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ORIGINAL INVESTIGATION

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Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and *d*-methamphetamine in healthy volunteers

Results of an experimental double-blind placebo-controlled study

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Abstract The aim of this study was to contribute to the characterization of the entactogen (ecstasy) substance group. The psychopathological, neuroendocrine and autonomic effects of common recreational doses of the entactogen 3,4-methylenedioxyethylamphetamine (MDE), the hallucinogen psilocybin, the stimulant *d*-methamphetamine and placebo were investigated in a double-blind study with healthy volunteers ($n = 32$). Psychological effects of the drugs were assessed by means of standardized rating scales, self assessment inventories and free descriptions. The most characteristic effects of MDE were pleasant emotional experiences of relaxation, peacefulness, content and closeness to others. However, significant stimulant and hallucinogen-like effects were also present, although the latter were weaker than the effects of psilocybin. MDE elicited the strongest endocrine and autonomic effects among the three drugs, including robust rises of serum cortisol and prolactin, elevations of blood pressure and heart rate, and a moderate, but significant rise of body temperature. The apparent contrast between psychological and autonomic effects (subjective relaxation versus physical activation) was a unique feature of the MDE state. Our findings are in line with both users' reports and results from previous experimental studies, and support the view that entactogens constitute a distinct psychoactive substance class taking an intermediate position between hallucinogens and stimulants.

Key words MDE · Ecstasy · Methamphetamine · Psilocybin · Entactogens · Psychopathology

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Introduction

The methylenedioxyamphetamines are a novel psychoactive substance group with close structural similarities to both stimulant amphetamines and hallucinogenic phenethylamines. The prototype, 3,4-methylenedioxymethamphetamine (MDMA), became originally known as "ecstasy" (Grob and Poland 1997). Meanwhile, MDMA-like drugs such as 3,4-methylenedioxyethylamphetamine (MDE), 3,4-methylenedioxyamphetamine (MDA) and *N*-methyl-1, 3-benzodioxolbutanamine (MBDB) are also dealt under the label "ecstasy" on the street (Saunders 1995; Milroy et al. 1996; Gouzoulis-Mayfrank, 1998). MDMA and MDMA-like drugs are thought to evoke mainly pleasant emotional effects of relaxation, feelings of happiness, increased empathy and closeness to others (Downing 1986; Greer and Tolbert 1986; Peroutka et al. 1988; Liester et al. 1992; Hermle et al. 1993; Cohen 1995). However, hallucinations, mental confusion and anxious experiences have been described in a number of case reports following ingestion of ecstasy (Whitaker-Azmitia and Aronson 1989; Benazzi and Mazzoli 1991; Creighton et al. 1991; Liester et al. 1992; McCann and Ricaurte 1992; Pallanti and Mazzi 1992; Gouzoulis et al. 1993b). The classification of the methylenedioxyamphetamines is still a matter of debate, with some experts regarding these drugs a stimulant and others regarding them a hallucinogenic

substance group. However, converging lines of evidence from psychological and pharmaceutical/pharmacological studies seem to support the hypothesis of a distinct psychoactive substance class (Solowji et al. 1992; Hermle et al. 1993; Nichols 1994; Parrott and Stuart 1997). This hypothetical new class was designated the entactogens (Nichols 1986).

MDMA and MDMA-like drugs display high affinities to serotonin and lower affinities to norepinephrine and dopamine uptake sites of central neurons (Battaglia et al. 1988). Their indirect serotonergic properties (release and reuptake inhibition of serotonin) are considered as the primary mode of action of this substance group (Johnson et al. 1986; Steele et al. 1987). In contrast, effects of stimulants are mediated primarily through indirect dopaminergic mechanisms (King and Ellinwood 1992). Finally, the crucial pharmacologic feature of hallucinogens is thought to be their direct agonistic action at 5-HT_{2A}binding sites (Aghajanian 1994; Pechnick and Ungerleider 1997).

The increasing use and abuse of ecstasy has become a serious public health problem (Grob and Poland 1997). Physical and psychological adverse effects, fatalities and possible long-term neurotoxic damage due to ecstasy abuse have been addressed in numerous investigations (Dowling et al. 1987; Henry et al. 1992; Krystal et al. 1992; Allen et al. 1993; McCann et al. 1994). In contrast, there are only few experimental data from recent open pilot or placebo-controlled studies on the acute effects of the entactogens in humans (Downing 1986; Gouzoulis et al. 1992, 1993a; Hermle et al. 1993; Grob et al. 1996; Gamma et al. 1997; Vollenweider et al. 1997). Because of the powerful psychological effects of MDMA-like drugs, a study design including different psychoactive drugs and placebo might offer methodological advantages. The present study includes the entactogen MDE (3,4-methylenedioxyethylamphetamine), the hallucinogen psilocybin, the stimulant *d*-methamphetamine, and placebo. The overlapping psychological effects of the drugs let the double-blind study design appear more realistic, and might permit more reliable interpretations regarding the classification of the entactogenic drug group. This study was part of a more comprehensive project, which included psychopathological, neuropsychological, neurometabolic, electrophysiological and neuroendocrine measures. In this paper, we report on the psychological, neuroendocrine and autonomic effects of the drugs.

Materials and methods

Subjects

Thirty-two healthy volunteers (male / female: 21/11; mean age: 34 years, range: 27–47) with no current or previous history of significant physical or psychiatric disease, no family history of severe psychiatric disorder in first degree relatives, and no regular medication were included in the study. Following the randomization plan, subjects were allocated to one of four drug groups (MDE, psilocybin, *d*-methamphetamine, placebo, $n = 8$ each) according to the sequence of their entering the study. The subject characteristics for the four groups were: MDE: m/f: 6/2, mean age: 33.7, range: 28–46; psilocybin: m/f: 3/5, mean age: 31.4, range: 28.5–36.5; *d*-methamphetamine: m/f: 6/2, mean age: 37, range: 28.5–47.5; placebo: m/f: 6/2, mean age: 34.6, range: 27–45. Female volunteers had a regular menstrual cycle and did not receive contraceptives. All subjects were either physicians ($n = 25$) or psychologists ($n = 7$). They had a scientific or clinical interest of their own in the study and received no payment for their participation (self-experiments). Each volunteer gave written informed consent. Before entering the study, subjects were screened by means of a medical history, clinical examination, electrocardiogram, laboratory testing including blood cell counts, electrolytes, plasma creatinine, and liver enzymes, as well as a standardized psychiatric interview according to DSM-III-R (SCID) supplemented by a clinical interview, and standard psychometric instruments (Freiburg Personality Inventory revised FPI-R, Fahrenberg et al. 1984; State Trait Anxiety Inventory/Trait form STAI-X2, Laux et al. 1981). No subject met DSM-III-R criteria for alcohol or substance abuse at present or in the past. Fourteen volunteers had single or sporadic experiences with hallucinogens or stimulants, and 23 volunteers had single or sporadic experiences with cannabis several years prior to the study (mostly during high school education). Three subjects had no prior experience with psychotropic substances. Each subject had been without any medication and had not been subject to excessive caffeine intake and stressful life events during the last 4 weeks prior to the study.

Substances

All substances were obtained from the Pharmaceutical Institute of the University of Tübingen, and were prepared as capsules of identical appearance. Psilocybin and *d*-methamphetamine were obtained in 2.5 mg and 10 mg capsules. MDE was obtained in 10 mg and 100 mg capsules. The calculated individual dose of each subject was made available by combination of these capsules. When necessary, empty placebo capsules were added, so that all volunteers received five capsules. Substances were given in the following doses: psilocybin: approximately 0.2 mg/kg, but not more than 15 mg total dose ($n = 8$); MDE: approximately 2 mg/kg, but not more than 140 mg ($n = 8$); *d*-methamphetamine: approximately 0.2 mg/kg, but not more than 17.5 mg ($n = 4$). In an interim evaluation this first methamphetamine dose was shown to induce only very subtle psychological and physiological effects in the first four subjects. Therefore, the dose was increased to approximately 0.4 mg/kg, but not more than 35 mg ($n = 4$). However, clinical effects did not intensify substantially with the higher dose. Data from both methamphetamine dose regimens were pooled together for statistical analysis ($n = 8$).

Experimental procedures

The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee at the Medical Faculty of the University of Technology Aachen, the Federal Health Administration (Bundesinstitut für Arzneimittel und Medizinprodukte) and the proper authorities for irradiation protection. Each subject participated in two experiments with the same substance 2–4 weeks apart in a double-blind design and pseudo-randomized order. Fasting subjects arrived at the hospital between 8:00 and 9:00 a.m, and intravenous catheters were placed in forearm veins of both arms immediately thereafter. Subjects had free access to water; otherwise they fasted during the experiment. A psychiatric interview was performed and the psychometric instruments were completed by the subject and the researcher (t_0). On the first

experimental day, neuropsychological tests were performed and on the second experimental day, a startle session was run about 1 h prior to drug ingestion. During the experiments, subjects were lying most of the time comfortably in a bed with head and upper trunk elevated, and were accompanied by one experienced psychiatrist and a medical student. Drugs were administered between 10:00 and 11:00 a.m. Cardiovascular parameters (systolic and diastolic blood pressure, heart rate) and sublingual temperature were measured twice before ingestion of the drug (at about −15 and −5 min), approximately every 20 min during the first 2 h after drug administration, and thereafter about every 60 min till the end of the experiment (Dinamap Vital Data Monitor 8100, Criricon; digital thermometer 15.20/88.06 Hartmann). On the second experimental day, blood was taken for the assessment of hormonal responses (prolactin, cortisol, growth hormone) and drug serum levels at –10, 0, +15, +30, +50, +70, +90, +110, +140, +180, +240, and +300 min after drug administration. In all female volunteers, this second experiment was performed during the early follicular phase of their menstrual cycle. After the psychological symptoms emerged and became prominent the neuropsychological tests or the startle session were repeated (mostly 75–95 min after drug ingestion). Subsequently, subjects were transported lying to the Department of Nuclear Medicine and underwent a positron emission tomography scan (PET) using 18-fluorodeoxyglucose. In the cases where no apparent psychological changes occurred, neuropsychological testing began 90 min and PET scanning procedure about 120 min after drug ingestion. After the PET examination, subjects were transported back to the Psychiatric Department and remained there for at least 2 h after resolution of the psychological effects (mostly 6–8 h after drug ingestion). During that time, subjects were interviewed on the drug effects and both subject and researcher completed the psychometric instruments regarding the time period of significant drug effects (t_1: about 60–240 min after intake). When discharged subjects were instructed to contact the researcher whenever problems such as anxiety, flashback etc. should occur during the following week. On the day after the experiment, an interview on possible delayed effects took place. Psychometric instruments were completed regarding the time period between the end of the experiment and 24 h after ingestion of the drug (t_2). Finally, 1 week after the experiment, subjects completed self assessment scales regarding the time period from 1 to 7 days after the experiment (t_3). In addition, subjects gave free written accounts of their experiences during the experiment and during the week following the experiment.

Assessment of psychological effects

Psychometric assessments are summarized in Table 1.

Self assessment inventories

Subjects completed two scales for the assessment of hallucinogen effects: The Hallucinogen Rating Scale HRS (Strassman et al. 1994) consists of six subscales: somatesthesia, affect, perception, cognition, volition and intensity. The APZ questionnaire (Abnormer Psychischer Zustand = altered state of consciousness) (Dittrich 1985; Dittrich et al. 1985) includes three subscales: OSE (ozeanische Selbstentgrenzung = oceanic boundlessness) measures pleasant, ecstatic experiences and feelings of eternity and unity; AIA (Angst vor der Ich-Auflösung = dread of ego dissolution) describes a disintegrative, anxious state ("bad trip"); VUS (visionäre Umstrukturierung = visionary restructuralization) includes hallucinatory phenomena and experiences of altered meaning and significance. In addition, subjects completed the State Anxiety Inventory STAI-X1 (Laux et al. 1981), and the Vegetative Lability Scale B-L (Beschwerdeliste, Von Zerssen 1976).

Psychiatric scales

We used the Positive and Negative Symptom Scale PANSS (Kay et al. 1987) for the assessment of psychotic symptoms and general psychopathology, and the Bech-Rafaelsen Mania and Melancholia Scales (BRMAS, BRMES; Bech et al. 1988) for the assessment of affective symptoms.

Hormonal assessments

Blood samples for the determination of hormone levels were drawn into 10 ml serum tubes containing granulate covered caolin (aluminium silicate), and were centrifuged immediately after drawing (+4°, 4000 U/min, 10 min). Serum was separated and stored at −7°C until the time of the assay. Cortisol was measured by heterogeneous competitive magnetic separation assay (MSA Bayer; coefficients of variation within run: 3.1–5.2%, between run: 4.5–7.9%). Prolactin was measured by heterogeneous sandwich magnetic separation assay (MSA Bayer; coefficients of variation within run: 1.6–2.0%, between run: 2.6–3.0%). Growth hormone was measured by sandwich-chemiluminescence immunoassay (Immulite Biermann, Bad Nauheim; coefficients of variation within run: 2.5–4.8%, between run: 3.1–5.0%).

Statistical analysis

Psychological trait measures

Freiburg Personality Inventory revised (FPI-R) and Trait Anxiety (STAI-X2) scores were analyzed by means of Kruskal-Wallis, Wilcoxon tests and subsequent Holm's procedure.

Psychopathological state measures

Acute effects (t_1) on the 2 experimental days were compared by means of Wilcoxon tests within each group ($n = 8$). All further

Table 1 Timetable of psychometric assessments during and after the experiments

	t_0: pre-drug	t_1: drug state	t_2: 24 h after	t_3: 7 days after
PANSS: Positive and Negative Symptom Scale	×	×	×	
BRMAS: Bech-Rafaelsen Mania Scale	×	×	×	
BRMES: Bech-Rafaelsen Melancholia Scale	×	×	×	
APZ: questionnaire Altered State of Consciousness	×[a]	×		
HRS: Hallucinogen Rating Scale	×[a]	×		
STAI-X1: State anxiety inventory	×	×	×	×
B-L: Vegetative Lability Scale	×	×	×	×
Written free account			×[b]	×[b]

[a]Retrospective assessment of the last 7 days prior to the experiment
[b]Retrospective account of the experiences regarding t_1 and the time periods t_1-t_2 and t_2-t_3, respectively

analyses were performed with the data of the first experimental day. Psychometric scores at t_1 were compared to the pre-drug values within each group by means of Wilcoxon tests (t_0/t_1). Scores of the three drug groups at t_1 were compared to placebo scores by means of Mann-Whitney *U*-tests. In case of significant effects, drug groups were compared to each other using Kruskal Wallis, *U*-tests and subsequent Holm's procedure. Possible delayed effects were assessed by means of Wilcoxon tests (t_0/t_2, t_0/t_3) within each drug group.

Neuroendocrine effects

The mean of the first two hormone values (−10, 0 min) formed the individual baseline. Subsequent values were transformed into difference values from baseline (Δ). Maximal Δ concentrations (C_{max}) were evaluated and the Δ areas under the curve (AUC) were calculated. Analysis was performed by means of Kruskal-Wallis and Mann-Whitney *U*-tests with subsequent Holm´s procedure.

Autonomic effects

The mean of the first two evaluations (at –15 and –5 min) formed the individual baseline. Subsequent measurements were transformed into difference values (Δ) from baseline, and maximal effects (Δ values) were evaluated. Statistical analysis was performed by means of Kruskal-Wallis and Mann-Whitney *U*-tests with subsequent Holm's procedure.

Results

Psychological trait measures

Compared to normative data our volunteers had average mean stanine values (4–6) in all but three Freiburg Personality Inventory (FPI-R) dimensions. Mean values were low in the dimensions somatic complaints (3.34 ± 1.40) and health concerns (3.31 ± 1.86) and high in the dimension openness (6.69 ± 1.31). Statistical analysis revealed no group differences except for the dimension openness (psilocybin: 4.62 ± 1.19, methamphetamine: 2.25 ± 0.89, $P < 0.05$). STAI-X2 trait anxiety scores were low (mean: 35.6 ± 6.37) and displayed no differences across groups. In summary, psychometric measures confirmed the clinical impression of mental health and psychological robustness of our sample.

Acute psychopathological effects on the first and second experimental day

Inspection of mean scores at t_1 suggests slightly stronger effects on the first experimental day in most cases. Statistical analyses revealed the following small, but significant differences (Wilcoxon test, $P < 0.05$): psilocybin: APZ-AIA (altered state of consciousness – subscale "bad trip"), BRMAS Mania Scale; MDE: Hallucinogen Rating Scale subscales somatesthesia and affect, B-L vegetative lability scale; methamphetamine: APZ total score. The somewhat weaker effects on the second experimental day might be the expression of pharmacological tolerance or the consequence of the subjects being more familiar to drug effects and experimental procedures. The subsequent statistical analyses were performed exclusively with the data from the first experimental day.

Analysis of acute psychopathological effects within drug groups

In the psilocybin and MDE groups, significant increases were obtained for all total and subscale scores except for STAI-X1 state anxiety (t_0/t_1, Wilcoxon tests, $P < 0.05$). In the methamphetamine group, significant increases were obtained only for the subscales intensity and affect of the Hallucinogen Rating Scale, and trend increases ($P < 0.1$) were obtained for BRMAS Mania Scale, and the OSE subscale of APZ (altered state of consciousness: pleasant, ecstatic feelings). In the placebo group, the only significant effect was a decrease of the STAI-X1 state anxiety score.

Analysis of acute psychopathological effects across drug groups

In general, mean scores at t_1 tended to be highest in the psilocybin group, followed by MDE. Most mean methamphetamine scores were substantially lower, and placebo scores were the lowest. Results are illustrated in Figs. 1 and 2. The psilocybin group scored significantly higher than the placebo group in all psychometric instruments except for the STAI-X1 state anxiety. The MDE group scored significantly higher than the placebo group in most psychometric instruments except for the subscale volition of the Hallucinogen Rating Scale and the STAI-X1 state anxiety inventory. Differences between the methamphetamine group and placebo did not reach statistical significance except for the PANSS positive symptom scale (Mann-Whitney *U*-tests, $P < 0.05$). The psilocybin group scored significantly higher than the MDE group in the subscale perception of the Hallucinogen Rating Scale, the subscale AIA of the APZ (altered state of consciousness: "bad trip"), the APZ total score, the PANSS general psychopathology scale, and the BRMES Melancholia Scale (Mann-Whitney *U*-tests, $P < 0.05$). The MDE group tended to score slightly higher than the psilocybin group in the affect subscale of the Hallucinogen Rating Scale and the BRMAS Mania Scale; however, these differences were not significant. The PANSS positive symptom scale scores differentiated between psilocybin and methamphetamine, but not between psilocybin and MDE, or MDE and methamphetamine (Kruskal-Wallis, Mann-Whitney *U*-tests, Holm's procedure).

Analysis of delayed psychological effects within drug groups

For psilocybin, analyses revealed a significant increase of the B-L vegetative lability score (Wilcoxon test, $P < 0.05$) and trend increases ($P < 0.1$) of the PANSS negative symptom scale and BRMES Melancholia score during t_2 (24 h after drug intake), but not during t_3 (7 days after drug intake) compared to t_0 (pre-drug state). For MDE, there were no statistical differences in any score between t_0 and t_2 or t_0 and t_3. For methamphetamine, the B-L vegetative lability score was significantly decreased in t_3 compared to t_0. For placebo, there was a significant decrease of the STAI-X1 state anxiety score during t_2 and a trend decrease of the B-L vegetative lability score during t_3 compared to t_0.

Summary of subjective descriptions of the drug states and observations of the researcher

Effects of psilocybin were most complex and variable across subjects. Vivid alterations of optic, acoustic and tactile perception, abnormal somatic sensations and

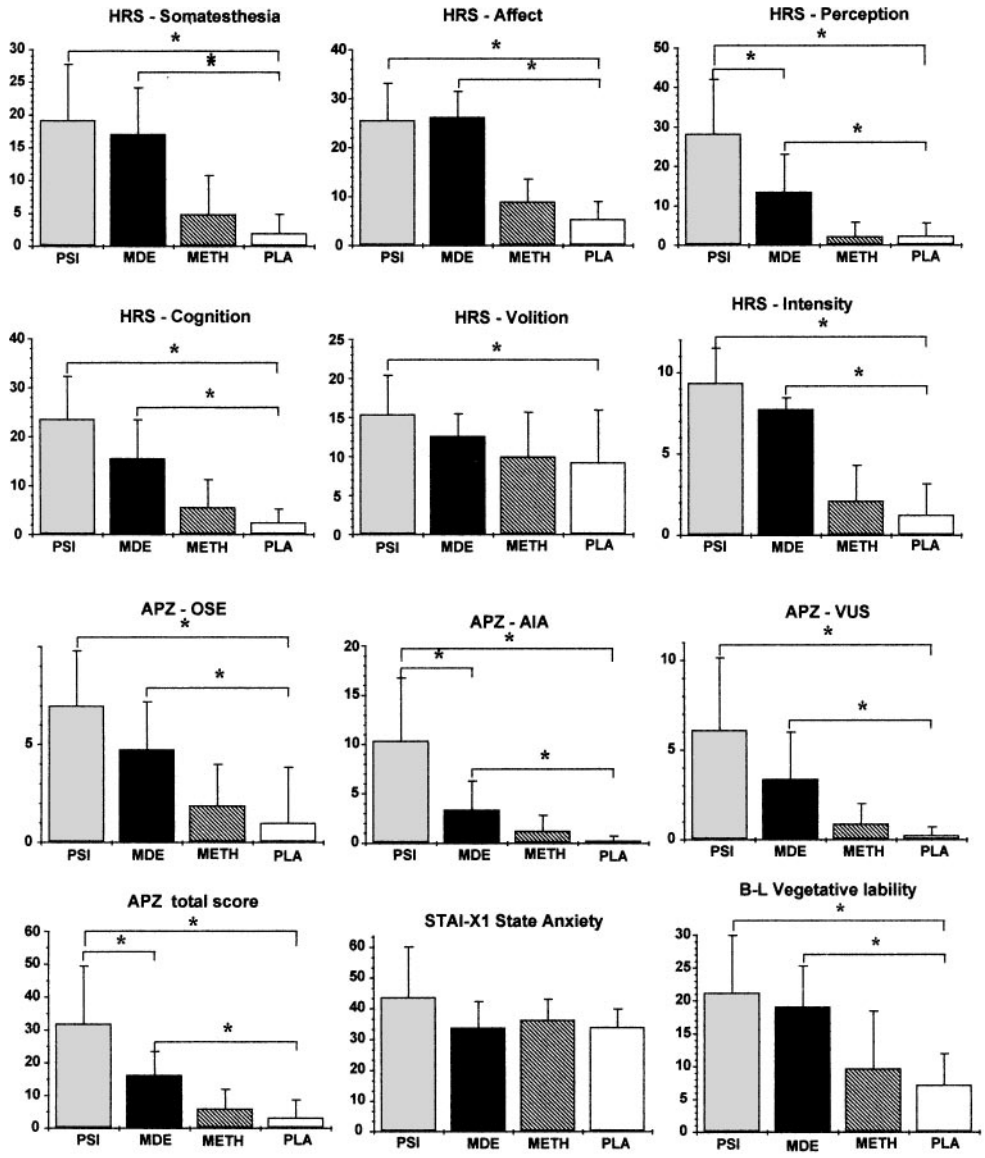

Fig. 1 Mean scores ± SD of the self assessment inventories HRS, APZ, STAI-X1 and B-L after ingestion of psilocybin (*PSI*), 3,4-methylenedioxyethylamphetamine (*MDE*), *d*-methamphetamine (*METH*) and placebo (*PLA*) (each group: $n = 8$). Significant differences (Mann-Whitney *U*-test, $P < 0.05$) are indicated by an *asterisk*. *HRS* Hallucinogen Rating Scale, *APZ* questionnaire Altered State of Consciousness (Abnormer Psychischer Zustand), *OSE* oceanic boundlessness (ozeanische Selbstentgrenzung): includes pleasant, ecstatic experiences, *AIA* dread of ego dissolution (Angst vor der Ich-Auflösung): reflects a "bad trip", *VUS* visionary restructuralization (visionäre Umstrukturierung): includes hallucinations, experiences of altered meaning and significance, *STAI-X1* state anxiety inventory, *B-L* vegetative lability scale (Beschwerde-Liste)

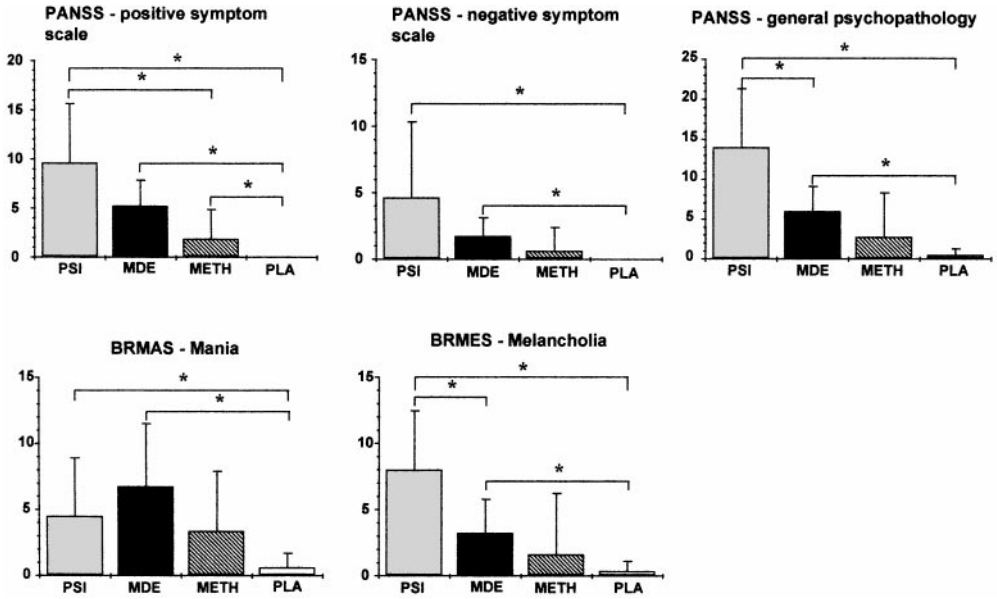

Fig. 2 Mean scores ± SD of the psychiatric scales PANSS, BRMAS and BRMES after ingestion of psilocybin (*PSI*), 3,4-methylenedioxyethylamphetamine (*MDE*), *d*-methamphetamine (*METH*) and placebo (*PLA*) (each group: $n = 8$). Significant differences (Mann-Whitney *U*-test, $P < 0.05$) are indicated by an *asterisk*. *PANSS* Positive and Negative Symptom Scale, *BRMAS* Bech-Rafaelsen Mania Scale, *BRMES* Bech-Rafaelsen Melancholia Scale

illusions were reported by all subjects. In addition, acoustic hallucinations occurred in two cases. Ego-control and insight into the experimental nature of the experience were mostly preserved. However, in four cases, there were transient paranoid thoughts and/or anxious experiences of loss of control, which could always be managed by merely talking down. Mood and drive varied across and within subjects. Intense emotions and primitive emotional displays, but also emotional blunting were observed. Single subjects displayed increased energy and drive, while others were apathetic and withdrawn. Formal thought was more or less impaired in all volunteers. The state was perceived as an extreme alteration of mind with no or minimal possibility for the subject to take influence on what was happening. Effects of MDE were more uniform across and within subjects. The state was also perceived as a strong alteration compared to the individual' s everyday experience, but at the same time subjects had the feeling that they remained in control of the situation. Insight into the experimental nature of the experience and ego-control were always preserved. The most characteristic effects were pleasant and emotional in nature (happiness, fearless state with feelings of increased closeness to others, sympathy, intimate feelings and openness for communication). Intense euphoria was present in two subjects; however, sad feelings were also reported. Most subjects displayed increased energy, drive and talkativeness. However, two subjects were rather quiet and withdrawn while experiencing strong emotional effects. Alterations of optic, acoustic or tactile perception and abnormal somatic sensations were reported by all subjects, but were more subtle than the effects of psilocybin. One subject experienced an optic hallucination, which she found fascinating to observe (a moving amoeba-like figure on the computer screen).

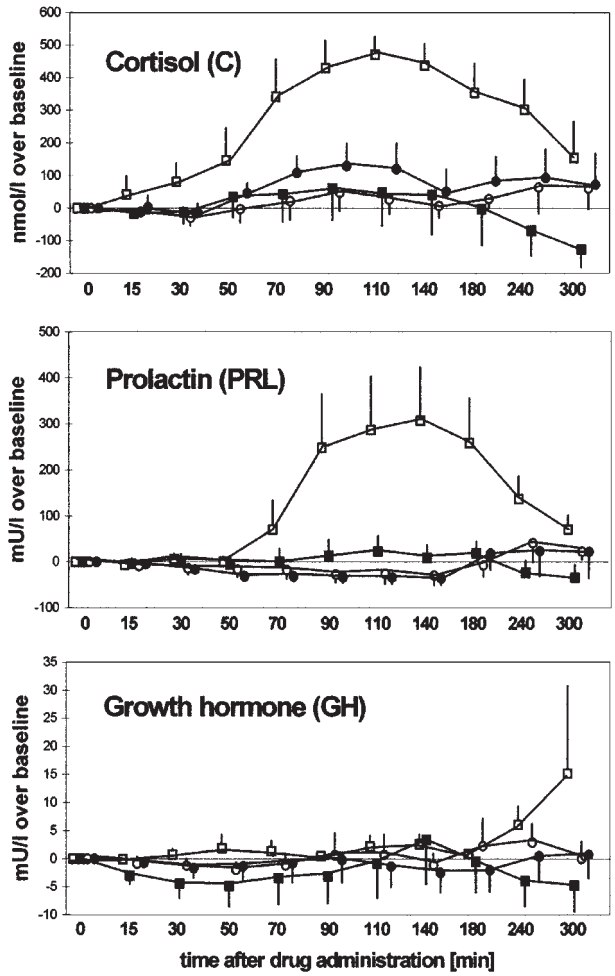

Fig. 3 Time-curves of hormonal responses (means ± SD) after intake of psilocybin (■), 3,4-methylenedioxyethylamphetamine (□, *MDE*), *d*-methamphetamine (●) and placebo (○) (each group: $n = 8$)

Table 2 Mean values ± SD of maximal autonomic effects (*Δ* values from baseline) of 3,4-methylenedioxyethylamphetamine (*MDE*), psilocybin (*PSI*), *d*-methamphetamine (*METH*) and placebo (*PLA*) (each group: $n = 8$). Significant or trend differences from placebo are indicated by: $^{**}P < 0.01$; $^{*}P < 0.05$; $(^{*})P < 0.1$ (Kruskal-Wallis, Mann-Whitney *U*-tests, Holm's procedure)

		Δ Systolic RR (mmHg)	*Δ* Diastolic RR (mmHg)	*Δ* Heart frequency (1/min)	*Δ* Sublingual temperature (°C)
MDE	Experiment 1	38.6 ± 7.3**	18.2 ± 7.3 (*)	44.8 ± 19.0**	0.37 ± 0.71
	Experiment 2	32.9 ± 16.5**	11.2 ± 10.8 (*)	39.3 ± 21.4**	0.59 ± 0.17**
PSI	Experiment 1	25.9 ± 11.7*	10.0 ± 7.6	10.4 ± 12.6	0.11 ± 0.49
	Experiment 2	16.8 ± 11.2	6.7 ± 14.4	−2.7 ± 14.5	0.39 ± 0.40*
METH	Experiment 1	17.1 ± 14.5	9.7 ± 7.7	5.6 ± 20.7	−0.18 ± 0.73
	Experiment 2	20.8 ± 11.9*	16.9 ± 6.3*	9.1 ± 20.1	0.03 ± 0.57
PLA	Experiment 1	4.8 ± 11.4	−1.3 ± 16.1	4.8 ± 10.5	−0.12 ± 0.47
	Experiment 2	5.1 ± 7.7	−3.5 ± 9.0	2.1 ± 8.1	−0.30 ± 0.37

Methamphetamine effects were relatively subtle in all but one case, and included slight to moderate general activation with increased vigilance and talkativeness. One volunteer displayed a slightly dysphoric, and two other subjects a slightly euphoric mood. Only one subject on the higher dose (0.4 mg/kg) experienced a profoundly altered state with alterations of formal thought, emotional responses and acoustic perception.

Neuroendocrine and autonomic effects

MDE induced robust increases in serum cortisol and prolactin (Fig. 3). Both the area under the curve (AUC) and the maximal plasma levels (C_{max}) of cortisol and prolactin were significantly higher in the MDE as compared to the other three groups (Kruskal-Wallis, Mann-Whitney *U*-tests, Holm's procedure; AUC and C_{max} cortisol: MDE/placebo: $P < 0.01$; all other pair comparisons: $P < 0.05$). Psilocybin and *d*-methamphetamine elicited no statistically significant hormonal responses compared to placebo. The effects of the drugs on cardiovascular parameters and body temperature are summarized in Table 2. MDE elicited the strongest autonomic effects including significant increases of systolic blood pressure of about 30–40 mmHg, significant rises of heart rate of about 40–45/min, trend increases of diastolic blood pressure, and a moderate, but significant increase of body temperature of 0.6°C on the second experimental day. Psilocybin elicited weaker, but significant increases of systolic blood pressure and body temperature. Finally, in the methamphetamine group there were moderate, but significant elevations of systolic and diastolic blood pressure.

Discussion

The psychological effects of typical recreational doses of an entactogen, a stimulant, and a hallucinogen were investigated in a double-blind experimental study. Ingestion of the hallucinogen psilocybin was followed by powerful alterations of perception, affect and cognition. The emotional changes were variable across and within subjects and ranged from serene and amusing to anxious and mournful moods or to apparent emotional blunting. Under the influence of psilocybin, we observed phenomena that are conceptualized both as positive *and* negative symptoms of schizophrenic psychoses. Ingestion of the stimulant methamphetamine was followed by slight to moderate general activation with increased vigilance, drive and talkativeness. Mood was not affected substantially in the majority of the volunteers. The only significant difference between methamphetamine and placebo was the score of the PANSS positive symptom scale. However, inspection of the data on the level of individual items indicates that the score was increased primarily due to high values of the relatively unspecific item agitation. Effects of the entactogen MDE were clearly more complex than the effects of the stimulant methamphetamine. The mind-altering qualities of MDE are expressed in the significant HRS (Hallucinogen Rating Scale) and APZ (questionnaire for the assessment of altered states of consciousness) scores. Scores on most psychometric scales were lower in the MDE group compared to the psilocybin group. Differences were significant particularly for scales assessing perceptional alterations, unpleasant and fearful experiences and negative, sad mood [HRS perception scale, AIA subscale of the APZ ("bad trip"), BRMES Melancholia Scale], but not for a scale assessing pleasant, positive experiences (OSE subscale of APZ: pleasant, ecstatic feelings). Moreover, MDE scores in scales assessing emotional alterations, positive mood and increased energy (HRS affect scale, BRMAS Mania Scale) were numerically slightly higher than psilocybin scores, although these differences were not significant. Thus, psychometric data and free narrative accounts of the subjects suggest that the emotional effects of MDE were more uniformly positive and pleasant than the variable emotional effects of psilocybin. These pleasant emotional effects are in line with reports on the entactogenic profile of ecstasy (Peroutka et al. 1988; Liester et al. 1992; Solowji et al. 1992; Cohen et al. 1995; Parrott and Stuart 1997) and with the findings of a previous, placebo-controlled MDE study of our group (Hermle et al. 1993). Delayed unpleasant or adverse effects in the days following ecstasy use have been frequently reported in the literature, and include depression, lethargy, tension and anxious feelings (Peroutka et al. 1988; Davison and

Parrott 1997). In our small sample, delayed adverse effects were not prominent, as indicated by group analyses of the psychometric measures. However, one subject reported depressive mood on the day following the second experiment.

The robust increases of plasma cortisol and prolactin followed by the ingestion of MDE are in line with the serotonergic properties of the ecstasy substance group (Fuller 1981; Van de Kar et al. 1985). They corroborate data from both animal studies with the related drug MDMA (Nash et al. 1988; Nash and Meltzer 1990) and a previous human experimental study of our group with MDE (Gouzoulis et al. 1993a). A trend towards decrease of growth hormone secretion, which was reported in our previous MDE study, could not be replicated now. Effects of psilocybin and *d*-methamphetamine on hormonal parameters did not reach statictical significance. Inspection of the hormone time curves suggests only slight tendencies towards the expected rise of cortisol serum level after intake of *d*-methamphetamine and prolactin serum level after intake of psilocybin (Brown et al. 1978; Meltzer et al. 1978; Dommisse et al. 1984). The lack of statistical significances may be partly due to the relatively low doses, or the insensitivity of the *d*-methamphetamine subjects to stimulant effects, respectively. Theoretically, sex might establish a further confounding variable for the interpretation of the neuroendocrine findings. This might be particularly critical for the prolactin data, where higher values would be expected in female subjects. However, inspection of the sex distribution revealed an equal number of female subjects in the MDE, methamphetamine and placebo groups, and a higher number in the psilocybin group. Thus, it is unlikely that sex effects contribute to the robust stimulation of prolactin secretion in the MDE group compared to the other three groups. Irrespective of these incertitudes, two distinct conclusions may be drawn from these data: first, the effect of MDE on cortisol secretion is unlikely to be an expression of stress, because in this case cortisol levels would be expected to be even higher in the psilocybin group. The cortisol effect of MDE is rather the expression of a robust acute potentiation of serotonergic transmission, which is stronger than the direct agonistic action of the hallucinogen psilocybin at the 5-HT_{2A} receptor (Pechnick and Ungerleider 1997). Second, the stimulation of prolactin secretion delineates MDE from *d*-methamphetamine. Effects of stimulant amphetamines are primarily dopaminergically mediated; therefore, an increase of prolactin levels after ingestion of stimulant amphetamines is not expected, and has not been reported before (Brown et al. 1978; Dommisse et al. 1984).

MDE elicited also the most robust autonomic effects compared to *d*-methamphetamine and psilocybin. The elevations of blood pressure and heart rate are consistent with the indirect catecholaminergic mechanisms, and the moderate rise of body temperature is consistent with the central serotonergic properties of ecstasy. Similar autonomic effects have been reported in two other human studies with MDMA (Downing 1986; Grob et al. 1996) and our previous study with MDE (Gouzoulis et al. 1993a). Interestingly, our volunteers had no discomfort or awareness of their physical state. They mostly felt calm and relaxed, and this was in apparent contrast to observable somatic effects such as tremor, trismus and sweating and their overall physical state. When they took notice of palpitations or other somatic changes, subjects were remarkably little perturbed or impressed. One subject noted: "It is (the heart palpitations) as if it doesn't concern me". This state of "psycho-vegetative uncoupling" was unique and a most characteristic feature of the MDE condition, which may have great dangers in typical settings of the drug and dance scene, and may account for a number of severe complications and fatalities in illegal ecstasy users (Henry et al. 1992).

The present study has two methodological limitations: first, drugs were given only in single doses, which were meant to induce significant, but not maximal effects, in order for the subjects to be able to cooperate in experimental tasks. Therefore, we cannot rule out the possibility, that not only stronger, but also qualitatively different effects might be elicited by higher drug doses. In this case, differences between the drugs might be attenuated. In particular, MDE might theoretically induce more pronounced hallucinogenic effects in higher doses. Second, *d*-methamphetamine elicited only slight psychological *and* physiological effects in our subject sample, and the dose regimen was changed from 0.2 to 0.4 mg/kg during the course of the investigation. Typical *d*-amphetamine doses used in human experimental studies are 0.1–0.5 mg/kg (Zahn et al. 1981; Angrist et al. 1987; Kelly et al. 1991), and the stimulant potency of methamphetamine is reported to be higher than the potency of amphetamine (Nichols 1994). However, even with the higher dose of 0.4 mg/kg, effects remained subtle in our sample. Toxicological analyses of blood samples in our subjects revealed *d*-methamphetamine levels that are in line with the literature, and higher serum levels with the higher dose regimen, as expected (Lindenblatt, PhD thesis, in preparation). Interindividual susceptibility for stimulant amphetamines varies greatly (Gunne 1977; Angrist 1994), and it seems that our subjects happened to be relatively insensitive. Therefore, our methamphetamine data must be interpreted with caution. More intense and qualitatively different effects than the effects seen in our experiments might occur in susceptible individuals after intake of comparable stimulant doses. The methodological limitations of our investigation are related to the apparent difficulties in planning and performing human studies with restricted drugs, which do not permit multiple dose designs and pre-testing procedures for evaluation of the individual optimal dose.

Irrespective of the above-mentioned methodological limitations, the results of the present study may be summarized as follows: moderate doses of typical representatives of the three substance classes hallucinogens, entactogens and stimulants elicited distinct psychological effects in healthy humans. The entactogen MDE took an intermediate position between the stimulant methamphetamine and the hallucinogen psilocybin and elicited highly characteristic emotional effects, that were qualitatively different from the effects of the other two drugs. Despite the overlap of psychological effects between the three substances, our data support the hypothesis that entactogens constitute a distinct psychoactive substance class (Nichols 1986).

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