Differential Actions of an Entactogen Compared to a Stimulant and a Hallucinogen in Healthy Humans

Euphrosyne Gouzoulis-Mayfrank, M.D.*

The methylenedioxyamphetamines or entactogens are chemically closely related to both stimulant amphetamines and hallucinogenic phenethylamines (Figure 1). The prototype entactogen, 3,4-methylenedioxymethamphetamine (MDMA), became originally known as "Ecstasy" (Grob and Poland 1997). However, other MDMA-like drugs with similar psychological effects such as 3,4-methylenedioxyethylamphetamine (MDE), 3,4-methylenedioxyamphetamine (MDA) and N-methyl-1,3-benzodioxolbutanamine (MBDB) are also included under the label "Ecstasy."

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. Finally, the crucial pharmacologic feature of hallucinogens is thought to be their direct agonistic action at 5-HT_{2A} binding sites.

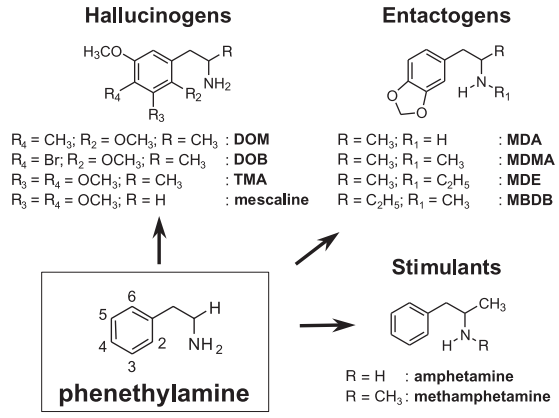

Figure 1. Chemical structures of stimulant amphetamines, entactogens and phenethylamine hallucinogens.

Entactogens evoke mainly pleasant emotional effects of relaxation, feelings of happiness, increased empathy, and closeness to others (Downing 1986; Greer & Tolbert 1986; Peroutka et al. 1988; Liester et al. 1992; Hermle et al. 1993; Cohen 1995; Vollenweider et al. 1998). However, hallucinations, mental confusion, and anxious experiences were described in a number of case reports following ingestion of Ecstasy. The classification of the entactogens has been 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 support the hypothesis of a distinct psychoactive substance class (Solowji et al. 1992; Parrott & Stuart 1997; Hermle et al. 1993; Nichols 1986, 1994).

Some years ago, we assessed the psychological, vegetative, hormonal, and sleep EEG effects of the entactogen MDE (3,4-methylenedioxyethylamphetamine) in healthy humans using a double-blind placebo-controlled cross-over design. The entactogenic effects (drop in defenses and anxiety, self-acceptance, empathy, peacefulness) were found to be a major and

* Department of Psychiatry and Psychotherapy, University of Technology (Rheinisch-Westfällische Technische Hochschule: RWTH) Aachen, Pauwelsstrasse 30, D-52074 Aachen, Germany
Tel: 0049 241 8089461; Fax: 0049 241 8888401
e-mail: egouzoulis@post.klinikum.rwth-aachen.de

unique part of the spectrum of psychological actions of MDE. However, the spectrum included also amphetamine-like and mild hallucinogenic effects. A robust rise of the pituitary hormone prolactin in blood distinguished MDE from stimulants. However, the effects of MDE on sleep architecture were mainly amphetamine-like. In summary, the results of these pilot studies with MDE did support the notion of a distinct substance class, but, in addition, they were indicative of the close relation of entactogens to both hallucinogens and stimulants (Hermle et al. 1993; Gouzoulis-Mayfrank et al. 1992; 1993a,b). The most important results were already reviewed in the first issue of the Heffter Review (Gouzoulis-Mayfrank & Hermle 1998).

There are obvious disadvantages, however, of placebo-controlled studies with psychoactive drugs as powerful as MDMA and MDE. Moreover, using a placebo-controlled design, comparisons to the effects of other drugs can only be drawn from literature data. More recently, we performed the first direct comparative study with the entactogen MDE, the hallucinogen psilocybin, the stimulant d-methamphetamine and placebo. The overlapping psychological effects of the drugs make the double-blind study design appear more realistic, and should permit for more reliable interpretations regarding the classification of the entactogenic drug group. This comprehensive project included psychopathological, neuropsychological, neurometabolic, electrophysiological, and neuroendocrine measures. The present publication reviews the most important results of the study. Parts of it were already published elsewhere (Gouzoulis-Mayfrank et al. 1998, 1999a,b, Schreckenberger et al. 1999).

General Description of the Study

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 and the proper authorities for irradiation protection.

Subjects

Thirty-two healthy volunteers (male / female: 21/11; mean age: 34 years) 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. Before entering the study subjects were screened by means of a medical history, clinical examination, electrocardiogram, laboratory testing, and extensive psychiatric interviews. No subject met diagnostic 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 or stressful life events during the last four 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. Substances were administered orally in the following doses: psilocybin: 0.2 mg/kg (n=8); MDE: 2 mg/kg (n=8); d-methamphetamine: 0.2 mg/kg (n=4) and 0.4 mg/kg (n=4). The methamphetamine dose was increased after a planned interim evaluation of the data, which revealed only very subtle psychological and physiological effects in the first four methamphetamine subjects. 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

Each subject participated in two experiments with the same substance 2- 4 weeks apart in a double-blind design and pseudorandomized 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. On the first experimental day neuropsychological tests were performed and on the second experimental day a startle session was run about one hour 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 before ingestion of the drug, and at regular intervals after drug administration. On the second experimental day blood was taken for the assessment of hormonal responses

(prolactin, cortisol, growth hormone) and drug serum levels at regular intervals. After the psychological symptoms emerged and became prominent the neuropsychological tests or the startle session were repeated (mostly 75 - 95 minutes after drug ingestion). Subsequently, subjects underwent a positron emission tomography scan (PET) using 18-fluorodeoxyglucose (FDG). In the cases where no apparent psychological changes occurred neuropsychological testing began 90 minutes and PET scanning procedure about 120 minutes after drug ingestion. After the PET examination subjects remained in the Psychiatric Department for at least two hours after resolution of the psychological effects (mostly 6 - 8 hours 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. When discharged, subjects were instructed to contact the researcher if any problems such as anxiety, flashback etc. should occur during the following week. One and seven days after the experiment an interview on possible delayed effects took place.

Profile of Psychological Effects

Narrative Description of Psychological Effects

The effects of **psilocybin** were most complex and variable across subjects. Vivid alterations of optic, acoustic, and tactile perception, abnormal somatic sensations and 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. The emotional changes ranged from serene and amusing to anxious and mournful moods or to apparent emotional blunting. 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 influence 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, a 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 intense 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 a visual hallucination, which she found fascinating to observe (a moving amoeba-like figure on the computer screen).

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.

Psychometric Instrument Scores

In addition to the interviews and direct observations, we used the following standardized psychometric instruments:

• HRS Hallucinogen Rating Scale (Strassman et al. 1994): consists of six subscales: somatesthesia, affect, perception, cognition, volition, and intensity.

• APZ questionnaire for the assessment of hallucinogen states and other similar altered states of consciousness (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.

• STAI-X1 State Anxiety Inventory (Laux et al. 1981)

• PANSS Positive and Negative Symptom Scale (Kay et al. 1987) for the assessment of psychotic symptoms and general psychopathology.

• BRMAS, BRMES Bech-Rafaelsen Mania and Melancholia Scales (Bech et al. 1988) for the assessment of affective symptoms.

In the psilocybin and MDE groups significant increases were obtained for all total and subscale scores

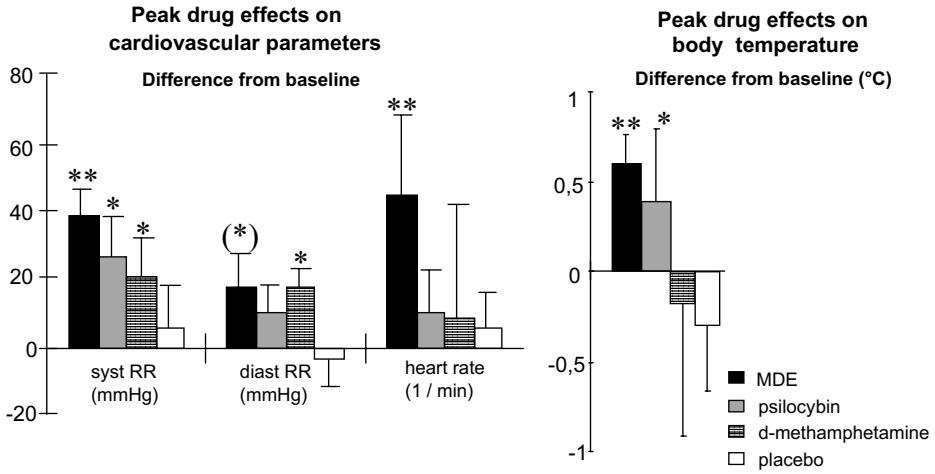

*Figure 2. Peak autonomic effects (D values from baseline) of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin (PSI), d-methamphetamine (METH) and placebo (PLA) (mean values ± SD, n=8 in each group). Significant or trend differences from placebo are indicated by: **: p<0.01; *: p<0.05; (*): p<0.1 (Kruskal Wallis, Mann-Whitney U-tests, Holm´s procedure).*

except for STAI-X1 state anxiety (pre-drug/on-drug). In the methamphetamine group significant increases were obtained only for the subscales intensity and affect of the Hallucinogen Rating Scale, and trend increases were obtained for the BRMAS Mania Scale, and the OSE subscale of the APZ. In the placebo group the only significant effect was a decrease of the STAI-X1 state anxiety score.

In general, mean scores after drug ingestion (on-drug) tended to be highest in the psilocybin group, followed by MDE. Most mean methamphetamine scores were substantially lower, and placebo scores were the lowest. 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. The MDE group scored significantly lower than the psilocybin 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. 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.

In summary, 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. Differences between MDE and psilocybin were significant, however, particularly for scales assessing perceptional alterations, unpleasant and fearful experiences, and negative, sad mood, but not for a scale assessing pleasant, positive experiences. Moreover, MDE scores in scales assessing emotional alterations, positive mood, and increased energy 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 in recreational settings (Peroutka et al. 1988; Liester et al. 1992; Solowji et al. 1992; Cohen et al. 1995; Parrott & Stuart 1997) and with the findings of previous, placebo-controlled studies with MDE and MDMA (Hermle et al. 1993; Vollenweider et al. 1998). Taken together, these data and observations confirm the notion that the psychological profile of entactogens is different from the profile of hallucinogens and stimulants, although there is overlap of effects between the three groups (Gouzoulis-Mayfrank et al. 1999b).

Autonomic Effects

The peak effects of the drugs on cardiovascular parameters and body temperature are summarized in Figure 2.

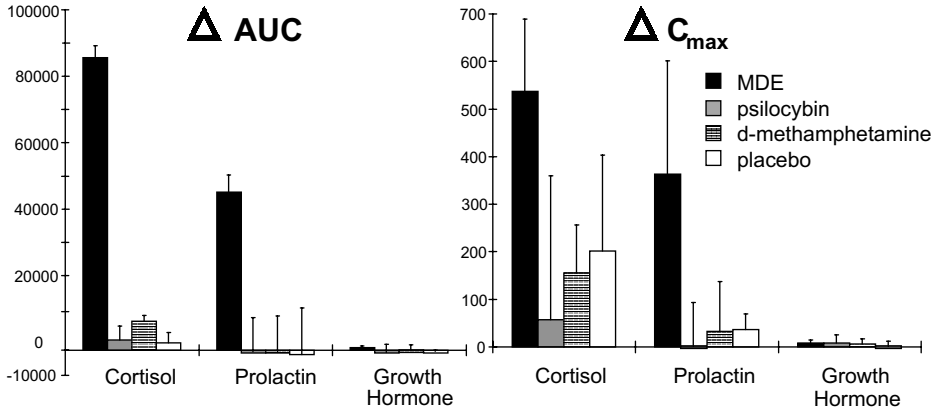

Figure 3. Hormonal responses after intake of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin (PSI), d-methamphetamine (METH) and placebo (PLA) (mean values ± SD, n=8 in each group). D: difference from baseline, AUC: Area under the curve, Cmax: peak. Differences between MDE and the other three groups were significant for AUC and Cmax of cortisol and prolactin (Kruskal Wallis, Mann-Whitney U-tests, Holm´s procedure, p<0.05).

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, a trend toward increased diastolic blood pressure, and a significant, although moderate increase of body temperature of 0.6 °C. Psilocybin elicited significant, although weaker, increases of systolic blood pressure and body temperature. Finally, in the methamphetamine group there were moderate elevations of systolic and diastolic blood pressure. The MDE-induced 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 the entactogens. Similar autonomic effects were reported in other human studies with MDMA (Downing 1986; Grob et al. 1996; Vollenweider et al. 1998; Mas et al. 1999) and in 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 dissociation" was unique and a most characteristic feature of the MDE condition (Gouzoulis-Mayfrank et al. 1999b).

Effects on Hormonal Secretion

The hormonal effects of the drugs are summarized in Figure 3.

MDE induced robust increases in serum cortisol and prolactin. 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. Psilocybin and d-methamphetamine elicited no statistically significant hormonal responses compared to placebo. 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. They corroborate data from previous studies with both MDMA and MDE (Gouzoulis et al. 1993a; Mas et al. 1999). 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 (Gouzoulis-Mayfrank et al. 1999b).

Effects on Brain Metabolism: Positron Emission Tomography (PET) Studies With Fluorodeoxyglucose (FDG)

The metabolic pattern under psilocybin was characterized by relative hypermetabolism in prefrontal and inferior temporal regions of the right hemisphere and relative hypometabolism in subcortical regions com-

pared to placebo. The most striking finding was a metabolic increase of nearly 10% in the right anterior cingulate. The thalamus and the left precentral region displayed diminished metabolic activity, and the right hemispheric cortical/subcortical ratio was increased. In the methamphetamine group the most striking finding was an increased metabolic activity of about 10% in the cerebellum compared to placebo.

Otherwise, changes were somewhat opposite to the changes which occurred under psilocybin. There was a tendency for widespread cortical hypometabolism predominantly in right hemispheric frontal, parietal and temporal regions, and the cortical / subcortical ratio was decreased. The MDE-induced metabolic effects were partly methamphetamine- and partly psilocybin-like. Methamphetamine-like effects included cerebellar hypermetabolism and cortical hypometabolism, which was more pronounced in frontal regions. Despite the overall diminished frontal activity in the MDE group the right anterior cingulate tended to be hyperactive (Gouzoulis-Mayfrank et al. 1999a).

Our psilocybin findings are in line with data from other functional imaging studies with hallucinogens demonstrating increased metabolic activity or blood flow in frontal cortical regions, particularly in the anterior cingulate, after administration of mescaline, ketamine and psilocybin (Hermle et al. 1992, Lahti et al. 1995, Vollenweider et al. 1997a,b). The anterior cingulate cortex is traditionally viewed as one of the principal limbic structures and has been linked to numerous functions such as selective attention, anticipation, motivation, emotion, maternal behavior, pain, and selection for action and motor reaction. An integrative view of cingulate function suggests that the anterior cingulate subserves primarily executive functions related to the emotional control of visceral, skeletal, and endocrine outflow (*Vogt et al. 1992*). Increased metabolism in the anterior cingulate appeared to be the common denominator of action across the hallucinogen psilocybin and the entactogen MDE. Profound sensory and emotional experiences absorbing the attention of subjects were present under both substances, but not under methamphetamine. Metabolic activity of the anterior cingulate correlated with stereotyped thoughts in the psilocybin group, and with deficits of attention in the MDE group. Regarding the correlation data, increased cingulate metabolic activity may be interpreted as a compensatory effort to overcome the apparent difficulties in attending to, selecting, and processing the emotionally significant experiences in the drug states.

Neocortical hypometabolism and cerebellar hypermetabolism was the common denominator of d-methamphetamine and MDE action. Diminished cortical activity has been described in several studies with both sedative and stimulant drugs of abuse such as benzodiazepines, morphine, amphetamines, and cocaine and has been viewed as a correlate of euphoria (London 1990a, b; Pearlson et al. 1993). In our studies, however, both cortical hypometabolism and cerebellar hypermetabolism were not associated with positive, but rather with unpleasant feelings such as anxiety and depression, cognitive disturbances, and general psychopathological signs. This finding is difficult to interpret, since MDE and d-methamphetamine elicited either minor or very pleasant emotional effects. Thus, secondary or compensatory mechanisms may be responsible for these neurometabolic effects. The change of cerebellar metabolic activity appears puzzling because the cerebellum has traditionally been viewed as a motor control region. This view has recently been challenged, however, by a growing body of data on the cerebellar involvement in mental operations such as selective attention, sensory discrimination, working memory, word-processing, timing, learning, and complex problem solving as well as in emotional processes and mental disorders. Consequently, the role of the cerebellum in psychoactive substance induced states needs to be evaluated further.

Taken together, our data demonstrate that the effects of MDE on brain metabolism take an intermediate position between the effects of stimulants and hallucinogens.

Neuropsychological Effects

A covert orienting of attention task (COVAT) and a lexical decision task were administered before and after ingestion of the drugs (pre-drug, on-drug). The COVAT is illustrated in Figure 4.

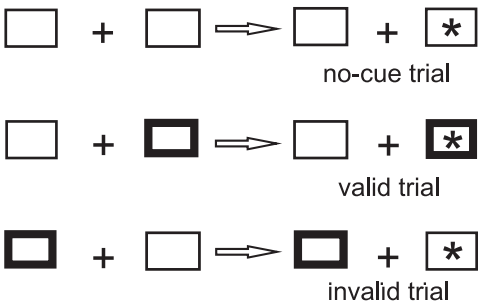

Figure 4. Schematic presentation of the covert orienting of attention task (COVAT).

Subjects were instructed to respond as rapidly as possible to the target by pressing a single key with the index finger of the dominant hand. The target was a star, which appeared within one of the two peripheral square boxes. In each block 20% of the trials were uncued. In the remaining cued trials one of the two boxes was brightened, and the target followed in the middle of the brightened square (valid trial) or opposite to the former cue location (invalid trial).

In the lexical decision task, subjects were presented with two kinds of targets: meaningful words of the German language or meaningless, legally spelled strings of letters (pseudo-words). The task was simply to read each target and to decide as quickly and accurately as possible whether it was a word or a pseudoword. The subjects´ responses consisted of pressing one of two keys on the computer keyboard ("yes" and "no").

Psilocybin and MDE caused overall slowing of reaction times in the COVAT, while d-methamphetamine tended to improve psychomotor speed, although this effect was not statistically significant. Besides their overall psychomotor retardation, subjects on psilocybin exhibited particularly slow reaction times in invalidly cued trials, indicating difficulty in disengaging attention from previously attended locations and reorienting it to targets in the contralateral visual field. In contrast, neither MDE nor d-methamphetamine interacted with the orienting effect of cues. Similarly, in the lexical decision task, reaction times were substantially prolonged in all subjects after psilocybin and in most subjects after MDE. In contrast, after ingestion of d-methamphetamine and placebo most subjects exhibited a slight, probably practice-related decrease of reaction times (Gouzoulis-Mayfrank et al. 1998).

Impaired performance under hallucinogens with slowing of reaction times, and behavioral activation under stimulants with increased alertness and enhanced performance are well-recognized phenomena (Martin & Sloan 1977; Gunne 1977). Thus, regarding the overall slowing of psychomotor performance, MDE elicited a hallucinogen-like effect on attentional performance. Although the decrement in performance after MDE was clearly less severe than the one caused by psilocybin, our data demonstrate that psychomotor speed may be substantially decreased under methylenedioxyamphetamines. This effect distinguishes the entactogens from stimulant amphetamines.

Summary of Results

The aim of this study was to contribute to the pharmacological characterization of the methylenedioxyamphetamines or entactogens. The psychopathological, neuroendocrine, autonomic, neurometabolic, and neuropsychological 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).

The most characteristic psychological effects of MDE were pleasant emotional experiences of relaxation, peacefulness, content, and closeness to others. Significant stimulant and hallucinogen-like effects were also present, however, 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 stimulation of prolactin secretion clearly distinguishes MDE from stimulant amphetamines. The apparent contrast between psychological and autonomic effects (subjective relaxation vs. physical activation = psychophysical dissociation) was a very characteristic and unique feature of the MDE state. The effects of MDE on brain metabolism were partly methamphetamine- and partly psilocybin-like. Finally, MDE slowed psychomotor performance in two neuropsychological tasks, although the impairment of performance was less severe than after ingestion of psilocybin. This effect distinguishes the entactogens from stimulant amphetamines.

Taken together, the results of the present study demontrate substantial overlap between the acute psychological and neurobiological effects of typical recreational doses of an entactogen, a hallucinogen, and a stimulant. However, the pattern of overlapping effects as well as some unique, characteristic effects of MDE support the view that entactogens constitute a distinct psychoactive substance class, which takes an intermediate position between stimulants and hallucinogens (Nichols 1986).

References

Battaglia, G., Brooks, B.P., Kulsakdinum, C., DeSouza, E.B. (1988) Pharmacologic profile of MDMA (3,4-methylenedioxymetamphetamine) at various brain recognition sites. *Eur. J. Pharmacol.* 149:159-163.

Cohen, R.S. (1995) Subjective reports on the effects of the MDMA ("Ecstasy") experience in humans. *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* 19: 1137-1145.

Downing, J. (1986) The psychological and physiological effects of MDMA on normal volunteers. *J. Psychoactive Drugs* 18:335-340.

Gouzoulis, E., Hermle, L. (1998) Are the entactogens a distinct psychoactive substance class? *The Heffter Review* 1: 56-50.

Gouzoulis, E., Steiger, A., Ensslin, M., Kovar, K-A., Hermle, L. (1992) Sleep EEG effects of 3,4-methylenedioxyethamphetamine (MDE; "Eve") in healthy volunteers. *Biol. Psychiatry* 32: 1108-1117.

Gouzoulis, E., Bardeleben, Uv., Rupp, A., Kovar, K-A., Hermle, L. (1993a) Neuroendocrine and cardiovascular effects of 3,4-methylenedioxyethamphetamine (MDE; "Eve") in healthy volunteers. *Neuropsychopharmacology* 8: 187-193.

Gouzoulis, E., Borchardt, D., Hermle, L. (1993b) A case of toxic psychosis induced by "Eve" (3,4-Methylenedioxyethylamphetamine). *Arch. Gen. Psychiatry* 50: 75.

Gouzoulis-Mayfrank, E., Thelen, B., Maier, S., Habermeyer, E., Spitzer, M, Sass, H. (1998) Modulation of semantic priming effects by psilocybin, MDE (ecstasy), and d-methamphetamine - Principles and applications of the model psychosis strategy. *Neurology, Psychiatry and Brain Research* 6: 19-28.

Gouzoulis-Mayfrank, E., Schreckenberger, M., Sabri, O., Arning, C., Thelen, B., Spitzer, M., Kovar, K-A., Büll, U., Sass, H. (1999a) Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [18F]FDG. *Neuropsychopharmacology* 20: 565-581.

Gouzoulis-Mayfrank, E., Thelen, B, Habermeyer, E, Kunert, H-J., Kovar, K-A, Hermle, L., Spitzer, M., Sass, H. (1999b) 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. *Psychopharmacology* 142: 41-50.

Greer, G.R., Tolbert, R. (1986) Subjective reports of the effects of MDMA in a clinical setting. *J. Psychoactive Drugs* 18: 319-327.

Grob, C.S., Polland, R.E., Chang, L., Ernst, T. (1996) Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. *Behav. Brain. Res.* 73: 103-107.

Grob, C.S., Poland, R.E. (1997) MDMA. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG (eds) Substance Abuse. A comprehensive textbook, 3rd ed. Williams and Wilkins, Baltimore, Maryland, pp. 269-275.

Gunne, L-M. (1977) Effects of amphetamines in humans. In: Martin WR (ed) Drug addiction II: Amphetamine, psychotogen and marihuana dependence. Handbook of experimental pharmacology, Vol. 45/II. Springer, Berlin, Heidelberg, New York, pp. 247-275.

Hermle, L., Fünfgeld, M., Oepen, G., Botsch, H., Borchardt, D., Gouzoulis, E, Fehrenbach, R.A., Spitzer, M. (1992) Mescaline-induced psychopathological, neuropsychological and neurometabolic effects in normal subjects. Experimental psychosis as a tool for psychiatric research. *Biol. Psychiatry* 32: 976-991.

Hermle, L., Spitzer, M., Borchardt, D., Kovar, K-A., Gouzoulis, E. (1993) Psychological effects of MDE in normal subjects. Are entactogens a new class of psychoactive agents? *Neuropsychopharmacology* 8: 171-176.

Johnson, M., Hoffmann, A.J., Nichols, D.E. (1986) Effects of the enantiomers of MDA, MDMA and related analogues on 3H-serotonin and 3H-dopamine release from superfused rat brain slices. *Eur. J. Pharmacol* 132: 269-276.

Lahti, A.C., Holcomb, H.H., Medoff, D.R., Tamminga, C.A. (1995) Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *NeuroReport* 6: 869-872.

Liester MB, Grob CS, Bravo GL, Walsh RN (1992) Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine. *J Nerv Ment Dis* 180: 345-352.

London, E.D., Broussole, E.P.M., Links, J.M., Wong, D.F., Cascella, N.G., Dannals, R.F., Sano, M., Herning, R., Snyder, F.R., Rippeton, L.R., Toung, T.J.K., Jaffe, H.J., Wagner, H.N. Jr., (1990a) Morphine-induced metabolic changes in human brain: studies with positron emission tomography and [fluorine 18] fluorodeoxyglucose. *Arch. Gen. Psychiatry* 47: 73-81.

London, E.D., Cascella, N.G., Wong, D.F., Phillips, R.L., Dannals, R.F., Links, J.M., Herning, R., Grayson, R., Jaffe, J.H., Wagner, H.N. (1990b)

Cocaine-induced reduction of glucose utilization in human brain. A study using positron emission tomography and [Fluorine 18]-Fluorodeoxyglucose. *Arch. Gen. Psychiatry* 47: 567-574.

Martin, W.R., Sloan, J.W. (1977) Pharmacology and classification of LSD-like hallucinogens. In: Martin, W.R. (Ed.), Drug addiction II: Amphetamine, psychotogen and marihuana dependence. Handbook of experimental pharmacology, Vol. 45/II. Springer, Berlin, Heidelberg, New York, pp. 305-368.

Mas, M., Farre, M., De La Torre, R., Roset, P.N., Ortuno, J., Segura, J., Cami, J. (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. *J. Pharmacol. Exp. Ther.* 290: 136-145.

Nichols, D.E. (1986) Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: Entactogens. *J. Psychoactive Drugs* 18: 305-313

Nichols, D.E. (1994) Medical chemistry and structure - activity relationships. In: Cho AK, Segal DS (eds) Amphetamine and its analogs. Pharmacology, Toxicology and abuse. Academic Press, San Diego, pp 3-41.

Parrott, A.C., Stuart, M. (1997) Ecstasy (MDMA), amphetamine, and LSD: comparative mood profiles in recreational polydrug users. *Human Psychopharmacology* 12: 501-504.

Pearlson, G.D., Jeffery, P.J., Harris, G.J., Ross, C.A., Fischman, M.W., Camargo EE (1993) Correlation of acute cocaine-induced changes in local cerebral blood flow with subjective effects. *Am. J. Psychiatry* 150: 495-497

Peroutka, S.J., Newman, H., Harris, H. (1988) Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology* 1:273-277

Schreckenberger, M., Gouzoulis-Mayfrank, E., Sabri, O., Arning, C., Zimny, M., Tuttass, T., Wagenknecht, G., Kaiser, H-J., Sass, H., Büll, U. (1999) "Ecstasy"-induced changes of cerebeal glucose metabolism and their correlation to acute psychopathology. An 18-FDG PET study. *Eur. J. Nucl. Med.* 26: 1572-1579

Solowji, N., Hall, W., Lee, N. (1992) Recreational MDMA use in Sydney: a profile of "ecstasy" users and their experiences with the drug. *Br. J. Addiction* 87: 1161-1172

Steele, T.D., Nichols, D.E., Yim, G.K.W. (1987) Stereochemical effects of 3,4-methylenedioxy-methamphetamine (MDMA) and related amphetamine derivatives on inhibition of uptake of [3H]monoamines into synaptosomes from different regions of rat brain. *Biochem. Pharmacol.* 36: 2297-2303.

Vogt, B.A., Finch, D.M., Olson, C.R. (1992) Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cerebral cortex 2: 435-443.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Antonini, A., Maguire, P., Missimer, J., Angst, J. (1997a) Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]fluorodeoxyglucose (FDG) *European Neuropsychopharmacology* 7: 9-24.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Maguire, P., Stadelmann, O., Angst J (1997b) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology* 16: 357-372.

Vollenweider, F.X., Gamma, A., Liechti, M., Huber, T. (1998) Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology* 19: 241-251.