
Neuroendocrine Abnormalities in Recreational Ecstasy (MDMA) Users: Is it Ecstasy or Cannabis?

Euphrosyne Gouzoulis-Mayfrank, Steffanie Becker, Susanne Pelz, Frank Tuchtenhagen, and Jörg Daumann

Background: *The purpose of this study was to investigate neuroendocrine function in ecstasy (3,4-methylenedioxymethamphetamine = MDMA) users and controls.*

Methods: *Prolactin response to d-fenfluramine was assessed in abstinent ecstasy users with concomitant use of cannabis only (n = 24, male/female 13/11) and in two control groups: healthy nonusers (n = 13, female) and exclusive cannabis users (n = 7, male).*

Results: *Prolactin response to d-fenfluramine was slightly blunted in female ecstasy users. Both male user samples exhibited a weak prolactin response to d-fenfluramine, but this was weaker in the group of cannabis users. Baseline prolactin and prolactin response to d-fenfluramine were associated with the extent of previous cannabis use.*

Conclusions: *Endocrinological abnormalities of ecstasy users may be closely related to their coincident cannabis use. Cannabis use may be an important confound in endocrinological studies of ecstasy users and should be looked for more systematically in future studies. Biol Psychiatry 2002;51:766–769*

Key Words: Ecstasy, MDMA, cannabis, neurotoxicity, serotonin, d-fenfluramine

Introduction

Ecstasy (3,4-methylenedioxymethamphetamine=MDMA and related congeners: MDA, MDEA) is a group of popular recreational drugs with neurotoxic effects upon central serotonergic systems in experimental animals and probably also in humans (Ricaurte et al 2000; McCann et al 2000). Neuroendocrine challenge studies with serotonergic agonists reported blunted or slightly blunted hormonal responses in ecstasy users, suggesting a low central serotonergic tone (Price et al 1989; Gerra et al 1998, 2000; Verkes et al 2001); however, others did not find any

abnormalities or their results were even opposite than expected (McCann et al 1994, 1999). An important methodological problem of most studies is related to the frequent polydrug use pattern of ecstasy users and the poor paralleling of control samples in respect to the use of other drugs (Curran 2000). Particularly, cannabis is known to influence prolactin secretion, and almost every ecstasy user smokes cannabis regularly (Fernandez-Ruiz et al 1997; Rodriguez et al 1999). In the present study, we examined ecstasy users with concomitant use of cannabis only and we enrolled control groups of nonusers and exclusive cannabis users. This design was chosen to disentangle the possible effects of cannabis from the effects of ecstasy on neuroendocrine secretion.

Methods and Materials

The study was originally designed to examine 30 regular users of ecstasy and cannabis, 30 exclusive cannabis users, and 30 healthy nonusers with a d-fenfluramine (FEN) challenge. Because of the withdrawal of FEN (Isomeride®) from the market, we were able to examine only 13 male and 11 female users of ecstasy and cannabis (E + C), 7 male and 2 female exclusive users of cannabis (C), and 3 male and 13 female nonusers. The data of the two female cannabis users and the three male nonusers were excluded from further analysis.

The E + C users reported regular ecstasy use over 6 months or longer (at least twice per month) or ecstasy use on at least 25 occasions during the last 2 years. Exclusion criteria were: a) regular use of other drugs (at least once per month over 6 months or longer within the last 2 years) except for cannabis, and b) regular heavy use of alcohol (drunkenness at least twice per month). The C users were matched for the extent of cannabis use with the E + C users, but they had no history of heavy alcohol or other drug use. The nonusers had never taken ecstasy and had no history of regular drug or heavy alcohol use. Exclusion criteria for all participants were any current or previous Axis I psychiatric disorder except for drug abuse in the two user groups, any organic brain disorder, any relevant general medical condition, any medication on the study day, and pregnancy.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All subjects gave written informed consent. Procedures included a Structured Interview according to DSM-IV, an additional de-

From the Department of Psychiatry and Psychotherapy, Medical Faculty of the University of Technology (RWTH), Aachen, Germany.

Address reprint requests to Dr. E. Gouzoulis-Mayfrank, Medical Faculty of the University of Technology (RWTH), Department of Psychiatry and Psychotherapy, Pauwelsstrasse 30, D-52074 Aachen, FRG, Germany.

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Table 1. Patterns of Ecstasy and Cannabis Use in the Two User Groups

Patterns of Use	Ecstasy Use		Cannabis Use		
	m E + C	f E + C	m E + C	m C	f E + C
Estimated total dose (tablets)	78.2 ± 88.6	81.4 ± 105.2	—	—	—
Average frequency of use (days per month)	2.4 ± 1.2	2.4 ± 2.1	21.2 ± 13.1	20.6 ± 12.0	9.6 ± 11.7
Average estimated daily dose (tablets or mg)	1.46 ± 0.85	1.27 ± 1.03	769.2 ± 793.6	707.1 ± 474.7	250 ± 224.7
Duration of regular use (months)	29.3 ± 18.4	20.2 ± 17.6	64.6 ± 37.8 ^a	24.8 ± 8.8	45.3 ± 52.5
Age at onset of use (years)	20.4 ± 3.2	18.2 ± 3.4	16.7 ± 3.7	16.9 ± 2.3	15.4 ± 1.1
Time since last dose (days)	30.9 ± 46.8	58.3 ± 102.3	5.7 ± 6.9	1.4 ± .8	18.9 ± 41.1
THC-screen in urine sample on study day			positive 9/negative 4	positive 6/negative 1	positive 6/negative 5

C, cannabis users; E + C, users of ecstasy and cannabis; f, female; m, male; THC, tetrahydrocannabinol.

^aSignificant difference to the group of male cannabis users (unpaired *t* test, 2-tailed, *p* < .05).

tailed interview on history of drug use, medical history, a clinical examination and an electrocardiogram. Users agreed to abstain from ecstasy use for at least 7 days before the study, but they agreed to abstain from cannabis use only on the study day. Immunoassay drug screens were performed on the study day with urine samples for the following substance groups: amphetamines and methamphetamines (including methylenedioxymphetamines = ecstasy), cocaine, marihuana, benzodiazepines, barbiturates, and opiates (RIDA ToxiQuick, r-Biopharm, Darmstadt). A positive screen except for cannabis was an exclusion criterion.

A d-fenfluramine challenge was performed using standard procedures (30 mg FEN orally at 10:00 AM). Baseline prolactin (PRL) was determined 15 and 5 min before and PRL responses were determined 1 to 5 hours after administration of FEN. Prolactin was measured by heterogeneous sandwich magnetic separation assay (MSA Bayer; coefficients of variation within run: 1.6–2.0%, between run: 2.6–3.0%). Serum concentrations of FEN and its metabolite nor-FEN were measured by high-pressure liquid chromatography (HPLC, threshold for detection: .1 µg/L). Due to difficulties to agree upon dates for the investigation five female E + C users were examined during the luteal phase of their menstrual cycle. All other female subjects were examined during the early follicular phase.

Results

The two male samples were similar for age (24.2 ± 2.4 vs. 22.3 ± 3.3 years), whereas the female E + C users were slightly younger than the nonusers (22.6 ± 2.7 vs. 28.3 ± 5.5 years, *t* test, *p* < .05). The male E + C users smoked cannabis for a longer period of time compared with the C users, otherwise the extent of previous use of cannabis was similar in both male samples (see Table 1).

All individual baseline PRL values were within normal range. d-fenfluramine plasma concentrations ranged from 4.5 to 45.5 µg/L and were not associated with PRL responses (see Figure 1). Regarding the female samples, repeated measures ANOVA revealed a significant effect

of time ($F = 45.3$, *p* < .001) and an interaction time x group ($F = 9.57$, *p* < .01), but no effect of group ($F = 9.2$, *p* = .325). Differences in PRL Δ peak and Δ AUC between the female samples did not reach statistical significance (unpaired *t* test, *p* = .147). Regarding the male samples, repeated measures ANOVA revealed significant effects of time and group ($F = 19.63$, *p* < .001, and $F = 4.98$, *p* < .05, respectively) without interaction time x group ($F = 9.3$, *p* = .348). Differences in PRL Δ peak and Δ AUC between the male user samples were significant (unpaired *t* tests, *p* < .05).

In the group of male E + C users, we found an association of a weak PRL response (Δ AUC) with a long period of regular ecstasy use ($r = -.599$, *p* < .05) and a high estimated total ecstasy dose ($r = -.658$, *p* < .05), but with a low average frequency of ecstasy use ($r = .614$, *p* < .05). The significant correlations between endocrinological parameters and the extent of previous cannabis use are summarized in Table 2.

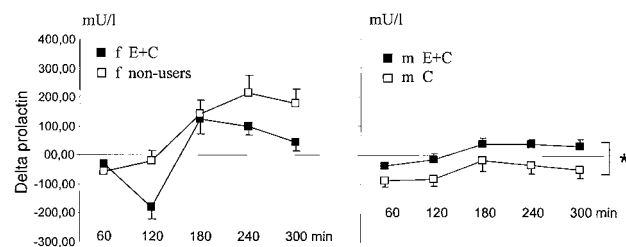


Figure 1. Time course of prolactin response to 30 mg d-fenfluramine in ecstasy users and controls (means and SE). C, cannabis users; E + C, users of ecstasy and cannabis; f, female; m, male; min, minutes after oral administration of FEN; *, significant main effect of group (*p* < .05, repeated measures ANOVA).

Table 2. Pearson Correlations between Aspects of Previous Cannabis Use and Endocrinological Parameters (PRL baseline values and PRL response to FEN)

Cannabis Use	f E + C			m C		
	Δ AUC	Δ Peak	baseline	Δ AUC	Δ Peak	baseline
Estimated daily dose (mg)	$r = .691^a$		$r = -.680^a$	$r = .891^b$	$r = .885^b$	$r = -.731^a$
Average frequency of use (days per month)	$r = .656^a$	$r = .822^b$				
Duration of regular use (months)				$r = .773^a$	$r = .781^a$	$r = -.709^a$

Only statistically significant coefficients are presented ($p < .05$, no correction for multiple testing).

PRL, prolactin; FEN, d-fenfluramine; f E + C, female users of ecstasy and cannabis; m C, male cannabis users.

^a $p < .05$, ^b $p < .01$.

Discussion

The PRL response to a FEN challenge was assessed in ecstasy users and controls. Male users of ecstasy and cannabis had a more robust response than male users of cannabis only; however, both male user samples exhibited a relatively weak PRL response compared with literature data from healthy subjects (Coccaro et al 1996; Gerra et al 2000; Verkes et al 2001). The female ecstasy and cannabis users had a slight, though insignificant blunting of hormonal response compared to the female nonusers. We found consistent associations between endocrinological parameters and the extent of previous cannabis use, whereas evidence for an association of ecstasy use and endocrinological parameters was weak and inconsistent. Heavier and longer regular cannabis use was associated with a relatively low baseline PRL value and a stronger PRL response to FEN. This suggests that complex neuroendocrine adaptation processes may follow chronic cannabis use and may account for group differences in studies with drug users.

The literature on neuroendocrine abnormalities in ecstasy users is inconsistent and confounded by methodological problems such as the polydrug use pattern of most study populations (Price et al 1989; McCann et al 1994, 1999; Gerra et al 1998, 2000; Verkes et al 2001). So far, the strongest evidence for an association of lasting neuroendocrine abnormalities with ecstasy use is provided by a longitudinal study by Gerra et al (2000). The authors reported blunting of PRL responses to FEN persisting after 1 year of abstinence and being associated with a longer duration of previous regular ecstasy use (Gerra et al 2000). Yet, although the Gerra et al studies (1998; 2000) are carefully designed and methodologically sound, episodic use of cannabis or alcohol was not an exclusion criterion in the longitudinal study and may have contributed to its results (Gerra et al 2000).

In animal studies, acute peripheral administration of cannabinoids induces a brief rise in plasma PRL levels followed by a prolonged suppression of PRL secretion (Fernandez-Ruiz et al 1997; Rodriguez et al 1999). Indi-

rect dopaminergic and direct cannabinoid receptor mechanisms are believed to mediate this biphasic response. Human studies yielded inconsistent results regarding both the acute and long-term effects of cannabinoids on hormonal secretion (Lemberger et al 1975; Mendelson et al 1984, 1985; Cone et al 1986; Dax et al 1989; Kolodny et al 1974; Olusi 1980). In regular cannabis users, PRL plasma levels increased gradually during short-term deprivation and returned to predeprivation levels again after smoking (Markianos and Stefanis 1982). In summary, cannabis influences neuroendocrine regulation and complex adaptation processes take place in states of drug deprivation.

Needless to say, our study has important methodological limitations resulting from the fact that we were unable to complete it properly. Nevertheless, our results indicate that cannabis use may be an important confound in endocrinological studies of ecstasy users. In consequence, future studies with ecstasy users should look for the aspect of concomitant cannabis use more systematically.

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References

- Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL (1996): Hormonal responses to d- and d,l-Fenfluramine in healthy human subjects. *Neuropsychopharmacology* 15:595–607.
- Cone EJ, Johnson RE, Moore JD, Roache JD (1986): Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects. *Pharmacol Biochem Behav* 24:1749–1754.
- Curran VH (2000): Is MDMA (Ecstasy) neurotoxic in humans? An overview of evidence and of methodological problems in research. *Neuropsychobiology* 42:34–41.

- Dax EM, Pilotte NS, Adler WH, Nagel JE, Lange WR (1989): The effects of 9-ene-tetrahydrocannabinol on hormone release and immune function. *J Steroid Biochem* 34:263–270.
- Fernandez-Ruiz JJ, Munoz RM, Romero J, Villanua MA, Makriyannis A, Ramos JA (1997): Time course of the effects of different cannabimimetics on prolactin and gonadotrophin secretion: Evidence for the presence of CB1 receptors in hypothalamic structures and their involvement in the effects of cannabimimetics. *Biochem Pharmacol* 53:1919–1927.
- Gerra G, Zaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, et al (2000): Long-lasting effects of 3,4-methylenedioxymethamphetamine (ecstasy) on serotonin function in humans. *Biol Psychiatry* 47:127–136.
- Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, et al (1998): Serotonergic function after 3,4-methylenedioxymethamphetamine (Ecstasy) in humans. *Int Clin Psychopharmacol* 13:1–9.
- Kolodny RC, Masters WH, Kolodner RM, Toro G (1974): Depression of plasma testosterone levels after chronic intensive marihuana use. *N Engl J Med* 290:872–874.
- Lemberger L, Crabtree R, Rowe H, Clemens J (1975): Tetrahydrocannabinol and serum prolactin levels in man. *Life Sci* 16:1339–1343.
- Markianos M, Stefanis C (1982): Effects of acute cannabis use and short-term deprivation on plasma prolactin and dopamine-beta-hydroxylase in long-term users. *Drug Alcohol Depend* 9:251–255.
- McCann DU, Eligulashvili V, Mertl M, Murphy DL, Ricaurte GA (1999): Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphetamine (MDMA) users. *Psychopharmacology* 147:56–65.
- McCann DU, Eligulashvili V, Ricaurte GA (2000): 3,4-methylenedioxymethamphetamine (Ecstasy)-induced serotonin neurotoxicity: Clinical studies. *Neuropsychobiology* 42:11–16.
- McCann DU, Ridenour A, Shaham Y, Ricaurte GA (1994): Serotonin neurotoxicity after 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy): A controlled study in humans. *Neuropsychopharmacology* 10:129–138.
- Mendelson JH, Ellingboe J, Mello NK (1984): Acute effects of natural and synthetic cannabis compounds on prolactin levels in human males. *Pharmacol Biochem Behav* 20:103–106.
- Mendelson JH, Mello NK, Ellingboe J (1985): Acute effects of marihuana smoking on prolactin levels in human females. *J Pharmacol Exp Ther* 232:220–222.
- Olusi SO (1980): Hyperprolactinaemia in patients with suspected cannabis-induced gynaecomastia [letter]. *Lancet* 1(8162): 255.
- Price LH, Ricaurte GA, Krystal JH, Heninger GR (1989): Neuroendocrine and mood responses to intravenous L-tryptophan in MDMA users. *Arch Gen Psychiatry* 46:20–22.
- Ricaurte GA, Yuan J, McCann DU (2000): 3,4-methylenedioxymethamphetamine (Ecstasy)-induced serotonin neurotoxicity Studies in animals. *Neuropsychobiology* 42:5–10.
- Rodriguez DF, Wenger T, Navarro M, Murphy LL (1999): Effects of delta9-THC on VIP-induced prolactin secretion in anterior pituitary cultures: Evidence for the presence of functional cannabinoid CB1 receptors in pituitary cells. *Brain Res* 841:114–122.
- Verkes RJ, Gijsman HJ, Pieters RC, de Visser S, Kuijpers M, Pennings JM, et al (2001): Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology* 153:196–202.