Neuroendocrine and Cardiovascular Effects of MDE in Healthy Volunteers

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The drug 3,4-methylenedioxyethamphetamine ([MDE] also known as "Eve") is a less toxic analog of 3,4-methylenedioxymethamphetamine (also known as "Ecstasy") with similar psychotropic effects in humans. In a double-blind placebo-controlled, cross-over study we administered 140 mg of MDE or placebo orally to eight healthy male volunteers at 1:30 P.M. Serum cortisol, prolactin (PRL), and growth hormone (GH) levels, as well as blood pressure, and heart rate were measured

every 20 minutes until 5:00 P.M. Administration of MDE was followed by statistically significant long-lasting increases of serum cortisol, PRL, systolic blood pressure, and heart rate, and by a trend toward blunting of GH secretion. The neuroendocrine and cardiovascular effects of MDE are comparable to those of other phenethylamines with the exception of the effect on GH secretion. [Neuropsychopharmacology 8:187–193, 1993]

The phenethylamines 3,4-methylenedioxymethamphetamine ([MDMA] also known as "Ecstasy") and 3,4-methylenedioxyethamphetamine ([MDE] also known as "Eve") are chemically related to amphetamines and psychedelics like mescaline and methylenedioxyamphetamine (MDA) (Climko et al. 1987). However, they were purported to exert unique psychotropic effects in humans, differentiating them from the aforementioned chemically related substances (Shulgin and Nichols 1978; Shulgin 1986). Both MDMA and MDE were reported to possess antidepressant and anxiolytic properties and to evoke a well-controllable emotional experience with relaxation, peaceful feelings, increased empathy, and a drop in fear responses, mostly with-

out distortion of sensory perception and thought and without marked stimulation (Greer and Tolbert 1986, 1990; Peroutka et al. 1988). Pharmacologic studies on the structure-activity relationships of MDMA and related compounds supported the view that MDMA and MDE might constitute a new psychoactive substance class, which was named the "entactogens" (Nichols 1986; Nichols and Oberlender 1990).

The reasons for the public controversy about MDMA are its growing popularity and illegal abuse during the past years (Seymour 1986; Beck and Morgan 1986; Beck 1990), its reported medical usefulness as an adjunct in insight-oriented psychotherapy (Grinspoon and Bakalar 1986; Greer and Tolbert 1990), and its possible neurotoxicity in humans (Price et al. 1989; Grob et al. 1990). In experimental animals, MDA and MDMA were shown to exert neurotoxic effects on central serotonergic neurons resulting in degeneration of axon terminals (Ricaurte et al. 1985, 1988; Battaglia et al. 1988b, 1990; Insel et al. 1989; Gibb et al. 1990; Schmidt et al. 1990). It is not yet clear whether this finding has a relevance for humans (Peroutka et al. 1987; Price et al. 1989; Grob et al. 1990), but it played an important role for the assignment of MDMA to Schedule I status by the Drug Enforcement Agency in 1985. After the

scheduling of MDMA its N-ethyl analog, MDE ("Eve"), became more popular and served as an MDMA substitute for recreational use (Beck 1990). The action of MDE is supposed to be more subtle and shorter (3 to 4 hours), but otherwise very similar to the action of MDMA. Studies of animal behavior underlined the similarity between MDE and MDMA (Boja and Schechter 1987). Neurochemical studies showed that MDE is far less toxic than MDA and MDMA (Schmidt 1987; Ricaurte et al. 1987; Stone et al. 1987; Gibb et al. 1990).

Both MDMA and MDE show high affinities at serotonin (5-HT) uptake sites, and lower affinities at norepinephrine and dopamine (DA) 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, the substances have low affinities at 5-HT_2-, 5-HT_1-, and D_2-binding sites, but those seem to be less important for the drugs' action (Lyon et al. 1986; Battaglia et al. 1988a).

In our literature review, we found only anecdotal reports about the psychotropic effects and no human experimental data on neurobiologic effects of the drugs. The aim of our investigation was to study the pharmacokinetics and metabolism, as well as the psychologic and neurobiologic effects (endocrine, polysomnographic, cardiovascular) of MDE in healthy volunteers, and to attempt a characterization of the substance. In this paper, we present the neuroendocrine and cardiovascular studies.

Studies of the neuroendocrine effects of centrally acting drugs may contribute to the pharmacologic characterization of these substances. Numerous studies demonstrate that 5-HT and 5-HT agonists stimulate hypothalamic neurons that regulate adrenocorticotropic hormone and corticosterone secretion from the pituitary and adrenocortex, respectively (Fuller 1981). The secretion of prolactin (PRL) from the anterior pituitary is regulated by inhibitory tuberoinfundibular dopaminergic neurons and by an indirect stimulatory serotonergic mechanism (Gudelsky 1981; Van de Kar et al. 1985a). The secretion of growth hormone (GH) is stimulated by enhanced catecholaminergic and serotonergic transmission (Brown et al. 1978; Matussek 1988; Meltzer and Nash 1988). Both MDMA and MDE provoke release and reuptake inhibition of 5-HT in the central nervous system (CNS), and to a lesser extent also of norepinephrine and dopamine (Johnson et al. 1986,1988; Steele et al. 1987). Thus, one might expect that the acute administration of MDMA or MDE in healthy volunteers would increase the secretion of corticosterone, GH, and probably PRL, resulting in elevated plasma levels. Such findings would also be in line with animal experimental data showing an enhancement of cortisol and PRL secretion induced by MDMA (Nash et al. 1988).

MATERIALS AND METHODS

Subjects

Eight physically and mentally healthy, drug-free, male volunteers (all academics: seven physicians, one engineer), ranging in age from 29 to 50 years (mean 38 years) were included in a randomized double-blind placebo-controlled cross-over study. They gave informed written consent and did not receive any payment for participating in the study. Three to 7 days prior to the trial they underwent extensive physical and mental examinations (medical history, physical examination, electroencephalography, electrocardiography (ECG), free psychiatric interview, structured clinical interview according to DSM-III-R, Freiburger Personality Inventory (FPI), State-Trait Anxiety Inventory X_2, and a questionnaire for vegetative lability). The exclusion criteria were any significant physical illness requiring therapy, any mental illness, and alcohol or substance abuse at present or in the past, as defined by DSM-III criteria. Mental illness in first degree relatives was also an exclusion criterion. No volunteer had previous experience with MDE. One subject reported one experience with MDMA 2 years before. Another subject reported sporadic experience with cannabis about 10 to 15 years before, and one experience with MDMA 1.5 years before. A third subject reported sporadic experience with cannabis and one experience with D-lysergic acid (LSD) about 7 to 10 years before. All psychometric measurements were within normal range, except for the FPI dimension "openness," in which a higher than average mean score was obtained. The complete psychometric data are reported in a separate paper (Hermle et al., 1993).

Substances

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

Experimental Design

Subjects arrived at the hospital at 12:00 A.M. They received a standardized calorie- and electrolyte-balanced diet for lunch, and then entered the laboratory. Subjects had to stay awake and supine with head and upper trunk elevated on a bed in a single sound-isolated room during the trial while they were observed by a video camera with a monitor located in the neighboring laboratory unit. An intravenous catheter was placed in a forearm vein between 1:15 P.M. and 1:25 P.M. and

was kept open during the trial by a slow infusion of saline solution. The cuff of the sphygmomanometer and ECG rate meter for registration of blood pressure and heart rate was placed round the other forearm. The catheter and the sphygmomanometer were connected to long tubes that passed through an opening in the wall into the adjacent laboratory. The taking of blood samples and cardiovascular measurements were performed in the laboratory room. Either MDE or placebo was given orally with some liquid at 1:30 P.M. Blood samples for the determination of serum cortisol, PRL, and GH concentrations, as well as for the determination of the MDE concentration were drawn every 20 minutes from 2:00 to 5:00 P.M. Blood samples for the determination of cortisol were drawn into 10 ml heparinized tubes (150 µl heparin solution, C = 125 IE/ml). Blood samples for determination of GH and PRL were drawn into 10 ml Trasylol and ethylenediaminetetraacetic acid (EDTA)-treated tubes (150 µl Trasylol solution, C = 333 KIE/ml, 250 µl EDTA solution, C = 1 mg/ml). Blood samples were centrifuged immediately after drawing at +4°C, 4000 U/min, for 10 minutes. Serum was separated, transferred to glass tubes, and stored at −70°C until the time of assay. The subjects were examined for heart rate and blood pressure every 20 minutes from 2:00 P.M. to 5:00 P.M. After the end of the trial subjects remained in the hospital for another 2 to 3 hours and were monitored clinically and cardiovascularly. If necessary, transportation home was arranged for them, and a staff member stayed with them until the next day. The second trial (placebo/MDE) was performed 1 to 4 weeks after the first trial.

The investigation was part of a pilot study on psychologic and neurobiologic effects of MDE on normal control subjects and was performed in accordance with the requirements of the Declaration of Helsinki. The study was approved by the local ethics committee of the University of Freiburg. In addition to the above described neuroendocrine and cardiovascular tests the volunteers participated in a series of psychometric tests, which were performed before ingestion of the drug, and at 2, 5, and 24 hours after ingestion of the drug, as well as 7 days after the trial. Pharmacokinetics and metabolism of the drug were investigated in the blood and urine samples of the subjects at the Institute of Pharmaceutics, University of Tübingen. Evaluation of the pharmaceutical/toxicological data is currently in progress. The psychometric data are reported in a separate paper (Hermle et al., 1993).

Hormone Determinations

Serum concentrations of cortisol, PRL, and GH were measured using commercial kits. Cortisol was measured by the solid face method with 125J-Cortisol (Gam-

macoat, Dade). Concentrations of PRL and GH were measured by immunoradiometric assays (Irma, IDS). The coefficients of variation were as follows. For cortisol: 4.4 to 7.9 (within assay) and 5.2 to 9.7 (between assay); for PRL 2.7 to 4.8 (within assay) and 3.9 to 7.3 (between assay); and for GH 3.7 to 5.7 (within assay) and 9.7 to 11.4 (between assay).

Statistical Analysis

Mean values and standard deviation (SD) were calculated for all data. The time course of hormone concentration and cardiovascular data were analyzed by multivariate analysis of variance (MANOVA) with repeated measurements. Further analysis was performed with two-tailed Student's t-tests, followed by the Bonferroni procedure. Statistically significant p values were considered to be those less than 0.05.

RESULTS

Neuroendocrine Data

Following placebo administration, cortisol and PRL levels were stable, except for a slight decrease in plasma cortisol during the registration period, which was interpreted as relief from stress. Significant long-lasting increases in serum cortisol and PRL were produced by MDE (MANOVA, $p = .001$ and $.0197$, respectively). Following placebo administration, four of the eight volunteers showed one or two secretion peaks for GH during the registration period. Following MDE administration the GH level remained stable in all volunteers during the entire registration period. However, the resulting difference in GH levels after MDE and placebo, indicating a blunting of GH secretion after MDE administration, was not statistically significant (MANOVA, $p = .0870$). The neuroendocrine data are shown in Figure 1 (t-test, Bonferroni procedure).

Cardiovascular Data

Blood pressure and heart rate remained stable after placebo administration. Long-lasting increases in systolic blood pressure and heart rate were produced by MDE (MANOVA, $p = .006$ and $.001$, respectively). The increase in diastolic blood pressure after MDE administration was not statistically significant (MANOVA, $p = .053$). The cardiovascular data are shown in Figure 2 (t-test, Bonferroni procedure).

DISCUSSION

Oral administration of 140 mg of MDE to eight healthy male volunteers was followed by significant increases
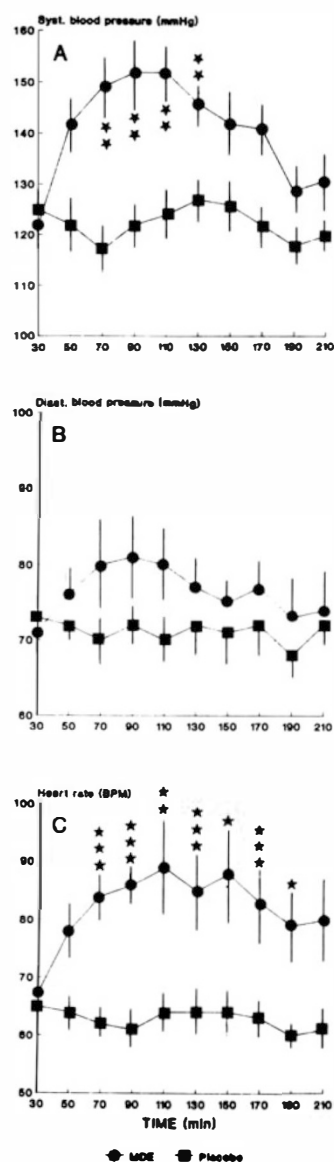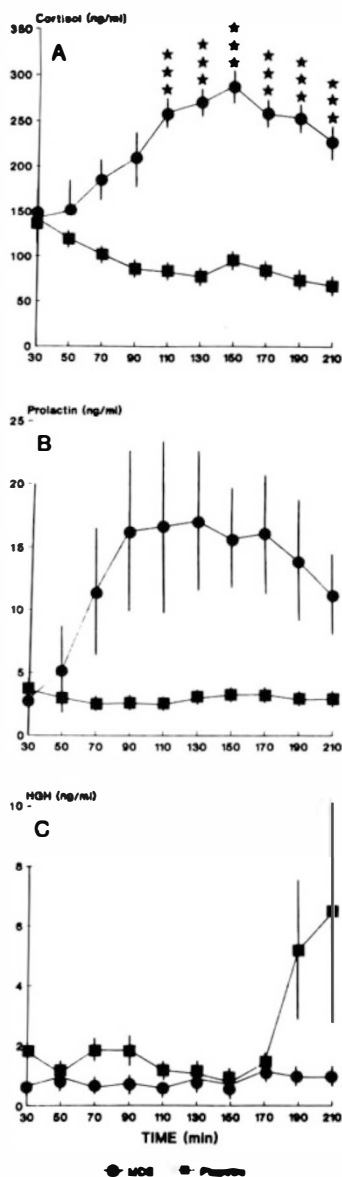
Figure 1. The effects of 140 mg MDE or placebo on serum levels of cortisol (**A**), prolactin (**B**), and growth hormone (HGH) (**C**) in eight healthy male volunteers ($\bar{x}$ and SD; t-test; Bonferroni procedure: $^*p < .05$; $^{**}p < .01$; $^{***}p < .001$). Time 0 = MDE/placebo administration.

Figure 2. The effects of 140 mg MDE or placebo on systolic blood pressure (**A**), diastolic blood pressure (**B**), and heart rate (**C**) in eight healthy male volunteers ($\bar{x}$ and SD; t-test; Bonferroni procedure: $^*p < .05$; $^{**}p < .01$; $^{***}p < .001$). Time 0 = MDE/placebo administration.

in plasma cortisol and PRL concentrations and a trend toward decrease of GH secretion.

A probable explanation for the effects of MDE on plasma cortisol and PRL levels might be an indirect serotonergic mechanism. This would be in line with experimental data from animal studies. In vitro studies on rat brain slices showed that MDMA and MDE evoke release and inhibit reuptake of endogenous 5-HT and catecholamines, the preferential effects being on the serotonergic, and the weakest effects on the DA systems (Johnson et al. 1986; Steele et al. 1987; Battaglia et al. 1988a). Serotonin and norepinephrine are known

to stimulate the secretion of cortisol and PRL (Laakmann 1990; Matussek 1988; Meltzer and Nash 1988). Nash et al. (1988) and Nash and Meltzer (1990) showed that MDMA stimulates the secretion of cortisol and PRL in the rat. In those studies the effect of MDMA on cortisol secretion was clearly shown to be mediated via serotonergic mechanisms, as it was blocked or blunted by 5-HT$_2$ antagonists or pretreatment with fluoxetine or p-chlorophenylalanine. The mechanism mediating PRL secretion could not be entirely clarified; however, the authors of that case hypothesized that a serotonergic mechanism was responsible, because the effect was

blunted after pretreatment with p-chlorophenylalanine. They came to the conclusion that MDMA requires endogenous 5-HT to stimulate the secretion of PRL and corticosterone (Nash et al. 1988). In studies with other amphetamine derivatives similar effects on plasma cortisol and PRL were also demonstrated (Mc Elroy et al. 1984; Van de Kar et al. 1985a, b). Finally, the phenethylamine psychedelic mescaline and the indole psychedelic N,N-dimethyltryptamine (N,N-DMT), which act via 5-HT-dependent mechanisms, were also shown to increase plasma PRL (Demisch and Neubauer 1979; Meltzer et al. 1978, 1981).

In contrast, the observed trend toward a decrease of serum GH following MDE administration is difficult to interpret. To our knowledge, there are no previous experimental data on the effect of MDMA or MDE on GH secretion. However, a substance enhancing release of endogenous 5-HT and catecholamines and acting as a direct 5-HT agonist would be expected to cause augmentation of GH secretion (Brown et al. 1978; Laakmann 1990; Meltzer and Nash 1988). The increase of GH plasma levels was demonstrated in numerous studies following administration of amphetamines (Besser et al. 1969; Parkes et al. 1977) and the hallucinogenic substances mescalin, N,N-DMT, and LSD (Demisch and Neubauer 1979; Meltzer et al. 1981). The observed trend toward blunting of GH secretion following MDE administration in our study might indeed support the hypothesis of a novel psychoactive substance class (Nichols 1986). However, this effect was not statistically significant. Further studies are needed to better assess this potentially interesting finding.

The cardiovascular effects of MDE with long-lasting significant rises in blood pressure and heart rate underline its sympathomimetic properties. Similar sympathomimetic effects were reported in a human pilot study (Downing 1986) after ingestion of MDMA and were frequently observed with the use of amphetamine and derivatives (Turek et al. 1974; Angrist et al. 1987). As in the study of Downing (1986), the volunteers had no particular discomfort or awareness of the altered cardiovascular parameters, and mostly felt calm and relaxed (unpublished data of the psychometric tests). The cardiovascular effects of MDE might be mediated via indirect catecholaminergic mechanisms (release and reuptake inhibition of norepinephrine).

In conclusion, the neuroendocrine and cardiovascular effects of MDE in normal control subjects were similar to the effects of other amphetamines and chemically related hallucinogens, as previously reported in the literature. The trend toward blunting of GH secretion is perhaps an exception in this respect and is a potentially interesting finding, but it was not statistically significant. Evaluation of the data derived from our studies on the subjective and polysomnographic effects of MDE in healthy volunteers also stresses the

similarities of MDE to stimulant amphetamines: in these studies a marked overall stimulation with increased vigility was shown to be the most robust effect of MDE. Also in those studies we found some potentially interesting trends (nonsuppression of slow-wave-sleep, simultaneous appearance of increased psychomotor drive, subjective feelings of relaxation, diminished anxiety, and depressed mood), that might indicate unique effect patterns of MDE, but those findings also did not reach statistical significance (unpublished data). Further investigations are needed in order to assess the neurobiologic and subjective effects of MDE and related substances and thus contribute to the pharmacologic characterization of the "entactogens."

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