Sleep EEG Effects of 3,4-Methylenedioxyethamphetamine (MDE; "Eve") in Healthy Volunteers

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3,4-methylenedioxyethamphetamine (MDE; "Eve") exerts similar psychotropic effects in humans as 3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy") and is less toxic in animal studies. We conducted a double-blind, placebo-controlled, cross-over sleep electroencephalogram (EEG) study with healthy volunteers. One hundred forty milligrams of MDE or placebo were administered PO in six subjects at 11 PM. Sleep EEG was registered from 11 PM–7 AM the next morning. All subjects had a normal sleep onset latency. They all awoke 60 to 120 min after administration of MDE and stayed awake for at least 150 min (total sleep time, TST MDE < placebo and intermittent time awake MDE > placebo: $p < 0.001$). After again falling asleep rapid eye movement (REM) sleep was totally suppressed (REM during time in bed, TIB MDE < placebo: $p < 0.001$). A cyclic alternation of relatively long periods of slow wave sleep (SWS) with periods of light sleep occurred in three subjects during the second part of the night (stage 4 in second part of night MDE > placebo: $p = 0.16$). The effects of MDE on sleep variables largely demonstrate the stimulant, amphetamine-like properties of MDE.

Introduction

During the last years, the amphetamine-derivative 3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy") was discussed controversially in scientific and general literature because of its increasing popularity and illegal abuse (Seymour 1986; Beck and Morgan 1986; Beck 1990), its possible neurotoxicity in humans (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 1990). After the assignment of MDMA to Schedule I status by the Drug Enforcement Administration (DEA) in 1985, its unrestricted N-ethyl-derivative, 3,4-methylenedioxyethamphetamine (MDE; "Eve"), became more popular on the streets (Beck 1990). The psychotropic profile of MDE was described as being very similar to the one of MDMA. This was also supported by drug discrimination studies with experimental animals (Boja and Schechter 1987). Both substances were

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reported to exert unique psychotropic effects in humans, distinguishing them from the chemically related stimulant amphetamines and from the substituted hallucinogenic amphetamines like methylenedioxyamphetamine (MDA), 2,5-dimethoxy-4-methylamphetamine (DOM), and mescaline (Shulgin and Nichols 1978; Shulgin 1986). MDMA and MDE were reported to possess antidepressant and anxiolytic properties and to evoke a subtle, well-controllable, emotional experience with relaxation, feelings of happiness, increased empathy, and a drop in fear responses and defense mechanisms, mostly without distortion of sensory perception and without marked stimulation or mental confusion (Greer and Tolbert 1986, 1990; Peroutka et al 1988). It was hypothesized, that MDMA and MDE might belong to a novel pharmacological class with a putative therapeutic value as adjuncts in psychotherapy. Drug discrimination experiments and pharmaceutical/pharmacological studies on the structure–activity relationships of MDMA and related compounds seemed to support the hypothesis of a distinct pharmacological class; for example, the d-isomer of these substances is more potent than the l-isomer, which holds also true for amphetamine, but not for the hallucinogenic amphetamine derivatives. On the other hand, the primary effects of these substances were shown to be serotonergically mediated, although the primary effects of amphetamine are dopaminergically mediated (Nichols 1986; Nichols and Oberlender 1990). Nichols (1986) proposed that the hypothetical new pharmacological class be designated "entactogens."

MDMA and MDE show high affinities to serotonin uptake sites and lower affinities to norepinephrine and dopamine uptake sites of central neurons (Battaglia et al 1988a). They are taken up into the neurons and cause release and reuptake inhibition of the endogenous transmitters (Johnson et al 1986, 1988; Steele et al 1987; Schmidt 1987). In addition, they interact directly with 5-HT2-, 5-HT1-, and D2- binding sites, but these properties seem to be less important for the drugs' action (Lyon et al 1986; Battaglia et al 1988a). In experimental animals, MDA, MDMA, and to a lesser extent MDE, were shown to exert neurotoxic effects on central serotonergic neurons in terms of degeneration of axon terminals (Ricaurte et al 1985, 1988; Battaglia et al 1988b, 1990; Insel et al 1989; Gibb et al 1990; Schmidt and Taylor 1990). However, the relevance of this finding for humans is still unclear (Price et al 1989; Grob et al 1990).

To date, almost all controlled data on pharmacological effects of MDMA and MDE are derived from animal studies. So far, only anecdotal reports about the psychological effects and no human experimental data on neurobiological effects are available. The aim of our investigation was to examine the neurobiological (endocrine, sleep electroencephalogram (EEG), vegetative and subjective effects of MDE in healthy volunteers. In this paper we report about the sleep EEG studies. According to a "specificity" hypothesis (Feinberg et al 1974), psychoactive drugs exert common effects on sleep EEG patterns within a pharmacological class, but distinct effects across different classes. The leading idea of the study was that a distinct sleep pattern differentiating MDE from amphetamines and hallucinogens might be detectable, provided that MDMA and MDE do constitute a new pharmacological class.

Materials, Subjects and Methods

MDE was synthetized in the Institute of Pharmaceutics, University of Tübingen, Germany, and was obtained in 70-mg capsules. Placebo capsules were obtained from the same institute. The volunteers received 140-mg MDE, a dose commonly taken for recreational use (Greer and Strassman 1985; Beck and Morgan 1986; Seymour 1986; Peroutka 1990).

Six physically and mentally healthy volunteers (three men and three women; all academics: five physicians, one psychologist) ranging from 28–33 years (mean 29.5) were included in a randomized, double-blind, placebo-controlled, cross-over study. Before participating in the study the subjects underwent a series of physical and mental examinations (medical history, clinical examination, electrocardiogram (ECG), EEG, free psychiatric interview, standard psychiatric interview SKID according to DSM-III-R, personality inventory FPI, trait-anxiety inventory STAI-X2, and questionnaire for vegetative lability B-L). Exclusion criteria were any physical or mental illness or substance abuse, also in the past, and mental illness in first-degree relatives. The subjects did not receive any drugs 3 weeks prior to and during the trial. They spent 4 nights in the sleep laboratory: 1 adaptation night and 1 consecutive night on 140-mg MDE or placebo and 2–6 weeks later another adaptation night and 1 consecutive night on placebo or 140-mg MDE. The drugs were administered orally with some liquid at 11 PM just before lights were switched off.

Sleep EEG recordings were performed between 11 PM and 7 AM using standard procedures: electroencephalogram (EEG; C3-A2, C4-A1), horizontal electrooculogram (EOG), and submental electromyogram (EMG). Electrodes were placed between 10 and 10:30 PM in standard position. Records were scored visually using the criteria of Rechtschaffen and Kales (1968). The next morning the volunteers completed a self-rating scale on their subjective quality of sleep (S.M.H. sleep questionnaire).

Time in bed (TIB) is the total registration time, that is, approximately 480 min. Sleep period time (SPT) is the time from sleep onset until final awakening. For the calculation of the total sleep time (TST), the intermittent time awake (W) and the movement time (MT) were subtracted from the SPT. The sleep efficiency index (SEI) was calculated by dividing TST by TIB multiplied by 100. Sleep onset latency (SOL) is the time measured from "lights off" to the appearance of the first 30 sec of sleep stage 2, 3, 4 or REM. REM latency is the time measured from sleep onset until the onset of the first REM period. Stage shifts is the number of shifts from one sleep stage to another. REM density is the mean population of 3-sec miniepisodes with at least one rapid eye movement on all miniepisodes of the REM periods.

Mean values and SD were calculated. Statistical analysis was performed by means of the paired, two-tailed Student *t*-test. Statistically significant *p* values were considered to be those less than 0.05.

The investigation was part of a pilot study on psychological and neurobiological effects of MDE in normal controls and was performed in accordance with the requirements of the Declaration of Helsinki. The subjects did not receive any payment for their participation. The study was approved by the ethical committee of the Faculty of Medicine, University of Freiburg. Informed written consent was obtained from all volunteers. Subjects participated in a series of psychometric tests before ingestion of the drug (at 10 PM), after awakening, 24 hr, and 7 days after the trial. Pharmacokinetics and drug metabolism were investigated in urine samples of the subjects in the Institute of Pharmaceutics, University of Tübingen. Evaluation of these data is in progress.

Results

Sleep Continuity

All volunteers feel asleep about 25–30 min after "lights off." There was no difference in SOL between MDE and placebo. All volunteers showed a normal sleep profile after

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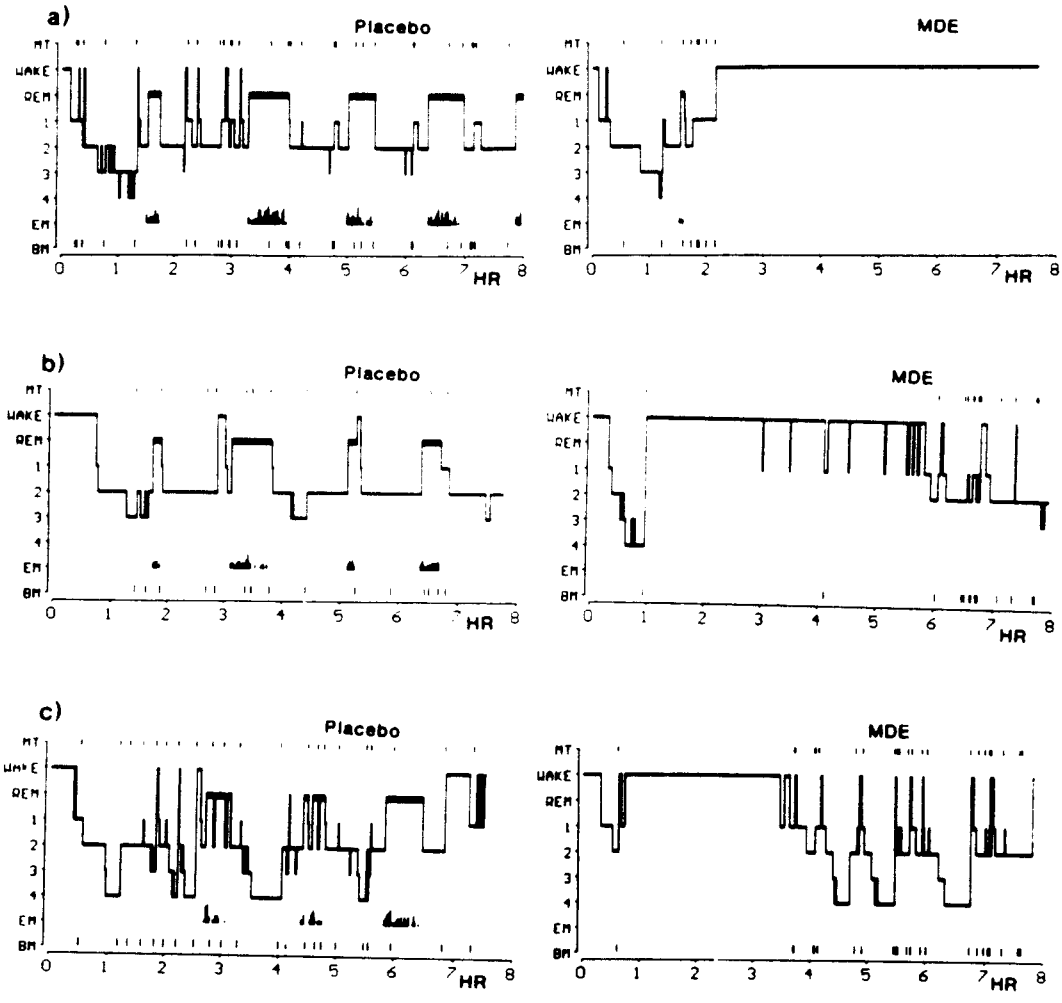

Figure 1. Sleep prints of three healthy volunteers after placebo (left) and after 140 mg MDE (right): (a) male, 27 years, (b) male, 33 years, (c) female 28 years.

ingestion of placebo. After ingestion of MDE all subjects awoke 60 to 120 min after "lights off." One volunteer did not fall asleep again for the entire registration period (Figure 1a). Two volunteers stayed awake 4.5–5 hr and had some light sleep (stage 1 and 2) in the remaining 1.5–2 hr until "lights on" (Figure 1b). Three volunteers stayed awake for 2.5–3 hr and had light and deep sleep (stage 3 and 4) in the second part of the night (Figure 1c). SPT was shorter after MDE than after placebo, but this finding was not significant. TST was significantly reduced ($p < 0.001$), and SEI was significantly decreased ($p < 0.05$) after MDE compared to placebo. Sleep variables are given in Table 1.

Sleep Architecture

Stage 2 was significantly ($p < 0.001$) shortened by MDE. This occurred mostly in favor of intermittent time awake (W), which was significantly ($p < 0.001$) increased. The increase of W was not significant during the second half of the night. Sleep architecture including REM sleep data were within normal range after placebo. After MDE only one volunteer (Figure 1a) had a small amount of REM sleep during the first sleep cycle before

Table 1. Sleep Initiation and Maintenance in Six Healthy Volunteers after Ingestion of 140 mg MDE or Placebo (mean ± SD, 2-tailed paired *t*-test)

Parameter	MDE	Placebo	*p*
Total time in bed (TIB) min	470.5 ± 6.4	470.0 ± 12.0	NS
Sleep period time (SPT) min	382.9 ± 146.2	434.8 ± 32.8	NS
Total sleep time (TST) min	207.4 ± 64.1	429.6 ± 25.6	<0.001
Sleep efficiency index (SEI) %	57.1 ± 23.3	96.6 ± 2.2	<0.01
Sleep onset latency (SOL) min	25.3 ± 9.2	28.1 ± 9.6	NS
Stage shifts	82.2 ± 36.7	122.8 ± 48.3	NS

waking up (REM latency 74 min). The other five subjects awakened before the appearance of the first REM phase of the night. After again falling asleep, REM sleep was totally suppressed in all subjects after MDE for the rest of the night. So, five subjects did not have any REM sleep during the entire registration period after MDE. REM density ($p < 0.01$) and the amount of REM sleep ($p < 0.001$) were significantly decreased after MDE. The three subjects with the relatively short intermittent time awake of 2.5–3 hr had a sleep architecture with cyclic shifts from one nonREM stage to another and a remarkable proportion of slow wave sleep (SWS) during the second part of the night (Figure 1c). There was a trend towards increase of stage-4 sleep during the second part of the night after MDE, but this finding was not statistically significant ($p = 0.16$). The data of the sleep architecture are listed in Table 2.

Discussion

MDE caused a clear-cut deterioration of objectively evaluated sleep in our sleep laboratory study. After a normal sleep onset latency and sleep duration of 30–90 min, all subjects awoke and stayed awake for at least 150 min. One subject did not fall asleep again at all. Total sleep time was shorter ($p < 0.001$) and the sleep efficiency index was decreased ($p < 0.05$) after MDE compared to placebo. Three subjects with the relatively long sleep time of 4–4.5 hr after again falling asleep, showed a sleep architecture with cyclic stage shifts from one nonREM stage to another and a remarkable amount of SWS (Figure 1c). These subjects "caught up" with SWS, which was "shifted" from the first to the second half of the night. There was a trend towards increase of stage-4 sleep during the second part of the night after MDE compared to placebo, but this finding was not statistically significant ($p = 0.16$). REM sleep was completely suppressed ($p < 0.001$) and did not occur in any volunteer after again falling asleep.

These effects mostly resemble the well-documented effects of amphetamine on sleep: Amphetamine and its derivatives suppress REM sleep, and in higher doses increase vigilance and disturb sleep continuity. Rechtschaffen and Marron (1964) demonstrated in their early study a decrease of REM period time and a prolonged REM latency after oral administration of 10–15 mg d-amphetamine just before bedtime. This finding was reproduced in all later studies for doses higher than 5 mg. Hartman and Cravens (1976) reported increased waking and decreased total sleep time after oral administration of 10 mg d-amphetamine 20 min before bedtime. Spiegel (1978) examined the effects of different single amphetamine doses given 30 min before beginning of registration and clearly demonstrated a dose-dependent deterioration of sleep: there were no measurable effects after 1.25 mg or 2.5 mg d-amphetamine, frequent stage shifts and increase of stage 1

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Table 2. Sleep Architecture in Six Healthy Volunteers after Ingestion of 140 mg MDE or Placebo (mean ± SD, 2-tailed paired *t*-test)

Parameter	MDE	Placebo	*p*
Total time in bed (percentage)			
stage 1 min	55.8 ± 44.7	36.5 ± 13.4	NS
	11.9 ± 9.5	7.7 ± 2.7	NS
stage 2 min	94.4 ± 29.7	238.6 ± 39.3	<0.001
	20.0 ± 6.1	50.6 ± 7.7	<0.001
stage 3 min	18.1 ± 4.5	35.1 ± 22.4	NS
	3.8 ± 1.0	7.4 ± 4.7	NS
stage 4 min	29.4 ± 27.0	25.5 ± 29.8	NS
	6.2 ± 5.7	5.5 ± 6.5	NS
intermittent time awake min	262.7 ± 61.9	40.2 ± 15.8	<0.001
	55.9 ± 13.4	8.6 ± 3.5	<0.001
movement time min	8.9 ± 3.6	12.7 ± 2.9	NS
	1.9 ± 0.8	2.7 ± 0.6	NS
First half of night (percentage)			
stage 1 min	18.6 ± 15.0	18.8 ± 9.8	NS
	8.0 ± 6.5	8.0 ± 4.0	NS
stage 2 min	29.0 ± 19.2	105.4 ± 22.4	<0.001
	12.4 ± 8.3	44.8 ± 8.9	<0.001
stage 3 min	11.5 ± 8.6	24.3 ± 15.8	NS
	4.9 ± 3.7	10.3 ± 6.6	NS
stage 4 min	11.5 ± 11.3	20.6 ± 22.7	NS
	4.9 ± 3.7	8.9 ± 9.8	NS
intermittent time awake min	161.3 ± 36.1	29.2 ± 14.2	<0.001
	68.4 ± 14.7	12.5 ± 6.1	<0.001
movement time min	2.2 ± 1.4	5.6 ± 1.1	<0.001
	0.9 ± 0.6	2.4 ± 0.4	<0.001
Second half of night (percentage)			
stage 1 min	37.2 ± 42.6	17.6 ± 5.2	NS
	15.8 ± 18.2	7.4 ± 2.1	NS
stage 2 min	65.4 ± 45.8	132.8 ± 26.6	<0.05
	27.6 ± 19.3	56.4 ± 10.8	<0.05
stage 3 min	6.6 ± 7.0	10.7 ± 12.0	NS
	2.8 ± 2.9	4.6 ± 5.1	NS
stage 4 min	17.8 ± 25.6	4.8 ± 9.0	NS (p = 0.16)
	7.5 ± 10.8	2.1 ± 4.0	NS (p = 0.16)
intermittent time awake min	101.4 ± 79.9	11.0 ± 12.8	NS (p = 0.59)
	43.3 ± 34.6	4.7 ± 5.5	NS (p = 0.62)
movement time min	6.6 ± 3.8	7.0 ± 2.2	NS
	2.2 ± 1.6	2.9 ± 0.8	NS
REM-sleep (percentage)			
REM density in TIB	0.2 ± 0.5	2.3 ± 0.6	<0.01
REM in TIB min	0.7 ± 1.6	81.5 ± 25.2	<0.001
	0.1 ± 0.4	17.3 ± 5.1	<0.001
REM in 1st half of night	0.6 ± 1.6	30.6 ± 16.0	<0.01
	0.2 ± 0.6	13.0 ± 6.6	<0.01
REM in 2nd half of night	0.0 ± 0.0	50.8 ± 20.9	<0.01
	0.0 ± 0.0	21.5 ± 8.6	<0.01
REM latency	—	77.0 ± 25.9	—

after 5 mg d-amphetamine, and decreased total sleep time after 10 mg d-amphetamine. Saletu et al (1989a, b) used a similar experimental design and reported similar effects on sleep after single doses of 10 mg and 20 mg d-amphetamine. Stage-2 sleep and SWS were shown to be dose-dependently reduced after 10 mg and 20 mg of d-amphetamine (Saletu et al 1989b).

Angrist et al (1987) conducted a study on early pharmacokinetics and subjective, behavioral, and cardiovascular effects of oral d-amphetamine in normal controls. The results of this study suggest a uniform absorption over the dose range of 0.25–0.5mg/kg with peak plasma levels after 2–4 hr. Cardiovascular, subjective, and behavioral effects were all at their maximum at 1–3 hr and were then substantially declining, in spite of stable or rising plasma levels (Angrist et al 1987). The findings in the above-cited sleep EEG studies are partly in line with the data of Angrist et al (1987): Hartmann and Cravens (1976) reported that almost all effects occurred during the first 4 hr of the night. Spiegel (1978) showed that the effects of the 5-mg dose of d-amphetamine on REM sleep lasted about 6 hr. However, the typical sleep records after 10 mg or 20 mg d-amphetamine demonstrated by Saletu et al (1989a, b) show that the drug was pharmacologically active during the whole night, particularly with the higher dose. The findings of Gillin et al (1975; 1978) also suggest a prolonged influence of amphetamines on sleep parameters: they conducted studies on the effects of early morning administration of amphetamine on sleep during the following night and could still demonstrate a reduction of TST and REM sleep in the night after administration of 20 mg d-amphetamine at 8:15 AM (Gillin et al 1978). After an even higher dose (30 mg 3-amphetamine at 7:25 AM), they additionally demonstrated lengthening of sleep-onset latency and a trend towards impairment of Delta sleep (Gillin et al 1975).

To our knowledge there are no published data on sleep EEG effects of phenethylamine hallucinogenic compounds (mescaline, MDA), which are chemically related to MDMA and MDE. The few existing reports on effects of other psychedelics on sleep continuity and architecture are inconsistent. LSD was shown to increase waking time and shorten both SWS and REM sleep in cats (Hobson 1964; Stern et al 1972). However, an increase of total REM time was also reported (Hartmann 1967). Marijuana was shown to have no major influence on sleep patterns (Karacan et al 1976), but other studies demonstrated an initial slight elevation and a subsequent slight decrease of slow-wave sleep (Barratt and Adams 1973; Barratt et al 1974).

In our study we administered MDE just before the beginning of the sleep EEG registration. As we already pointed out, there are no previous human experimental data on dose–response relationships, pharmacokinetics, and the plasma concentration-response relationship of MDE or MDMA. The dose used (140 mg) is a medium dose commonly taken for recreational use according to anecdotal reports (Greer and Strassman 1985; Beck and Morgan 1986; Seymour 1986; Peroutka 1990). Our data and the typical sleep prints of our subjects (Figure 1) demonstrate to a large extent the similarity of the sleep EEG effects of MDE to the effects of 10 mg and higher doses of d-amphetamine (Saletu et al 1989a, b) in respect to onset and duration of action, decrease of total sleep time, and suppression of REM sleep. But, in contrast to amphetamines, MDE allowed a cyclic sleep pattern to appear in three subjects after again falling asleep 2.5–3.5 hr after the initial awakening, that is, 3.5–4.5 hr after drug intake. This sleep pattern appeared while MDE was still pharmacologically active in terms of REM sleep suppression. A cyclic alternation of light sleep and deep sleep, and a "shift" of SWS from the first to the second half of the night were observed in those three volunteers, who slept 4–4.5 hr in the second

part of the night (Figure 1c). This finding might indeed indicate a unique effect pattern of MDE on sleep with increase of vigilance and suppression of REM sleep, but lacking suppression of cyclic sleep architecture and SWS. This effect pattern was not reported before, neither after amphetamine administration, nor after administration of hallucinogenic compounds. However, these data must be cautiously interpreted because of the limited number of subjects and the lack of statistical significance. A possible hypothesis might be that the subjects who were more susceptible to the effects of MDE showed a more marked decrease of sleep time, resembling the effect of higher amphetamine doses, and that the three subjects who were less susceptible to MDE were able to sleep during the second half of the night and showed the more specific effects on sleep. If this is true, one might expect that the specific effects become more obvious after the administration of smaller doses of MDE.

The data on subjective effects of MDE obtained from our study are also difficult to interpret, but are more indicative of the close relation of MDE to psychedelelics than to stimulants. Five out of the six subjects described their feelings in a way similar to the anecdotal reports about "entactogenic" effects: relaxation, feelings of self-acceptance and peacefulness. But, in addition, they described depersonalization/derealization experiences and mild disturbances of sensory perception (Hermle et al, in press). Moreover, one of the six subjects experienced a psychotic state with hallucinations and delusional ideation for the duration of 3 hr (Gouzoulis et al, in press). Although all subjects showed pronounced insomnia after MDE, the quality of the subjective experience was not mainly stimulatory (Hermle et al, in press).

In conclusion, it is still not possible to securely position MDE within the range of chemically related substituted amphetamine derivatives. The present sleep laboratory data stress the similarity of MDE to stimulant amphetamines and do not sufficiently support the hypothesis that MDMA and MDE constitute a new pharmacological substance class (Nichols 1986). However, putative specific effects of MDE on sleep patterns distinguishing MDE from amphetamines might become more obvious after smaller doses causing less impairment of sleep maintenance. Subsequent sleep laboratory studies with various doses, longer registration periods, EEG recordings during consecutive nights, and control trials with amphetamines and other substituted amphetamine derivatives are required for further evaluation of the effects of MDE on sleep.

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