. 1998).

18.3.2 The Roles of Some Neurotransmitters in Acupuncture Treatment for Opioid Dependence

The EA on the acupoint Zusanli (ST-36) (Song et al. 2001) is presumed to inhibit the release of dopamine, norepinephrine, and 5-serotonin after terminating the use of morphine in the morphine-dependent mouse. Thus, it is believed that withdrawal syndrome could be improved by acupuncture. In addition, EA is also observed to inhibit the content of nitric oxide (NO) and the activity of nitric oxide synthase (NOS) in the brain and blood, which play an important role during the withdrawal period.

Another research reported (Ao et al. 1996) that both 2-Hz and 10 Hz EA might enhance spontaneous discharge of excitatory neurons, but inhibit the reinforcement response. The reinforcement response to 2 Hz EA was totally blocked by naloxone, while that to 10 Hz EA was partly blocked. Hence, it was presumed that 2 Hz and 10 Hz could stimulate excitatory neurons in the ventromedial area of medulla oblongata and relieve pain mainly through the endogenous opioid. Besides the opioid system, the non-opioid system has also been considered to be involved in the regulation of 10 Hz EA, and the central κ receptor as well as its endogenous ligand, dynorphin, are believed to mediate this effect (Yu et al. 1999).

In addition, EA on the acupoint Shenshu (BL-23) is considered to decrease the c-Fos expression in the periaqueductal gray matter (PAG), paraventricular nucleus of the hypothalamus (PVN), lateral hypothalamic area (LHA), hippocampus A1, hippocampus A3, and dentate gyrus, and increase the c-Fos expression in the lateral and central nucleus of the amygdaloid body and nucleus accumbens septum. These nuclei are observed to be related to both addiction behaviors and psychological dependence. This result indicates that EA acts wildly on the central nuclei (Liu et al. 2005).

18.3.3 Regulation of Immunity

The function of the immune system is completely in drug-dependent patients; however, acupuncture may play an important role to effectively restore this function (Song et al. 1999). In morphine-dependent mouse, acupuncture is believed to improve the proliferation ability of the impaired lymphocytes, increase the levels of interleukin-1 (IL-1), interleukin-2 (IL-2), and β-endorphin in the serum, increase the body weight of the mouse, and accelerate the excretion of harmful substances (Ou et al. 1999; Song et al. 2001). The EA on the acupoint Zusanli (ST-36) is believed to increase the β-endorphin content in the serum and pituitary, serum IL-1 and IL-2, as well as the ratio of the immune organ to the body weight. Furthermore, pituitary β-endorphin showed a positive correlation with IL-1, suggesting the role of β-endorphin on cytokine (Song et al. 2001).

18.3.4 Changes in the Function of Endocrinology

The effects of acupuncture treatment for opioid dependence might be related to the function of hypothalamus-pituitary-adrenal axis (HPAA). It was reported (Tian and Yang 1997) that acupuncture might accelerate the adrenocorticotrophic hormone (ACTH) release and improve the function of HPAA. The ACTH could bind with the B receptors on the cell membrane, activate cyclic adenosine monophosphate (cAMP), and relieve the dependence of prostaglandin E to cAMP.

Compared with normal rats, the level of blood motilin of the morphine-dependent rats was lower, while that of brain motilin was higher. Both blood motilin as well as brain motilin demonstrated a tendency to reach the normal level after acupuncture treatment (Zhu 2002).

18.3.5 Alterations in Psychology

Patients with opioid-dependence symptoms may generally be anxious and depressed, especially during the withdrawal period or at the end of the withdrawal period. The symptoms include palpitation, insomnia, feeling of crisis, self-abasement, and desperation, which may result in loss of confidence and an urge to restart to the use of opioid drugs (Fan 1998).

The Award theory postulated by Blum is very interesting and attractive, which states that the tendency of dependence originates from the imbalance of neuro-chemistry. Imbalance of neurochemistry might lead to anxiety and desire, as well as behavior disorders. However, opioid drugs could relieve these symptoms. The award centre was regarded to be located at the hypothalamus, which is the important region for passion and award. When acupunctured at certain acupoints, the nerve impulse was transmitted to the spinal cord dorsal horn, and was subsequently conducted along various fibers in the antero-lateral bundle. Some fibers, especially the spinoreticular tract and mesencephalon tract, directly influenced the descending 5-hydroxytryptamine (5-HT) system. Furthermore, there were feedbacks and regulatory neuron circuits between the hypothalamus and midbrain. Thus, accelerated dopamine in the nucleus accumbens and nucleus amygdalae could produce a feeling of joy. Neurons in the reticular formation might be recovered by acupuncture and could stimulate the hypothalamus to activate the award system, similar to the mechanism of AA. Compared with clonidine and methadone, the role of acupuncture is observed to be evidently better in the amelioration of passion and depression (Wu et al. 2001).

In conclusion, acupuncture regulates nervous, immune and endocrine systems, thus inducing a therapeutic effect on drug addiction. In addition, the efficacy needs the psychological and social support according to biological-psychological-social medical model. The schematic mechanism is shown in Fig. 18.3.

18.4 Concluding Remarks

In clinic, auriculo-acupuncture, body acupuncture, EA, and HANS are widely adopted to treat drug addiction. Auriculo-acupuncture is generally considered to be the most effective and convenient technique. Some researchers carried out studies on the mechanisms of acupuncture for the treatment of drug addiction nearly 30 years ago. Nervous, immune, and endocrine systems have all been proved to

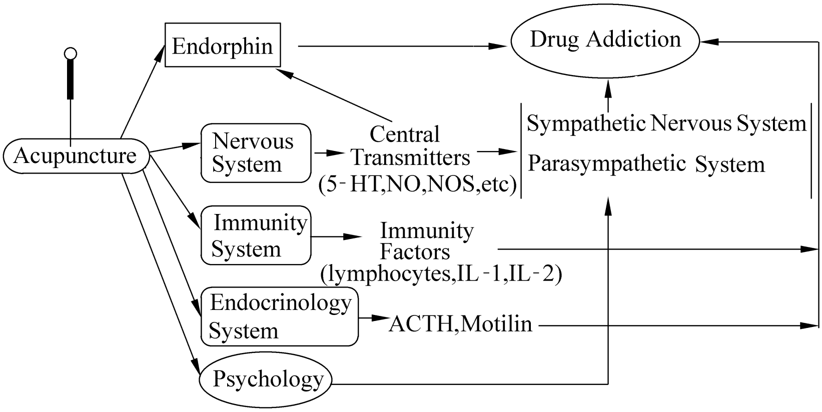

Figure 18.3 Possible pathways leading to the attenuation of drug addiction by acupuncture. Acupuncture may relieve the withdrawal symptoms through the nervous, immune, and endocrine systems of the body. Endorphin is the important and core factor in the whole mechanism. Furthermore, psychology and will of the patients are also vital to the final outcome.

participate in acupuncture regulation. Furthermore, endorphin has been found to be the key and core factor. However, high recurrence rate, unstable immediate effect, and lower curative effect are still observed in acupuncture therapy, and we can overcome these limitations by elucidating the pathways of acupuncture.

In conclusion, acupuncture treatment for opioid dependence is observed to be extremely safe, effective, and cheap, especially when other treatments are ineffective. It has more advantages when compared with the pharmacological methods, and can possibly replace pharmacology. However, the therapeutic effect and mechanisms of acupuncture treatment need to be proved. In future, more studies should focus on the mechanism research. Primate animals are the best models to mimic human behaviors induced by drug addiction, and the CNS may be the important target and the key to disclose the mystery of the mechanism of acupuncture treatment for drug addiction.

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Appendix A Milestone of Acupuncture Research: Correlation Between Peripheral Nerves and Meridians-Acupoints

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Before 1950s, there was no direct evidence regarding the correlation between the nervous system and meridians-acupoints. A systemic investigation into the relationship between peripheral nerves and meridians-acupoints was initiated in later 1950s by Drs. Peihua Zhou, Peide Qian and Dengkai Huang in the Department of Anatomy and Drs. Huayun Gu and Huiren Wang in the Department of Histology at Shanghai First Medical College (now Shanghai Medical College of Fudan University), Shanghai, China. Dr. Ding Li, then a renowned acupuncturist at Shanghai College of Traditional Chinese Medicine (now Shanghai University of Traditional Chinese Medicine), Shanghai, China, specifically localized all acupoints they studied with acupuncture needles.

In this pioneer study, they used anatomical and histological approaches to carefully dissect out the surrounding tissues of the meridians and acupoints in human cadavers and found that all acupoints studied were abundant in nerve tissues. Their initial data were published in 1959 (Department of Anatomy at Shanghai First Medical College 1959). Then, the contents were included in a book entitled "***Anatomy of Commonly Used Meridians-Acupoints***" by Shanghai Scientific & Technical Publisher in 1960 (Department of Anatomy at Shanghai First Medical College 1960). After more comprehensive work, they completed their studies on all major acupoints, i.e., 324 acupoints in total, in the body. With 8 adult cadavers, 49 detached upper extremities and 24 lower extremities, they detailed the topographical relation between the peripheral nerves and 324 acupoints of the 13 meridians including Ren meridian. Their data show that peripheral nerves are richly distributed in all these meridian points though in different ways, which was published by Shanghai People's Publishing House in 1973 (Department of Anatomy at Shanghai First Medical College 1973). Also, they presented the intriguing results in English at the National Symposia of Acupuncture-Moxibustion & Acupuncture Anesthesia (Beijing) in 1979 (Zhou et al. 1979).

Their work was indeed a milestone of acupuncture research, which provided an initial direction for Chinese scientists and acupuncturists to explore the mystery of acupuncture. However, this important work was rarely known in the non-Chinese community of acupuncture research because of language barrier. We therefore mention it here as a memory of the pioneer research.

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