.

6. Are The "Entactogens" a Distinct Psychoactive Substance Class? The Contribution of Human Experimental Studies to the Classification of MDMA and Other Chemically Related Methylenedioxyamphetamine Derivatives

Euphrosyne Gouzoulis-Mayfrank, M.D. and Leo Hermle, M.D.

Introduction

MDMA (methylenedioxymethamphetamine; "Ecstasy") and its analogs MDE (methylenedioxy-ethylamphetamine; "Eve"), methylenedioxybenzo-dioxoylbutanamine (MBDB) and methoxymethylene-dioxyamphetamine (MMDA) are ring-substituted amphetamine-derivatives. Their chemical structures are closely related to both the stimulant amphetamines and the psychedelic phenethylamines and methoxyamphet-amines like mescaline, DOM and DOB (Figure 1). However, they are thought to exert unique psychological effects in humans, distinguishing them both from the stimulant and the psychedelic amphetamines (Shulgin and Nichols 1978, Shulgin 1986). During the last decade, there has been an intensive controversial discussion of MDMA in the scientific and general media. The dimension of this still ongoing discussion is motivated by the popularity of MDMA as an illegal recreational drug (Seymour 1986, Beck and Morgan 1986, Beck 1990), its neurotoxic potential (Price et al 1989, Grob et al 1990) and its claimed medical usefulness as an adjunct in insight-oriented psychotherapy (Grinspoon and Bakalar 1986, Greer and Tolbert 1986, 1990).

Studies with laboratory animals demonstrated that high and repeated doses of MDMA cause long-lasting or even irreversible degeneration of brain cells containing the endogenous transmitter serotonin (Ricaurte et al 1992). This is not a unique finding with MDMA, because a similar or even stronger neurotoxic potential can be shown in animal studies for many amphetamines. The clinical significance of these experimental data is unclear. However, they built a strong argument for the scheuling of MDMA in 1985.

According to anecdotal evidence MDMA possesses anxiolytic and antidepressive properties. It evokes a subtle, easily controllable altered state of consciousness with an emphasis on emotional aspects, relaxation, feelings of happiness, heightened self-acceptance and empathy, openness for communication and decrease of fear responses. In contrast, perceptual alterations, alterations of thinking and orientation and amphetamine-like stimulatory effects are not generally reported (Greer and Tolbert 1986). This psychotropic profile makes MDMA, in the view of some psychotherapists, a valuable tool for psycholytic psychotherapy. Psycholytic therapies with psyche-delics (mostly LSD) were performed in many European and American centers in the 1950s and 1960s. The rationale of psycholytic therapy has its analogy in dream analysis: during the psychedelic state defense mechanisms diminish and defended, unconscious conflict material is visualized in a symbolic way; facilitating the approach to this material for analysis and interpretation after the psycholytic session. Before MDMA was scheduled in 1985 it was used by some therapists, predominantly on the west coast, in indi-vidual settings and in marital therapy (Greer and Tolbert 1990). In Switzerland, a small group of psychotherapists with psychoanalytic background founded the Swiss Medical Society for Psycholytic Therapy in 1988. They obtained time-limited licences for the use of LSD and MDMA in psycholytic sessions and treated over a hundred patients with neurotic and psychoreactive disorders during the years 1988 till 1994 (Styk 1994). Both U.S. and Swiss psycho-therapists gave enthusiastic reports of the beneficial effects of MDMA sessions on the therapeutic process (Greer and Tolbert 1986, Widmer 1989). According to these reports, MDMA helps overcome strong defenses, enables the therapist to confront the patient with deep conflicts by reducing his/her anxiety and may even be the only possibility to overcome stagnation of the psychotherapeutic process in treatment-resistant cases with substantial chronicity. A recent follow-up study of 121 treated patients in Switzerland demonstated improvement in 90% of the cases (Gasser, in press).

It was hypothesized that MDMA, MBDB and MDE constitute a novel psychoactive substance class. Animal drug discrimination experiments and pharmacological studies on the structure-activity relationships of MDMA and related compounds support the hypothesis of a distinct pharmacological class (Nichols 1986, Nichols and Oberlender 1990). Nichols (1986) proposed that the hypothetical new class be designated "entactogens." This new term is composed of the roots "en," "tactus," and "gen" and makes a strong reference

.

to the psychotherapeutic usefulness of the substances.

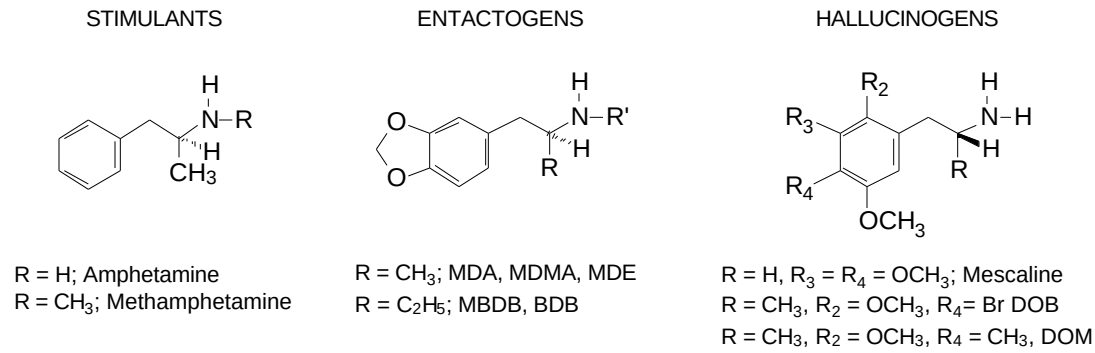

Figure 1. Chemical structures of stimulant amphetamines, entactogens, and phenethylamine psychedelics.

Nichols (1986): "Just as the word "tact" has the connotation of communicating information in a senstitive and careful way so as to avoid offense, it seemed that the Latin root of this word, tactus, would be appropriate as part of the term. Addition of the Greek roots en (within or inside) and gen (to produce) created the term entactogen, having the connotation of producing a touching within."

However, there are also reports of panic reactions, amphetamine-like stimulation and perceptual alterations with recreational MDMA use (Peroutka et al 1988, Whitaker-Azmitia and Aronson 1989, Dowling et al 1987). Reports of recreational users are difficult to interpret because of the various influences of the set and setting (personality, personal and environmental situative factors) on the effects of the drug and because of the frequent concomitant use of other substances or alcohol. Moreover, tablets sold as "Ecstasy" may contain mixtures of MDMA with amphetamines or even psychedelics or in some cases may lack MDMA altogether. In consequence, the position of the entactogens within the range of the chemically related psychotropic drugs is uncertain.

Human experimental studies with MDE ("Eve")

The most direct way to explore the question of a distinct pharmacological entity is to assess the effects of an entactogen in a standardized human experimental setting. Due to the current legal situation, human studies with hallucinogens and related psychoactive substances are difficult to realize. However, it is not impossible to obtain the approvals needed from the responsible state authorities. Our group has already performed a pilot study on the subjective and neurobiological effects of MDE in healthy volunteers. Further studies are currently in progress. We chose to work with MDE, because it was shown to be less neurotoxic than MDMA in animal studies (Schmidt 1987, Ricaurte et al 1987, Gibb et al 1990). The experimental design was random double-blind, placebo-controlled, cross-over, i.e. every volunteer took part in one active (a single 140 mg oral dose) and one placebo experiment.

Fourteen healthy volunteers participated in this first study. The psychological effects of MDE were assessed using several questionnaires and scales. In addition, we studied the neurohormonal influences of the drug in eight of the fourteen subjects. The remaining six subjects participated in a sleep EEG study in order to assess the effects of MDE on sleep architecture.

Neurobiological effects of MDE

Effects on hormonal secretion

The secretion of cortisol, prolactin, and growth hormone is regulated by endogenous transmitters such as serotonin and norepinephrine acting in the hypothalamus and hypophyseal gland of the brain. Drugs interacting with these endogenous transmitters (e.g. amphetamines and psychedelics) alter neurohormonal secretion. Thus, to compare the neuroendocrine effects of psychotropic drugs is one possible approach to their pharmacologic characterization.

Eight healthy male volunteers took 140 mg of MDE or placebo at noon time after a standardized light lunch. For the following 3.5 hours blood samples were taken every 20 minutes for an analysis of the time-course of the effects on neurohormonal secretion. After the intake of MDE, there were sharp rises in cortisol and prolactin plasma levels, which declined after about two hours, but were still above the pre-drug level at the

end of the experiment. In contrast, growth hormone levels did not rise above the pre-drug level (Gouzoulis et al 1993a). From previous studies of other groups it is known that stimulant amphetamines and psychedelic amphetamine derivatives enhance cortisol and prolactin secretion. So, these effects do not differentiate between the entactogens and the other chemically related substances. However, amphetamines are also known to enhance the secretion of growth hormone. In our study, this was not true for MDE. Our growth hormone data might be indicative of distinct pharmacological mechanisms supporting the hypothesis of a novel psychoactive substance class (Gouzoulis et al 1993a), but have to be replicated before further interpretations are made.

Alteration of sleep architecture

In the sleep laboratory study MDE caused mostly, but not exclusively, amphetamine-like effects. Subjects took 140 mg MDE or placebo at 11:00 p.m. and lights were switched off immediately. After a normal sleep onset latency and sleep duration of about one hour, all subjects awoke due to the drug effects and stayed awake for at least 2.5 hours during the night on MDE (Gouzoulis et al 1992). There was a clear reduction of total sleep time and an increase in intermittent time awake after MDE. REM sleep, the sleep phase with the most prominent dream activity, was completely suppressed and did not occur at all after again falling asleep. The effects described so far are amphetamine-like. The overall reduction of sleep time affected all sleep stages, but was more prominent for the functionally less important light sleep (sleep stage 2). In contrast, there was a trend towards increase of deep sleep (sleep stage 4) during the second part of the night after MDE compared to placebo, i.e. subjects caught up with this most restorative sleep phase. Moreover, the cyclic sleep architecture was preserved during the second part of the night. The missing suppression of deep sleep and cyclic sleep architecture in the context of otherwise amphetamine-like effects is unusual and might indicate a distinct effect pattern of MDE on sleep, supporting the hypothesis of a novel psychoactive substance class. Interpretation of these data, however, as well as the data on growth hormone secretion, must be cautious because of the limited number of subjects (Gouzoulis et al 1992).

Psychological effects

There was a strong interindividual variability in the psychological effects of MDE (Hermle et al 1993a, b). Effects began 30 to 90 minutes after ingestion of the drug and lasted two to three hours.

All subjects displayed a significant stimulation with increased vigilance, drive and pressure of speech, together with sympathomimetic vegetative signs like sweating, slight tremor and moderate rises in blood pressure and heart rate Most subjects expressed subjective feelings of increased physical and mental vitality. This amphetamine-like effect pattern was the only uniform effect of the drug

The emotional quality of the experience was variable. Eleven subjects had an overall pleasant experience, which was free of anxiety and included feelings of euphoria, happiness, relaxation, security, and self-acceptance. Four out of these eleven subjects were engaged with important personal themes and were remarkably open for communication in a way that reminded us of the definition of an "entactogen." It may sound contradictory, but these subjects described their mood as being "sad." However, they felt at the same time a deep self-acceptance, so the overall experience was very positive. Three out of the eleven subjects additionally described cosmic-mystic feelings (unity with other people and the universe, religious feelings) during the experiment.

The experience of the remaining three subjects was very different and included negative emotional feelings. One subject reported marked depersonalization and derealization, blocking of normal thinking and attenuated emotionality. Another subject had an unpleasant experience of MDE-induced amphetamine-like psychomotor excitement and he felt very dysphoric. Finally, one volunteer experienced a psychosis with hallucinations, delusional ideas, anxious behavior and loss of insight and control of the situation for the duration of three hours (Gouzoulis et al 1993b). All other subjects except this one kept control over their altered state and insight into the experimental nature of their experience. However, half of the subjects did have some minor perceptual alterations including mainly visual, but also tactile and auditory phenomena e.g. colors were percieved as being more bright, their own own body felt heavier or lighter, etc. These phenomena and the one case of psychotic reaction are indicative of the underlying hallucinogenic potential of MDE.

One of the scales we used is the APZ-Questionnaire (Dittrich 1985) for the assessment of altered states of consciousness (ASC), which can be induced by psychedelic drugs as well as by various psychological conditions such as sensory deprivation or overstimulation and certain meditation techniques. The items of the questionnaire build three subscales: the subscale "oceanic boundlessness" (OSE) refers to positive emotional states, mystic experiences of unity and feelings of happiness. The subscale "Dread for

Ego-Dissolution" (AIA) refers to negative emotional experiences with anxiety and panic reactions like a horror trip. The subscale "Visionary Restructuralization" (VUS) includes hallucinatory behavior and ideas of reference. We compared the mean values of the 14 subjects of our MDE study to the mean values of 12 volunteers of a former study of our group with the hallucinogenic phenethylamine mescaline (Hermle et al 1992). The intake of mescaline resulted in significant effects on all three subscales. The effects of MDE were also significant, but less marked than the effects of mescaline (Figure 2), the difference being stronger for the "negative" and "hallucinogenic" subscales AIA and VUS (Hermle et al 1993a). The MDE-induced state was generally milder, more easy to control and with an emphasis on emotional aspects compared to the state induced by a classic hallucinogen like mescaline.

In summary, the data of our first pilot study with MDE are indicative of the close relation of the entactogens to both psychedelics and stimulants (Hermle et al 1993b). MDMA, MDE and MBDB probably take an intermediate position within the range of chemically related stimulant amphetamines and hallucinogenic phenethylamines. The entactogenic effects (reduction of anxiety and defenses, self-acceptance, empathy, peacefulness) are a major and unique part of the spectrum of action of the entactogens. However, this spectrum also includes amphetamine-like and mild hallucinogenic effects.

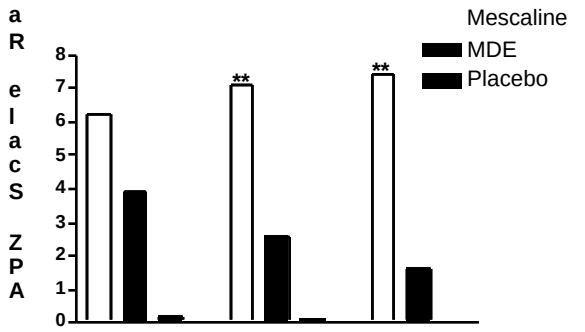

Figure 2. Comparison of the altered state of consciousness (ASC) induced by mescaline (n = 12) and MDE (n = 14) in healthy volunteers (subscales of the APZ questionnaire (Hermle et al 1993a))

Ongoing direct comparative studies with MDE and other psychoactive phenethylamines

A disadvantage of our placebo-controlled studies with MDE is that we can directly compare the drug´s actions only to placebo. Comparisons to the effects of other psychoactive substances can be drawn from literature data, but this procedure has significant methodological problems. Direct comparative studies with an entactogen and representatives of the other two categories of chemically related phenethylamines will provide us with stronger evidence for or against the case of a distinct pharmacological class. At present, our group is conducting an experimental project of this kind in collaboration with the Department of Nuclear Medicine in Aachen (U. Büll), the Psychiatric Department of the University of Heidelberg (M. Spitzer), the Pharmaceutical Department of the University of Tübingen (K.-A. Kovar) and the Psychiatric Department of UC San Diego (M. Geyer).

Every volunteer of our ongoing project participates in two experimental sessions with the same substance; this may be MDE, methamphetamine (representative of the stimulant class), psilocybin (representative of the psychedelic class), or placebo. Both the volunteer and our team are blind concerning the substance (double-blind design). Subjects undergo a series of examinations during the experiments: those include standardized psychopathological assessments, computer-based neuropsychological studies of attention and memory, PET studies of regional cerebral metabolism, electrophysiological studies of habituation and pre-pulse inhibition of the startle reflex, assessments of the neuroendocrine secretion and studies of pharmacokinetics and drug metabolism. With this project, we hope that we will be able to make a substantial contribution to the understanding of the mechanism of action of the entactogens, as well as the mechanism of action of stimulants and psychedelics.

References:

Beck, J. (1990) The public health implications of MDMA use. In: Peroutka, S.J. (ed.), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Kluwer Academic Publishers, pp 77-103.

Beck, J., and Morgan, P.A. (1986) Designer drug confusion: A focus on MDMA. *J Drug Educ* 16, 287-302.

Dittrich, A., von Arx, S., and Staub, S. (1985) International study on altered states of consciousness (ISASC). Summary of the results. *German J Psychol* 9, 319-339.

Dowling, G.P., McDonough, E.T., and Bost, R.O. (1987) "Eve" and "Ecstasy": a report of five deaths associated with the use of MDEA and MDMA. *JAMA*257, 1615-1617.

Ensslin, H.K., Maurer H.H., Gouzoulis, E., Hermle, L., Kovar, K.-A. (in press) Metabolism of racemic 3,4-methylenedioxyethylamphetamine (MDE) in

humans. Isolation, identification, quantification and synthesis of urine metabolites. *Drug Metabolism and Disposition.*

Gasser P. (in press) Die psycholytische Psychotherapie in der Schweiz von 1988-1993. *Schweizer Archiv Neurol Psychiat*.

Gibb, J.W., Stone, D., Johnson, M., and Hanson, G.R. (1990) Neurochemical effects of MDMA. In: Peroutka, S.J. (ed), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Boston, Kluwer Academic Publishers, pp 133-150.

Gouzoulis, E., Steiger, A., Ensslin, H., Kovar, K.-A., and Hermle, L. (1992) Sleep-EEG effects of 3,4-Methylenedioxyethamphetamine (MDE; "Eve") in healthy volunteers. *Biol Psychiatry* 32, 1108-117

Gouzoulis, E., Bardeleben, U.v., Rupp, A., Kovar, K.-A., and Hermle, L. (1993a) Neuroendocrine and cardiovascular effects of MDE in healthy volunteers. *Neuropsychopharmacology* 8, 187-193.

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

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

Greer, G., and Tolbert, R. (1990) The therapeutic use of MDMA. In: Peroutka, S.J. (ed), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Kluwer Academic Publishers, pp 21-35.

Grinspoon, L., and Bakalar, J.M. (1986) Can drugs be used to enhance the psychotherapeutic process? *Am J Psychotherapy* XL, 393-404.

Grob, C., Bravo, G., and Walsh, R. (1990) Second thoughts on 3,4-methylenedioxymeth-amphetamine (MDMA) neurotoxicity. *Arch Gen Psychiatry* 47,288.

Hermle, L., Fünfgeld, M., Oepen, G., Bosch, 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., Gouzoulis, E., Oepen, G., Spitzer, M., Kovar, K.-A., Borchardt, D., Fünfgeld, M., Berger, M. (1993a) The significance of hallucinogenic research in psychiatry: history and present status. *Nervenarzt* 64, 562-571.

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

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

Nichols, D.E., and Oberlender, R. (1990) Structure-Activity relationships of MDMA and related compounds: a new class of psychoactive agents?. In: Peroutka, S.J. (ed), Ecstasy: The clinical, pharmacological and neurotoxicological effects of the drug MDMA. Kluwer Academic Publishers, pp 105-131.

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

Price, L.H., Ricaurte, G.A., Krystal, J.H., and Heninger, G.R. (1989) Neuroendocrine and mood responses to intravenous L-tryptophan in MDMA users. *Arch Gen Psychiatry* 46, 20-22.

Ricaurte, G.A., Finnegan, K.F., Nichols, D.E., DeLanney, L.E., Erwin, I., and Langston, J.W. (1987) MDE, a novel analogue of MDMA, produces long-lasting depletion of serotonin in rat brain. *Eur J Pharmacol* 137, 265-268.

Ricaurte, G.A., Martello, A.L., Katz, J.L., Martello, M.B. (1992) Lasting effects of MDMA on central serotonergic neurons in nonhuman primates: neurochemical observations. *J Pharmacol Exp Ther* 261, 616-622.

Schmidt, C.J. (1987) Acute administration of methylenedioxymethamphetamine: comparison with the neurochemical effects of its N-desmethyl and N-ethyl analogs. *Eur J Pharmacol* 136, 81-88.

Seymour, R.B. (1986) MDMA. San Francisco, Haight-Ashbury Publications.

Shulgin, A.T., and Nichols, D.E. (1978) Characterization of three new psychotomimetics. In: Stillman, R.C., and Willette, R.E. (eds), The Psychopharmacology of Hallucinogens. Pergamon Press, New York, pp 74-83.

Shulgin, A.T. (1986) The background and chemistry of MDMA. *J Psychoactive Drugs* 18, 291-304.

Styk, J. (1994) Rückblick auf die letzten sieben Jahre der Schweizerischen Ärztegesellschaft für Psycholytische Therapie. In: Dittrich, A., Hofmann, A., and Leuner, H.C. (eds). Welten des Bewußtseins, Band 4. Verlag für Wisenschaft und Bildung, Berlin, pp 149-154.

Widmer, P.S. (1989) Fallbeispiel einer

psycholytischen Psychotherapie. In: Schlichting, H., and Leuner, H.C. (eds) Psychoaktive Substanzen und veränderte Bewußtseinszustände in Forschung und Therapie. ECBS Göttingen, pp 163-168.

Whitaker-Azmitia, P.A., and Aronson, T. (1989). Panic attacks associated with MDMA (ecstasy). *Am J Psychiatry* 146, 119.