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Effects of Betel Chewing on the Central and Autonomic Nervous Systems

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Key Words

Betel nut · Betel nut chewing · Central nervous system · Autonomic nervous system · Addiction

Abstract

Betel chewing has been claimed to produce a sense of well-being, euphoria, heightened alertness, sweating, salivation, a hot sensation in the body and increased capacity to work. Betel chewing also leads to habituation, addiction and withdrawal. However, the mechanisms underlying these effects remain poorly understood. Arecoline, the major alkaloid of Areca nut, has been extensively studied, and several effects of betel chewing are thought to be related to the actions of this parasympathomimetic constituent. However, betel chewing may produce complex reactions and interactions. In the presence of lime, arecoline and guvacoline in Areca nut are hydrolyzed into arecaidine and guvacine, respectively, which are strong inhibitors of GABA uptake. *Piper betle* flower or leaf contains aromatic phenolic compounds which have been found to stimulate the release of catecholamines in vitro. Thus, betel chewing may affect parasympathetic, GABAnergic and sympathetic functions. Betel chewing produces an increase in heart rate, blood pressure, sweating and body temperature. In addition, EEG shows widespread cortical desynchronization indicating a state of arousal. In autonomic function tests, both the sympathetic skin response and RR interval variation are affected. Betel chewing also increases plasma concentrations of norepinephrine and epinephrine. These results suggest that betel chewing mainly affects the central and autonomic nervous systems. Future studies should investigate both the acute and chronic effects of betel chewing. Such studies may further elucidate the psychoactive mechanisms responsible for the undiminished popularity of betel chewing since antiquity.

Introduction

Peruvian coca leaf, Indian hemp, Asian poppy, Mexican marijuana and American tobacco are well-known ethnopsychopharmacologic agents of great antiquity. However, there are lesser-known psychoactive plants of similar antiquity on the Asian continent [3, 5]. The most important are betel, kava and pituri. The use of betel nut masticatory has been widespread and it is highly valued for its psychoactive properties which reduce tension, for producing a sense of well-being and for providing a means of social interaction and ritual [2, 3, 5].

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Although its popularity has declined in recent years, betel chewing [betel chewing, betel nut chewing and betel quid chewing are used to denote chewing of betel nut preparation (the quid, the chew); these terms are interchangeable unless otherwise specified] is still widespread in Asia, particularly the South Pacific islands, Southeast Asia, Papua New Guinea, Bangladesh, Pakistan and India [3, 5]. It has been estimated that there are 200–400 million users. Curiously enough, the use of betel nut has remained mostly within these ethnic and cultural subgroups and was largely unknown to the West until recently [17, 28, 32].

In the past two decades, betel nut chewing has become popular again in Taiwan. The Department of Agriculture reported in 1996 that the annual production of betel nuts had a net worth of USD 485 million, second only to rice among all crops grown in Taiwan [20]. The Department of Health estimated that the number of people who habitually chewed betel nuts was about 2.4 million, or 11.4% of the total population [20]. The expansion of betel palm tree planting and betel nut consumption has caused considerable alarm concerning the detrimental effects on the environment, agriculture, public health, economy, medical care and even social order [22]. For example, 90% of those who suffer from oral cancer are betel nut users, and oral cancer has become the fifth leading cause of death among men in Taiwan [20, 23].

Despite the government's declaration of war against betel nut use, this habit has remained popular. In the biomedical research on betel nut use, the government has been mainly concerned about oral cancer. However, the root of the popularity of betel nut seems to be the neurological mechanisms responsible for the mild kick, creating psychological well-being and dependency.

Because the psychological and neurological effects of betel nut use have not been systematically investigated until recently, a review of this subject seems important. This review will focus on the effects of betel chewing on the nervous system, and will include a review of the literature in general and some studies from Taiwan in particular.

History

Like other psychoactive plants of antiquity, betel nut has been used by mankind since the pre-Christian era [3]. The earliest record is in the Maharamsa, a Ceylonese document from 504 BC in which there is a story of a princess rewarding her nurse with a present of betel nut chew [3].

In India in the early Christian era, betel nut use was frequently referred to in Sanskrit medical literature and later also in Hindu and Buddhist writings. Subsequently, the custom spread to southern Tibet and southern China as a result of the expansion of Buddhist practice [3]. Betel nut use in those early periods was both medical and psychosomatic, e.g. as a breath refresher, digestive agent, worm expellent, aphrodisiac and to maintain stamina [3, 5].

In China, betel nut use was first documented in the Wei-Chien dynasty in 421 AD, and was regarded as a valued masticatory [6]. During the Middle Ages, betel nut was widely employed by Arabian physicians, and Avicenna in the 10th century used it frequently for medical purposes [3]. However, its popular use was not promoted because of the Islamic prohibition against alcohol and other central stimulants. The use of betel nut in Europe was markedly limited. It was an ingredient in toothpaste for a brief period in 19th-century England [33].

Betel nut was introduced to Taiwan about 300 years ago from Malaysia by the Dutch, and became popular among aborigines [6]. Later, the custom also spread to Chinese immigrants on the island. During the Japanese colonial period, the use of betel nut was strictly prohibited. As there was no more enforcement of this law by the Nationalist government, the custom has gradually regained popularity in the past 50 years.

Despite some variations, betel nut preparations (the chew, the quid) consist of three major ingredients: the nut of the palm tree *Areca catechu,* quicklime and the psychoactive leaf of certain plants such as rubiaceous *Mitrogyna speciosa* in Southeast Asia, nutmeg *Myristica fragrans* in India, *Piper methysticum* in Melanesia and *Piper betle* in Papua New Guinea [5]. The most popular betel quid in Taiwan is 'red lime betel nut', which consists of the fresh nut of *Areca catechu, Piper betle* flower and slacked lime paste which stains red from the addition of an extract of the Chinese herb *Acacia catechu.* Also popular is 'white lime betel nut', which consists of Areca nut, *Piper betle* leaf and slacked lime [16, 23, 45].

Claimed Effects of Betel Chewing

The claimed effects of betel chewing mentioned in the literature are listed in table 1. These claims are mainly personal observations.

We investigated the initial and subsequent effects of betel chewing in 170 habitual users [16]. The first instance of betel chewing occurred between 10 and 20 years of age

Table 1. Reported effects of betel nut use

Psychosomatic effects
A sense of well-being
Euphoria
Heightened alertness
Sweating and warm sensation
Increased salivation
Prevention of hunger
Increased capacity to work
Suppression of boredom
Medical uses
Antihelminthic
Strengthening of teeth and gums
Mental illness
Aphrodisiac
Digestive agent
Social and cultural functions
A primary means of initiating and promoting interpersonal relationships
Ceremonial purposes
Inspiration in art and literature

Table 2. The initial and subsequent effects of betel chewing among 170 habitual users

	Percent
Initial effects	
Dizziness	67
Hot sensation	65
Palpitation	44
Sweating	28
Heightened alertness	16
Epigastric discomfort	9
Subsequent effects	
Heightened alertness	64
Hot sensation	62
Palpitation	47
Combat of cold	43
Sweating	41
Diminished thirst	38
Diarrhea	34
Happy feeling	19
Calmness	17
Dizziness	15
Alleviation of constipation	15
Epigastric discomfort	15
Prevention of hunger	11
Increased respiration	10

in 60% and between 20 and 30 years in 30% of these users. The reasons for trying it were curiosity in 50% and social or peer pressure in 30%.

Reported effects of the first and subsequent betel chewings in these habitual users are listed in table 2. These effects seem to suggest that both central and autonomic nervous systems are affected. Surprisingly, only 20% of habitual users admitted dependency on the habit. The withdrawal symptoms included low spirits, general body discomfort, loosening of the gums, loss of concentration and bad temper.

Interpretation of these data requires caution. As betel chewing has been discouraged by society and the government, our impression was that the users might tend to deemphasize the beneficial effects as well as deny the problem of psychological dependency.

Ingredients of the Betel Quid

The main ingredient of the betel nut *Areca catechu* is arecoline, which is one of the three major natural cholinomimetic alkaloids [40]. The other two alkaloids are pilocarpine and muscarine [40]. Many effects from betel chewing have been attributed to the actions of arecoline [29, 34, 40, 42].

Several active compounds of the Areca nut, *Piper betle* flower and *Acacia catechu* have been identified [21, 43–46]. Areca nut contains four major alkaloids: arecoline (7.5 mg/g weight), arecaidine (1.5 mg/g weight), guvacoline (2.0 mg/g weight) and guvacine (2.9 mg/g weight) [46]. The Areca nut also contains phenolic compounds, mainly hydroxychavicol and safrole [46]. Seven phenolic compounds are found in *Piper betle* flower. The major one is safrole. The others are hydroxychavicol, eugenol, methyl eugenol, isoeugenol, flavone and quercetin [23]. *Piper betle* leaf contains a large amount of carotenes (80.5 mg/g weight), as well as smaller amounts of phenolic compounds (21.9 mg/g weight) and ascorbic acid (1.9 mg/g weight) [44]. *Acacia catechu* contains predominantly (+)-catechin and (–)-epicatechin [44].

Complex reactions may occur during chewing of the betel quid [30, 48]. In the presence of lime, with its high alkalinity, arecoline and guvacoline are largely hydrolyzed into arecaidine and guvacine, respectively [40]. Both Areca nut and *Piper betle* contain phenolic compounds [43]. After release from the betel quid during chewing, the contents of these compounds are reduced [48]. Appreciable reduction is seen in safrole, (+)-catechin, hydroxychavicol, eugenol and methyl eugenol [43].

Animal Studies

Arecoline acts on both muscarinic and nicotinic receptors, promoting peristalsis and glandular secretion, contracting bronchial muscles, producing miosis, reducing the heart rate, lowering the blood pressure and stimulating respiration [40, 42]. Intravenous injection of arecoline in cats evokes a cortical arousal or activation response, an effect similar to that provoked by acetylcholine or by electrical stimulation of the brain stem reticular formation [19, 34]. Arecoline also increases motility and the brain acetylcholine level in mice [27]. Arecoline may release endogenous corticotropin-releasing hormone in rats by stimulating the hypothalamic-pituitary-adrenal axis [4].

Arecaidine lacks the typical parasympathomimetic effects of arecoline [29, 40]. Arecaidine affects the behavior of mice, reducing motility and exploration [29]. One study using rat brain slices has shown that arecaidine and guvacine act as substrate-competitive inhibitors of GABA uptake [22]. Another study using cat spinal cord slices demonstrated that arecaidine enhanced the inhibitory actions of GABA and β-alanine, while guvacine enhanced the inhibition by GABA but not that by glycine [24]. On the other hand, intravenous administration of arecaidine failed to affect GABA effects, suggesting that arecaidine itself may not cross the blood-brain barrier, and the central effects of *Areca catechu* may involve transmitters other than GABA [24].

In an in vitro study investigating the secretion of catecholamines from chromaffin cells, both arecoline and arecaidine increased secretion in a dose-response fashion [45]. The data suggest that arecoline and arecaidine may have sympathomimetic actions. Similarly, hydroxychavicol, isoeugenol and eugenol, which are phenolic compounds in *Piper betle* flower or leaf, have also been found to stimulate the release of catecholamines from chromaffin cells, and thus may also contribute to the psychostimulating effects of betel chewing [21].

More interesting was the in vitro secretion of catecholamines by different salivas collected from volunteers who were asked to chew various combinations of Areca nut, *Piper betle* flower and red lime [45]. The saliva collected from chewing a mixture of betel nut and red lime released more catecholamines than the saliva from chewing betel nut only or a mixture of *Piper betle* flower and red lime. The saliva from chewing a mixture of betel nut and *Piper betle* flower had an even stronger effect. These data seem to suggest that both betel nut and *Piper betle* flower have sympathomimetic effects in vitro.

Human Studies

Acute Effects

First-time use or heavy consumption by habitual users may elicit a cholinergic toxicity with tremor, salivation, sweating, lacrimation, diarrhea, gastrointestinal upset and emesis [40]. In habitual users, the claimed effects are listed in tables 1 and 2.

Cardiovascular Responses

Over half of habitual users experience palpitations during betel chewing, indicating an increase in heart rate [16]. Early reports from Papua New Guinea observed that the predominant effect of betel chewing in habitual users was an increase in heart rate [18, 48].

In a more comprehensive study, betel chewing was shown to increase the heart rate in new, occasional and habitual users, but only new users showed an increase in systolic blood pressure [9]. The cardioacceleratory effect began within 2 min of chewing, reached a maximal effect within 4–6 min and lasted for an average of 16.8 min. Furthermore, the mean increase in heart rate (beats per min) was 17.0 for new chewers, 16.2 for occasional chewers and 13.3 for habitual users, while the duration of the effects was the longest for new chewers, the shortest for chronic chewers and in between for occasional chewers. These findings seem to indicate a physiological manifestation of tolerance or habituation.

In psychiatric or neurological patients who were pretreated with a peripheral cholinergic blocker, intravenous or subcutaneous administration of arecoline in low doses also produced an increase in the heart rate [1, 30, 31, 37]. In one study, heart rate and blood pressure were significantly elevated, while the body temperature was significantly reduced [31]. The results of these studies suggest that arecoline exerts cardiovascular and thermic effects through central cholinergic mechanisms.

Alerting Effects

Betel chewing has been claimed to heighten alertness and to facilitate performance, but the results of studies on these claims are conflicting.

Stricherz and Pratt [38] performed a simple reaction time task under three experimental conditions: no quid, partial quid (betel nut and piper leaf) and full quid (betel nut, piper leaf and lime). Reaction time latencies were significantly lengthened only following the ingestion of total quid during the first 20 reaction time trials or within an initial 5-min interval. Although the effect was interpreted as an inhibition of familiarity during the initial trials, the

task seemed to be initiated too early for the full effect of betel chewing to occur [9]. Furthermore, the initial intense chewing per se might also interfere with task performance.

Wyatt [48] studied visual choice reaction time, digit span, eye-hand coordination, pulse rate and blood pressure during betel quid chewing. All measurements were completed within 15–17 min, which included 1-min trials with a 10- to 15-second pause in between for each task and a rest interval of 30 s between tasks. Only the pulse rate was significantly increased. Interpretation of these results is difficult, because performing these five measurements within such a short time might pose considerable difficulty for both study subjects and experimenters.

We have investigated the effects of betel quid chewing on simple and choice reaction times in habitual users [12]. The controls were chewing gum and practice groups. Both simple and choice reaction times were corrected for age. Simple reaction times were not different among the three groups studied. In choice reaction time tasks, both the betel chewing and chewing gum groups showed a significant shortening of choice reaction time, but in the betel chewing group there was a higher degree of statistical significance ($p < 0.0001$ vs. $p = 0.0379$). It was concluded that the shortening of choice reaction time was probably partly due to the chewing itself and partly due to a cholinergic arousal mechanism.

EEG spectral analysis and topographic mapping provides an objective and quantitative evaluation of betel chewing on brain activity [10]. Betel chewing increased both alpha and beta activities, while theta activity was decreased. These effects were most prominent for beta rhythm. Topographic mapping revealed that altered spectral rhythms were mainly restricted to the occipital area for the alpha band but were more widespread for both beta and theta bands. These data suggest that betel chewing causes EEG changes associated with a state of arousal and to a lesser degree a state of relaxation.

Temperature Effects

Betel chewers often claim that betel chewing produces facial flushing and a warm sensation in the body which are associated with sweating [16].

In our study, the skin temperature of the ear and forehead during betel chewing showed a mean increase of 2 and 0.5 °C, respectively [14]. The hyperthermic response was almost completely abolished by atropine and partially inhibited by propranolol, suggesting that both parasympathetic and sympathetic mechanisms are involved.

In our preliminary study using carotid Doppler to measure blood flow, the peak-systolic and end-diastolic blood velocity and volume during betel chewing were significantly increased only in the common and external carotid arteries but not in the internal carotid artery. This flow increase was associated with a facial flushing sensation.

Autonomic Effects

Autonomic effects of betel chewing were studied by sympathetic skin response (SSR) and RR interval variation (RRIV). The SSR is a psychophysical response mediated by the central and peripheral sympathetic pathways [35], while the RRIV depends partly on the parasympathetic reflex mediated by the vagus nerve [36].

In the SSR study, the response latency remained unchanged while the response amplitude showed a progressive reduction during chewing and a gradual recovery after chewing [11]. This amplitude reduction is also seen in palmar hyperhidrosis [8]. The result was interpreted as the combined effects of sympathetic activation and arousal which may reduce the novelty of the stimulus.

In the RRIV study, the main effect was a cardioacceleratory response when one or two betel quids were consumed [13]. When the consumption was increased further, there was a reduction in RRIV, particularly during deep breathing, suggesting a parasympathetic activation. The data suggest that consumption of a small amount of betel quid causes mainly a sympathetic activation, while consumption of a large amount causes additional parasympathetic activation.

When plasma concentrations of norepinephrine, epinephrine and dopamine were measured following chewing of betel quid or betel nut only, the concentrations of norepinephrine and epinephrine were significantly elevated only in the betel quid group, although the concentration of norepinephrine was marginally elevated ($p = 0.0607$) in the betel nut group [15]. It is generally believed that plasma norepinephrine concentration is an index of sympathetic nervous system activity, while the epinephrine level is a response to sympathetic activation [26, 41]. These data suggest that cardiovascular responses following betel chewing are primarily mediated by sympathoadrenal activation, and that chewing of Areca nut only may have a mild sympathetic effect.

Learning Effects

In a report by Sitaram et al. [37], subcutaneous administration of arecoline and choline, a precursor of acetylcholine, significantly enhanced serial learning in normal human subjects, and the degree of enhancement was

inversely proportional to the subject's performance with a placebo; that is, 'poor' performers were more vulnerable to the enhancing effect of arecoline and choline than 'good' performers.

On the other hand, betel chewing did not have a significant effect on critical flicker fusion, which is an index of the efficiency of the visual processing system. Betel chewing also had no effect on the performance in digit span [48].

Habituation, Addiction and Withdrawal

Burton-Bradley [2] described three medical syndromes associated with betel chewing: habituation, addiction and toxic psychosis. Others have also reported withdrawal syndrome [16, 39, 47].

Addiction to betel chewing is usually mild to moderate. Habitual users often need to consume several to a few dozen betel quids every day [2, 16, 23]. Heavy habitual users may consume over 60 betel quids per day [16, 23] and a day without betel chewing is impossible [2].

The withdrawal syndrome is usually mild. Symptoms include poor concentration, sensation of unease, general lassitude, anxiety, fidgeting, despondency and even episodes of paranoia [3, 16, 47].

Neurological Complications

Neurological complications associated with betel chewing seem to be rare. An acute toxic psychosis is characterized by auditory hallucinations or grandiose or persecutory delusions. These symptoms tend to occur in heavy users who have not been chewing for some time and then suddenly consume a large amount when visiting friends or relatives, or on ceremonial occasions [4]. Acute psychosis seems more likely to occur in persons who are predisposed to mental illness [2]. These neurological complications are reversible. There are no reports of 'bad trips' following excessive chewing.

An extrapyramidal syndrome resembling parkinsonism has been reported in two chronic schizophrenia patients on depot neuroleptics following a period of heavy betel nut consumption [17]. The extrapyramidal syndrome was also reversible and subsided several weeks after abstinence from betel chewing.

Therapeutic Trials

Cholinergic mechanisms have been implicated in some mental disorders and neurological diseases. Therefore, arecoline has been tried in psychiatric and neurological disorders, as described below.

Psychiatric Diseases. Intravenous administration of arecoline in patients with major depressive disorder resulted in a significant correlation between the magnitude of heart rate increase and the latency of onset of the second REM period, suggesting some central cholinergic sensitivity [37]. On the other hand, subcutaneous administration of arecoline resulted in nonspecific neurochemical effects in patients with bipolar affective disorder [30].

Neurological Diseases. In patients with Huntington disease, arecoline tended to exacerbate the choreic movements [31]. In patients with Alzheimer presenile dementia, arecoline, like physostigmine, significantly improved performance on a picture recognition test, but for the majority of patients, the improvement was only slight [7].

Comments

Several claimed effects of betel chewing have been confirmed by objective, psychophysiological or neurophysiological experiments. These effects include (1) palpitations, demonstrated by increased pulse rate; (2) a warm sensation in the face and body, demonstrated by increased body temperature and increased blood flow to the face; (3) profuse sweating, shown by an altered sympathetic skin response, and (4) heightened alertness, as shown by shortened performance reaction time and EEG desynchronization. Other claimed effects require further studies.

Interpretation of these effects is difficult because the following conditions are not yet certain: (1) the sites and modes of betel chewing effects; (2) the amounts of active compounds released from betel chewing and also those that are absorbed into the circulation and the brain, and (3) possible complex interactions between various absorbed active compounds in the brain and the autonomic nervous system.

Some effects of betel chewing, such as cardioacceleration and hyperthermia, are likely due to sympathetic activation. The notion of sympathetic activation is supported by a significant elevation in the plasma concentrations of norepinephrine and epinephrine during betel quid chewing [16]. However, administration of arecoline in humans who were pretreated with a peripheral cholinergic blocker also caused an increase in heart rate and blood pressure [30, 37], suggesting that these cardiovascular responses are mediated by central cholinergic mechanisms which then activate the sympathetic system.

In an in vitro study, both arecoline and arecaidine increased the release of catecholamines [45]. In humans,

chewing of Areca nut may slightly elevate plasma concentrations of norepinephrine, while chewing of betel quid significantly elevates plasma concentrations of both epinephrine and norepinephrine [16]. These findings suggest that alkaloids of Areca nut may be capable of sympathetic activation and that a sympathoadrenal response is also elicited during betel quid chewing.

Some of the phenolic compounds in *Piper betle* flower also stimulate catecholamine release [21, 45]. These in vitro experiments suggest that chewing of betel quid, Areca nut or *Piper betle* flower may produce various degrees of sympathetic activation. It is therefore important to analyze various compounds released from actual chewing of betel quid, and also various compounds that are absorbed into the circulation.

Human studies have shown that the effects of betel quid chewing on heart rate, blood pressure and body temperature occurred within 2 min after chewing and reached a peak within 4–6 min [9, 14]. These findings suggest that active compounds released during betel chewing are absorbed rapidly from the oral cavity, and this surge of absorption may be responsible for the initial kick experienced by users.

Human studies have further shown that the effects of betel quid chewing depend on the duration and severity of the chewing habit [9], suggesting the development of habituation. Furthermore, the RRIV study has shown that the effect of betel chewing was dose related [13]. The major effect of the usual consumption of betel quid is mainly due to sympathetic activation, but continued consumption of a large quantity will affect parasympathetic function.

Two main central effects of betel chewing are heightened alertness and increased performance. Betel chewing produces a widespread EEG desynchronization indicating an arousal response [12]. In addition, betel chewing shortens choice reaction time, which requires sustained alertness and a central decision process to execute the motor response. These effects are likely related to EEG desynchronization, which is seen not only during arousal but also during focused attention or when performing various mental tasks [25]. Whether these two effects are mainly due to the actions of arecoline remain to be determined. On the other hand, a sympathetic mechanism may contribute, at least partly, to these effects, because both cholinergic and adrenergic drugs are capable of inducing EEG cortical arousal [25].

Conclusions

Recent human studies have shown that the predominant effects of betel quid chewing appear to be exerted on the central and autonomic nervous systems, and these effects are habit related and dose dependent. Although arecoline has been thought to be responsible for several symptoms of betel quid chewing, results of recent studies have suggested that arecoline, arecaidine and several phenolic compounds may have a stimulating effect on the sympathetic system. The phenomena of habituation, addiction and withdrawal remain inadequately investigated. Further studies on the active compounds absorbed, the sites and modes of their actions and the mechanisms of addiction are warranted.

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