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ORIGINAL INVESTIGATION

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Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans

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Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA) is a widely used phenethylamine. Reports have described the effects of MDMA in a controlled laboratory setting, but the full range of effects of MDMA in humans is still not completely characterized. *Objectives:* To describe the physiological, subjective, and hormonal changes after single doses of MDMA in a laboratory setting and examine relationships between these effects. *Methods:* Eight MDMA-experienced volunteers each received placebo, 0.5 mg/kg, and 1.5 mg/kg oral doses of MDMA in a double-blind crossover study. *Results:* The 1.5 mg/kg dose (comparable to that typically used by most participants) produced significant subjective effects, peaking at about 2 h after dosing, including some effects commonly associated with stimulant drugs, hallucinogens, and entactogens. MDMA significantly increased plasma cortisol, prolactin, and dehydroepiandrosterone (DHEA) levels. Increase in plasma cortisol after the 1.5 mg/kg dose correlated with increased heart rate, rate-pressure product, and drug liking. Rise in DHEA correlated with euphoria. *Conclusions:* A typically used dose of MDMA produced effects commonly associated with stimulants and hallucinogens. Subjects liked MDMA. Correlations between cortisol and DHEA levels and some physiological and psychological effects are consistent with animal data suggesting that hormones modulate some responses to drugs of abuse.

Keywords MDMA · DHEA · Cortisol · Psychological · Hormone · Physiological

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a substituted phenethylamine with structural similarities to methamphetamine and mescaline. It achieved notoriety in the mid-1980s with the street name "ecstasy" and became associated with dance parties called "raves." MDMA was also used as a psychotherapy adjunct in the mid-1970s (Grinspoon and Bakalar 1986; Greer and Tolbert 1998). Reports of adverse events following MDMA use (Cohen and Cocores 1997; Williamson et al. 1997), animal studies describing long-term decreases in markers of serotonergic functioning after high or repeated dose MDMA administration (reviewed in Seiden and Sabol 1996), and cognitive, physiological, and imaging findings in humans (Parrott et al. 1998; Dafters et al. 1999; McCann et al. 1999a, 1999b; Gouzoulis-Mayfrank et al. 2000; Ricaurte et al. 2000; Croft et al. 2001; Verkes et al. 2001; and reviewed in McCann et al. 2000) have not greatly diminished MDMA use. For example, in 2000, 8.2% of 12th graders in the United States reported that they had used MDMA in the past year (Johnston et al. 2001).

MDMA and other 3,4-methylenedioxy-substituted phenethylamines have been postulated to represent a new class of pharmacological agents termed entactogens with effects only partially overlapping those of psychostimulants and serotonergic hallucinogens (Nichols 1986). Reported effects of entactogens include enhanced feelings of closeness to others, empathy, well-being, and insightfulness, with relatively little hallucinatory effect (Grinspoon and Bakalar 1986; Hegadoren et al. 1999; Nichols 1986). Reports have described many effects of MDMA in a controlled laboratory setting (Grob et al. 1996; Vollenweider et al. 1998, 1999; Mas et al. 1999; Pacifici et al. 1999; Cami et al. 2000; de la Torre et al. 2000; Gamma et al. 2000; Liechti and Vollenweider 2000; Liechti et al. 2000a, 2000b, 2001a, 2001b; Tancer and Johanson 2001), but the full range of pharmacological effects of MDMA in humans still may not be completely characterized.

The pharmacological effects of MDMA are probably mediated through a number of mechanisms. MDMA increases extracellular serotonin and dopamine (reviewed in White et al. 1996) and has high affinity for the serotonin reuptake transporter. It also has micromolar affinity for 5-HT-2, alpha-2 adrenergic, M-1 muscarinic, and H-1 histamine receptors (Battaglia et al. 1988; Lavelle et al. 1999). In addition to neurotransmitter and receptor effects, neuroendocrine mechanisms may mediate some of the effects of MDMA. MDMA increases corticotropin (ACTH), cortisol, and prolactin in humans (Grob et al. 1996; Mas et al. 1999).

The objectives of this study were to measure the physiological, subjective, and hormonal changes after single doses of MDMA in a laboratory setting and to examine relationships among MDMA's subjective, physiological, and hormonal effects.

Because of the relationships between serotonin, cortisol, and prolactin, we examined correlations with cardiovascular effects and the LSD scale of the SDEQ, since LSD is considered a serotonergic drug. Because of evidence linking corticosteroids with the rewarding effects of stimulant drugs (Goeders and Guerin 1996; Piazza et al. 1996), we examined correlations between cortisol and several indices of rewarding effect: Drug Liking, Good Drug Effect, and Euphoria. Because of a report of a relationship between DHEA and "wellbeing" (McCraty et al. 1998), we also examined correlations between DHEA and rewarding effects.

Materials and methods

Racemic MDMA was provided by David Nichols, Purdue University (West Lafayette, Ind., USA). Chromatography and mass spectrometry confirmed identity and purity. MDMA hydrochloride and lactose placebo were administered in identical gelatin capsules.

Volunteers

Volunteers had used MDMA on at least four occasions in the last 3 years and were in good health, confirmed with medical examination, laboratory tests (including hematologic, hepatic, renal serum chemistries, and urinalysis), and electrocardiogram. None were pregnant. Potential volunteers were excluded if they had been treated for drug abuse or addiction in the past year or were currently dependent on any drug (except nicotine or caffeine). Cardiovascular risk factors of cholesterol over 250 mg/dl or smoking >2 packs/day of tobacco cigarettes were also criteria for exclusion. All volunteers provided informed consent. The protocol was approved by the local Institutional Review Board at the University of California, San Francisco.

Potential volunteers were screened for cytochrome P450 2D6 (CYP2D6) deficiency using dextromethorphan. For the CYP2D6 test, 30 mg dextromethorphan was administered orally and urine was collected for 8 h. Urine was assayed for dextromethorphan/dextrorphan ratio using high pressure liquid chromatography (Lam and Rodriguez 1993). An excreted dextromethorphan/dextrorphan ratio of >0.3 was considered indicative of poor metabolizer status for CYP2D6 (Schmid et al. 1985). Since 3–10% of the population is CYP2D6 deficient (Nies and Spielberg 1996) and CYP2D6 deficiency has been postulated to increase the risk of acute adverse reaction (Tucker et al. 1994), poor metabolizers were excluded from this study. Two of the 13 individuals evaluated for CYP2D6 status were excluded for this reason.

Potential volunteers were also screened for inducible myocardial ischemia using a dobutamine stress test. The dobutamine test is described in detail in Lester et al. (2000) and followed standard procedures (Mason et al. 1984). All volunteers tolerated this test well.

Drug administration

Each volunteer was tested in three inpatient sessions at least 7 days apart and was given in partially balanced order an oral dose of placebo, 0.5 mg/kg MDMA, or 1.5 mg/kg MDMA. The higher dose was comparable to the initial dose (100 mg) administered by some therapists to new patients for whom sensitivity to MDMA effects was unknown (Shulgin and Shulgin 1997). Treatment sequence used a partially balanced 3×3 Latin Square design. For safety reasons, each volunteer received the lower dose of MDMA before the higher one. The order of placebo dose was randomized.

Experimental sessions were in a laboratory setting. Volunteers were admitted to the UCSF General Clinical Research Center the afternoon before and remained until 48 h after drug administration.

To minimize confounding effects of circadian rhythm and meals on cortisol levels, drug dosing took place at approximately the same time (usually about 1100 hours), approximately 4 h after breakfast, with a late lunch after peak effects.

Before each laboratory session, volunteers were queried about their licit and illicit drug use during the previous week. Volunteers described the frequency, quantity, and dollar amount of use. A qualitative urine drug screen was obtained at each session.

Measures

Heart rate, blood pressure, respiratory rate, and skin and core (tympanic) temperatures were measured before drug administration and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 24, and 48 h after dosing using an Escort II 300 Patient Monitor (Medical Data Electronics, Arleta, Calif., USA) and a Mallinkrodt Mon-a-therm 6500 (Mallinkrodt Inc., St Louis, Mo., USA) with thermocouples on the index finger and near the tympanic membrane. Rate pressure product, a measure of cardiac work, was calculated as the product of systolic blood pressure and heart rate. Pupil size was measured before and at 2, 8, and 24 h after dosing with a Macro 5 SLR Polaroid camera (Polaroid Corp., Cambridge, Mass., USA).

Subjective MDMA effects identified from review of user surveys and uncontrolled clinical reports (Greer and Tolbert 1986; Peroutka et al. 1988; Solowij and Lee 1992) were administered as visual analog scales (VAS) at the same time as physiological measures. VAS reports included: Closeness to Others, Energetic, Talkative, Friendly, Confident, Insightful, and Anxious. Other VAS items included: High, Any Drug Effect, Good Drug Effect, Bad Drug Effect, and level of Drug Liking. The 100 mm VAS ranged from 0 (defined as not at all) to 100 (the most ever). Intoxication was reported verbally using a 0 (not at all) to 100 (the most intoxicated ever on MDMA) scale to allow for comparisons to volunteer's prior MDMA experiences.

The Subjective Drug Effects Questionnaire (SDEQ), a 272-item self-report instrument measuring perceptual, mood, and somatic changes (Katz et al. 1968), was administered before and at 2, 7, 24, and 48 h after dosing. The SDEQ is a validated instrument with subscales shown to be sensitive to both hallucinogen (LSD, Ambivalence, and Cognitive Impairment scales) and psychostimulant (Autonomic Arousal, Mood Euphoria, Relaxation, Tension, and Cognitive Improvement scales) drug effects. During its development it was designed and used to characterize subjective effects of LSD and amphetamine in volunteers given those drugs in a controlled setting. The SDEQ takes about 20 min to complete. We modified the SDEQ from its original present or absent subjective effect ratings to instead ask volunteers to use a 0–4 point scale (0="not at all"; 4="extremely") for reporting subjective states in

order to better investigate intensity of effects with other factors. In addition to the previously established a priori and empirical cluster analysis derived subscales, we also report results of individual SDEQ items and investigator constructed clusters of items describing subjective effects previously reported in the literature to follow the use of MDMA. Two SDEQ items address interpersonal feelings believed by some users to be produced by MDMA and other entactogens – "Have you had a greater feeling of love for others?" and "Have you liked having people around more?" Other SDEQ items ask about somatic, sensory, and perceptual acute effects of MDMA (Greer and Tolbert 1986; Peroutka et al. 1988; Solowij and Lee 1992) (see Table 2). To maximize their detection, previously reported MDMA effects were defined broadly. For example the effect "paresthesias" was characterized by eight SDEQ items asking about tingling, numbness, sensitivity, or "funny feelings" in the lips, skin, or limbs. The effect "Altered sound perception" included SDEQ items referring to hearing one's own voice or other sounds closer or further away, slower or faster, smoother or slurred.

The Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), a scored 30-item instrument similar to the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), was used to rate symptom intensity and addressed a range of psychopathology on a 1–7 point scale. Subscales include Positive Symptoms, Negative Symptoms, and General Psychopathology. The PANSS was administered at baseline and at 2.5 and 24 h after dosing. Two follow-up PANSS ratings were performed at 1 week and 2 weeks after the last dose.

In addition to the VAS and SDEQ self reports and the PANSS, volunteers were also instructed to report to observers any other drug effects and experiences as they occurred to detect symptoms that might not be captured with the standardized subjective testing. At 8 h after dosing, volunteers were asked how much they would have paid for the dose.

Plasma cortisol and DHEA concentrations were measured before and at 30-min intervals until 6 h after dosing with an additional sample at 8 h. Serum levels of prolactin and luteinizing hormone (LH) were measured before and at 2 h after dosing. In female volunteers, serum was analyzed for progesterone, follicle-stimulating hormone (FSH), and estradiol before and at 2 h after dosing. Plasma and serum hormone concentrations were assayed in duplicate at the Drug and Alcohol Research Center at McLean Hospital, Harvard Medical School, using commercially-available radioimmunoassay kits (DHEA, progesterone, and estradiol kits from Diagnostic Products Corp., Los Angeles, Calif., USA; LH kits from ICN Biomedicals, Costa Mesa, Calif., USA; prolactin kit from Pantex, Santa Monica, Calif., USA; and cortisol kit from Diasorin Corp., Stillwater, Minn., USA).

Plasma and urine samples were obtained for pharmacokinetic analysis of MDMA and methylenedioxyamphetamine (MDA) concentrations and will be reported in a subsequent paper. Transthoracic two-dimensional and Doppler echocardiograms were taken at each session and are reported elsewhere (Lester et al. 2000).

Data analysis

Differences between conditions were assessed using repeated measures analysis of variance using changes from baseline. Time points included in the analysis were for all the times data were collected except for DHEA, for which 0–5 h was used because of a postprandial rise in DHEA starting at 5 h, confounding the data. Drug conditions and observation times were considered within-subjects factors. After a significant F-test, pairwise comparisons were performed using the least squares means analysis. Data were adjusted for sphericity using the Huynh-Feldt adjustment factor. Huynh-Feldt corrected significant values are reported. Effects were considered statistically significant at $P<0.05$. Correlations between rise in hormone levels and peak effects were assessed using Kendall's Tau, a non-parametric test of association. Changes from baseline to mean peak time values were correlated. Mean peak time was used because mean peaks occurred in close temporal proximity.

Results

Demographic and background data

The eight volunteers were Caucasian, 24–39 years old with at least 3 years of college. Three were women. Prior MDMA use ranged from 5 to 200 times. The reason given by all eight participants for their use of MDMA was to deepen self-understanding, although additional reasons were given by some. They typically took 1–2 tablets or about $25 worth of what they thought was MDMA. The number of volunteers reporting past experience with other drugs of abuse was: alcohol eight (50 to >1000 times); marijuana eight (35 to >1000 times); hallucinogens eight (6 to >100 times); cocaine or amphetamines seven (3–150 times); nitrous oxide six (3–150 times); heroin, morphine, or opium four (3–160 times); other opioids (usually as prescription analgesics) five (2–750 times); gamma-hydroxybutyrate (GHB) four (4–500 times); and benzodiazepines three (4–20 times). No volunteer showed evidence of recent drug use by report, observation, or urine toxicology.

Physiological measures

Cardiovascular response has been reported in detail in Lester et al. (2000). In summary, 1.5 mg/kg MDMA increased systolic and diastolic blood pressure by 20±10 (mean±SD) mmHg and 13±5 mmHg, respectively. Heart rate increased by 26±20 beats per min. Pupil size increased 2.5±1.0 mm. Although skin temperature decreased 5.0±4.1°C from pretreatment levels after 1.5 mg/kg MDMA, it was not significantly lower (time course analysis) than in the placebo condition. MDMA 0.5 mg/kg did not significantly change those measures.

Subjective reports and observer measures

Peak changes in subjective self-reports are in Table 1. Time course for subjective measures is in Fig. 1. The time courses for Intoxication rating and High, Any Drug Effect, Good Drug Effect, Confident, and Insightful are almost identical. All had significant condition by time interactions.

The 0.5 mg/kg MDMA dose produced relatively modest subjective effects. Only three volunteers felt that amount was worth paying anything for, each valuing it at $10. However, one volunteer indicated that he preferred the 0.5 mg/kg to the 1.5 mg/kg dose because the subjective effects of the lower dose felt less "artificial" to him.

As illustrated in Table 1, 1.5 mg/kg MDMA produced more subjective effects than 0.5 mg/kg MDMA. Most

Table 1 Summary of subjective changes

Measure (range)	Time of measured maximum (h)	Maximum change from baseline[a] (mean±SD)		
		Placebo	0.5 mg/kg	1.5 mg/kg
VAS				
High (0–100)	2	3±8	15±17	52±24***
Any drug effect (0–100)	1.5	4±7	17±17	51±27***
Good drug effect (0–100)	2	3±7	20±28	55±28***
Bad drug effect (0–100)	4	0±0	2±3	5±10**
Drug liking (0–100)	2	2±5	23±29	55±22**
Insightful (0–100)	2.5	–2±12	5±15	26±19*
Confident (0–100)	2	–4±10	4±8	19±19*
Closeness to others (0–100)	1.5	0±13	11±20	18±14
Friendly (0–100)	3	–8±20	2±17	17±26
SDEQ a priori and empirical Scales				
LSD (0–176)	2	1±1	10±11	24±11**
Ambivalence (0–268)	2	0±0	4±5	17±14*
Cognitive impairment (0–28)	2	0±0	1± 2	6±4**
Mood euphoria (0–64)	2	0±1	10±12*	21±14**
Autonomic arousal (0–24)	2	0±0	2±4	4±2*
Relaxation (0–48)	2	0±0	6±6*	13±6***
Tension (0–44)	2	1±2	3±2*	5±3**
Cognitive improvement (0–48)	2	0±1	3±3	9±6**

[a] Based on group mean peak values
Statistics based on time course analysis of changes from baseline:
* P<0.05, significantly different from placebo **$P<0.001$, significantly different from placebo
*** $P<0.0001$, significantly different from placebo

volunteers reported that 1.5 mg/kg MDMA was a "medium" to "somewhat strong" dose, although one felt the amount was "somewhat weak." Two volunteers reported that they would have used more. All felt the amount was worth paying for and estimated value for the dose was $19±4 (range $15–25), comparable to reported prices for illicit MDMA ($20–30) (Community Epidemiology Work Group 1998). Monetary value of the 0.5 mg/kg dose was judged to be $5±5. No one would have paid for the placebo dose ($0±0). By this measure, the 1.5 mg/kg dose was estimated by volunteers as comparable to that they typically used, but the other two doses were not.

Table 1 also contains several SDEQ scales of effects typically associated with LSD and amphetamine. Effects of 1.5 mg/kg MDMA were significantly greater than placebo for all SDEQ scales for condition by time interactions, while 0.5 mg/kg MDMA significantly increased only SDEQ Tension, Mood Euphoria, and Relaxation scales. Effects from the SDEQ LSD scale frequently reported as present at 2 h after 1.5 mg/kg MDMA were: throat drier (seven of eight volunteers); thinking seems clearer (seven); body feels better than usual (six); altered feeling in arms or legs (stronger, weaker, tighter, looser, numb, heavier, lighter, or tingling) (six); sillier, feels like laughing, or sees the comical side of things more (six); and more excited (five). Five felt they had less control of their body, thoughts, or feelings.

Subjective reports of Friendly and Closeness to Others did not display significant condition by time interactions, but showed a trend toward increased effects after 1.5 mg/kg MDMA. Five volunteers reported "a greater feeling of love for others" and they "liked having people around more" on the SDEQ after the 1.5 mg/kg dose (Table 2). One subject volunteered: "People seem more interesting.... It makes me want to observe them and know more about them. What do all these people have on their mind; what are they thinking; what are their problems?"

The incidence of commonly described effects of MDMA from the SDEQ which at least half our volunteers reported is summarized in Table 2. In addition to these effects, which were quantified using relevant SDEQ items, five volunteers spontaneously reported jaw clenching, one reported lower back pain, and one reported restlessness ("desire to dance") after 1.5 mg/kg MDMA.

Mean PANSS scores changed little after MDMA, even in the high dose condition. Mean ratings in the high dose condition typically rose 1 point or remained the same for the Total PANSS Score, the General Psychopathology Scale, the Positive Scale and the Negative Scale. However, several volunteers reported during the PANSS interview the appearance of beliefs not present pre-MDMA. One volunteer described developing a belief in special abilities in his field of work well beyond his description at baseline. Another described having the belief that he had "mentally transported" himself to Alaska and was seeing actual images there, although he questioned this belief. Another volunteer mentioned telepathic abilities, which were also questioned by him. These effects were rated as minimal to mild on the Delusions item on the PANSS, since they were tenuously held. The beliefs diminished over the next few hours and were gone by the following day. Two volunteers reported visual illusions (objects in room "breathing," grass stains on shoes "glowing," or things looking "dreamy" or

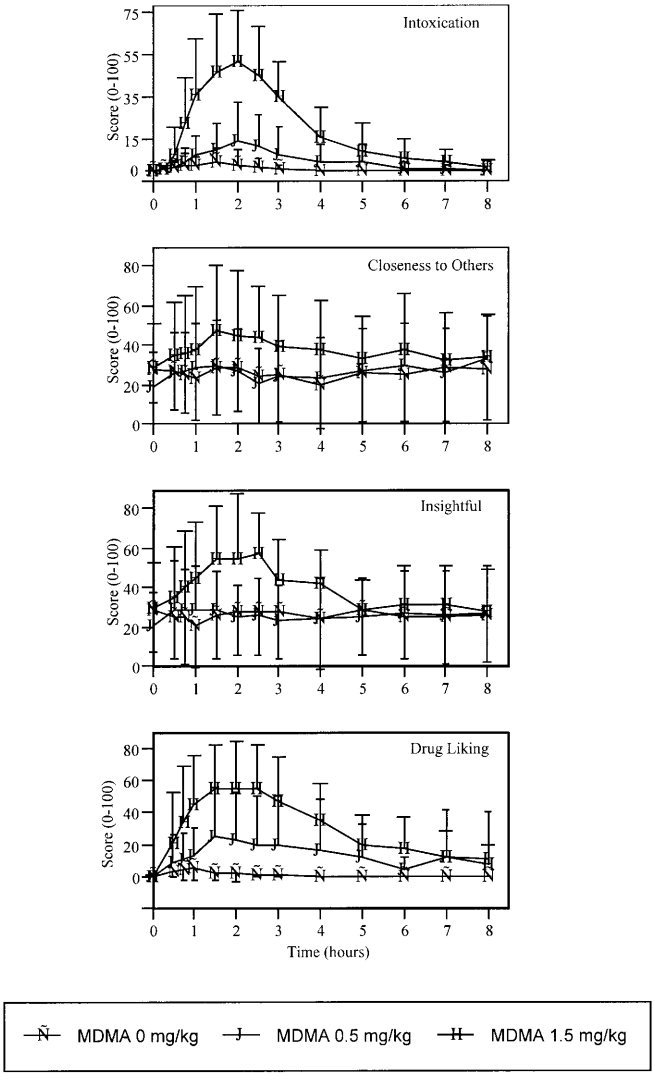

Fig. 1 Time course for subjective measures

magnified). One other mentioned the above reported scenes of Alaska with his eyes closed. These effects occurred during the higher dose condition about the time of peak effects (2.5 h after dosing). No residual symptoms were observed or reported at the follow up visits up to 2 weeks after the last dose.

Hormonal response

Time courses of cortisol, DHEA, and prolactin changes are in Fig. 2. Levels of these hormones were significantly different after 1.5 mg/kg MDMA than after placebo at 2–2.5 h post-dose. Compared to placebo, time course analysis of plasma cortisol levels showed significant increases following administration of the 1.5 mg/kg MDMA (P=0.0001) and the 0.5 mg/kg MDMA dose (P=0.01). Plasma cortisol levels following the 1.5 mg/kg MDMA dose were also significantly higher than from the 0.5 mg/kg MDMA dose (P<0.04). Plasma concentrations of cortisol returned to predose values at 5 h post-dose. The mean cortisol peak following the 1.5 mg/kg dose was 28 mcg/dl with a mean rise of 17 mcg/dl. By comparison, the upper limit of normal range is 25 mcg/dl and 50 mg of smoked cocaine produced a rise of about 10 mcg/dl (Ward et al. 1998).

Prolactin levels were measured only at baseline and 2 h after dosing. Prolactin levels following the 1.5 mg/kg dose were significantly greater than those following both the placebo dose (P=0.0001) and the 0.5 mg/kg dose (P=0.0001). Prolactin levels following the 0.5 mg/kg dose were not significantly different from placebo. The mean peak prolactin level of 46 ng/ml was above the normal physiological upper limit of 20 ng/ml.

Plasma DHEA levels showed a significant condition-time interaction for the time course analysis of the 5 h after dosing with the 1.5 mg/kg dose of MDMA significantly different from the placebo condition

Table 2 Acute effects of MDMA

Effect	Number of volunteers reporting effects (n=8)							
	0.5 mg/kg				1.5 mg/kg			
	Pre	2 h	7 h	24 h	Pre	2 h	7 h	24 h
Throat or mouth dry	0	2	0	0	0	7	4	1
Hot or cold sensations	1	4	1	0	0	6	2	1
Altered sound perception:								
Own voice	0	2	0	0	0	6	1	0
Other sounds	0	1	0	0	0	6	0	0
Colors brighter	0	2	0	0	0	5	0	0
Heartbeat felt faster	0	1	0	1	0	5	1	0
Paresthesias	1	3	0	0	0	6	1	0
Sweating	0	0	0	0	0	4	1	0
Body tense	0	3	1	0	0	4	2	0
Decreased appetite	0	2	0	0	0	4	5	2
Headache	0	0	1	0	0	0	4	0
Dizziness and vertigo	0	4	0	0	0	6	0	0
Feeling of love for others	0	2	0	1	0	5	3	1
Like having people around	0	3	2	0	0	5	1	1
Harder to concentrate	0	2	1	1	1	7	2	0
At peace with the world	1	5	0	0	0	6	2	2

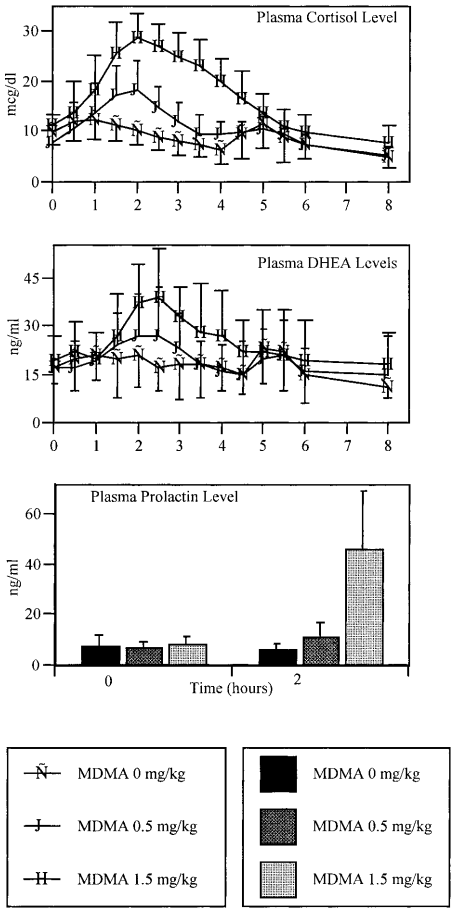

Fig. 2 Time course for cortisol, prolactin, and DHEA changes

(P<0.04) from 2 to 3 h after dosing. DHEA levels after the 0.5 mg/kg dose showed a trend toward significance (P<0.08) compared to placebo. Although the level almost doubled in the 1.5 mg/kg MDMA dose condition (mean peak concentration 39.1 ng/ml), it was still well within the generally accepted broad physiological range, which has an upper limit of about 90 ng/ml.

Mean progesterone and FSH levels from the three female volunteers rose after 1.5 mg/kg, but the changes were not statistically significant. For FSH, values from one of the three women who was at day 14 of her menstrual cycle accounted for all of the mean rise. Estradiol in the women and LH showed no significant change.

Relationships of measures

Most mean physiological, subjective effects, and hormonal effects peaked at about 2 h after dosing except for heart rate, which peaked 1 h afterwards. After the higher MDMA dose, change in plasma cortisol from baseline to mean peak time of 2 h after dosing was significantly positively correlated with change in heart rate (τ=+0.64, P<0.03) and rate pressure product (τ=+0.57, P<0.05), although it must be remembered the latter measure is derived in part from heart rate. Change in plasma cortisol level was also significantly positively correlated with Drug Liking (τ=+0.57, P<0.05). Absolute and change scores for most psychometric measures were identical due to a baseline of 0. Cortisol rise was not significantly correlated to the SDEQ LSD scale.

Plasma prolactin rise in the 1.5 mg/kg condition was directly related to rise in cortisol (τ=+0.64, P<0.03), rise in heart rate (τ=+0.71, P<0.02), and inversely to the SDEQ LSD scale (τ=–0.64, P<0.03) using the 0–4 format to take into account intensity of effect.

Rise in DHEA from baseline to mean peak time at 2.25 h after dosing in the 1.5 mg/kg condition was significantly positively correlated with the SDEQ total euphoria (τ=0.64, P<0.03) and SDEQ mood euphoria scale (τ=0.62, P<0.04) using the 0–4 SDEQ format but not with other measures.

Discussion

MDMA had significant cardiovascular, hormonal, and subjective effects. In general, our results are consistent with other reports (Grob et al. 1996; Vollenweider et al. 1998, 1999; Mas et al. 1999; Pacifici et al. 1999; Cami et al. 2000; Gamma et al. 2000; Liechti and Vollenweider 2000; Liechti et al. 2000a, 2000b, 2001a, 2001b; Tancer and Johanson 2001).

Three volunteers reported what we considered mild delusions after the 1.5 mg/kg MDMA dose. However, there were no statistically significant changes in any PANSS scale. Gouzoulis-Mayfrank and colleagues (1999) reported significant increases in the PANSS scales for positive, negative, and general psychopathology after 2.0 mg/kg of the MDMA analogue 3,4-methylenedioxyethylamphetamine (MDE). The difference in PANSS scale results could be due to different pharmacological effects of the different compounds or to the higher dose used in the MDE study.

Cardiovascular pressor effects, increases in verbal reports of feeling confident, happy, and talkative, and the increased SDEQ ratings of Euphoria, Relaxation, Tension, Cognitive Improvement, and Autonomic Arousal scales are consistent with a psychostimulant-like effect (Katz et al. 1968; Mendelson et al. 1995; O'Brien 1996).

Volunteers reported some hallucinogen-like effects on the SDEQ LSD and Ambivalence scales and on the PANSS, but the more clear-cut and dramatic effects typically produced by LSD-like hallucinogens (at least after the higher 100–200 mcg doses commonly used in the past few decades) were not evident after the commonly used 1.5 mg/kg dose of MDMA. Although higher doses of MDMA may produce more frequent and intense hallucinogen-like effects, these effects appeared modest at a dose which had otherwise robust subjective effects in our laboratory setting. In contrast, Tancer and Johanson (2001), using a different hallucinogen symptom rating scale, found more hallucinogen effects, although their

middle dose, which was closest to our high dose, appeared to show fewer hallucinogen symptoms than did their higher or lower doses.

Feelings of closeness to others or empathy have been reported as effects which distinguish MDMA and other putative entactogens from hallucinogens or psychostimulants (Nichols 1986; Peroutka et al. 1988). We attempted to measure these effects by self-reports of feeling Closeness to Others and Friendly. Although a trend was found for increased self-ratings of Closeness to Others, these items did not achieve statistical significance, possibly due to the laboratory setting or the small sample size. Volunteers did report some entactogen-like effects commonly associated with MDMA use, "a greater feeling of love for others" and liking "having others around more" on individual SDEQ items. Answers to several other SDEQ items were consistent with entactogen drug effects, although not specific to them. Increase in feeling "Insightful" was consistent with reasons sometimes given by users for use of MDMA and as a reason for other hallucinogen use as well. Other possible drug classifications have been suggested. Martin and Sloan (1977) proposed a category called "probably LSD-like but with other properties," in which they include methylenedioxyamphetamine (MDA), a related phenethylamine. Ungerleider and Pechnick (1992) wrote that MDMA is sometimes called a "stimulant hallucinogen." Our findings are consistent with either of these terms or with the category entactogen but did not clearly support the notion that MDMA represents a new drug class. Comparisons of various hallucinogens and other stimulant drugs in the same research volunteers might better help to determine where MDMA best fits.

Prolactin, cortisol, and DHEA levels increased after MDMA administration. DHEA changes following MDMA have not been previously reported. MDMA-induced increases in plasma cortisol and prolactin levels are consistent with that reported by Grob et al. (1996) (ACTH and prolactin) and Mas et al. (1999) (cortisol and prolactin).

MDMA leads to dopamine and serotonin release in animals (White et al. 1996). A rise in cortisol (Lefebvre et al. 1992) or prolactin (Prescott et al. 1984) may reflect serotonergic activity. Liechti et al. (2000a, 2000b) and Liechti and Vollenweider (2000) used neurotransmitter uptake inhibition and receptor blockade to study the role of neurotransmitters on MDMA response in humans. Based on an absence of effect of dopamine blockade on cardiovascular changes, they suggested that response may be more mediated by serotonin or norepinephrine. Our findings of a correlation between increased cortisol level and cardiac rate-pressure product are consistent with a serotonin effect, since cortisol level may more reflect serotonin activity. Liechti and colleagues' work suggests serotonin mediates some hallucinogenic effects of MDMA but that dopamine also plays a role in other subjective effects. Since LSD is a serotonergic drug, the LSD symptoms scale scores might be expected to reflect the rise in cortisol or prolactin levels (as a reflection of serotonin activity). However, in our study this was not evident. Some of the SDEQ LSD scale items commonly reported in our study resemble the effects Liechti et al. (2000b) described as reduced by the serotonin $2_{A/C}$ antagonist ketanserin, but some effects may of course have been mediated by other pathways. The only partial overlap of effects may explain the lack of relationship between magnitude of cortisol rise and LSD scale scores.

Hormonal changes can sometimes offer clues to neurotransmitter activity. Studies on the rewarding effects of stimulants in animals with adrenals removed (Goeders and Guerin 1996; Piazza et al. 1996) suggest that corticosteroids may be more than a mere reflection of neurotransmitter activity. Corticosteroids themselves may modulate response to drugs with potential for abuse through their effects on neurotransmitters, such as dopamine (Piazza et al. 1996) and serotonin (reviewed in Chaouloff 1995), the latter possibly by modulation of sensory input to the lateral amygdala (through inhibitory mechanisms) (Stutzmann et al. 1998). Interestingly, MDMA decreases regional blood flow in the left amygdala (Gamma et al. 2000). Adrenalectomy abolishes the pressor response of serotonin (Dedeoglu and Fisher 1996), consistent with the correlations between cortisol level and rate-pressure product in our study. That the rise in cortisol levels was correlated with increase in Drug Liking in our study is consistent with animal experiments investigating links between corticosterone levels and stimulant self-administration (Piazza et al. 1991; Goeders and Guerin 1994, 1996). Both lines of evidence suggest that corticosteroids may enhance the rewarding effects of stimulant drugs.

DHEA levels correlated with measures of euphoria. DHEA or its sulfate, DHEA-S, modulates 5-HT_{2A} receptor expression in the amygdala (Cyr et al. 2000) and beta-endorphin secretion (Stomati et al. 1999), and increases GABAergic tone (Akwa and Baulieu 1999), and antagonizes some effects of glucocorticoids in amygdala and other areas (Singh et al. 1994). The correlation between DHEA level and euphoria is consistent with DHEA's relationship to what was termed "warmheartedness" (McCraty et al. 1998) and with the inverse relationship between DHEA level and depressive symptoms (Wolkowitz and Reus 2000). Correlations between cortisol and DHEA levels and some psychological effects are consistent with data from animals mentioned in the preceding paragraph suggesting that some hormones may modulate the rewarding effects of some drugs of abuse. Our results are similar to the close temporal relationships evident between ACTH and other hormones and euphoria after cocaine administration (Mendelson et al. 2002). Perhaps stimulant drugs that are as pharmacologically different as MDMA and cocaine may have similar common pathways of response. Further exploration of the possible roles of these hormones in the differing subjective profiles of stimulant drugs is appropriate.

Interpreting the findings from our study is limited by the relatively modest number of volunteers and the use of only two dose levels. MDMA effects less frequent, small

in magnitude, or only evident at higher doses may well have been missed. A laboratory setting unlike that of a dance party likely dampened some subjective effects, particularly those associated with empathy or closeness to others. All volunteers were experienced users of "ecstasy" and their expectations and past experiences may have influenced subjective reports. Statistical correlations between measures were not corrected for the multiple comparisons and should, therefore, be considered preliminary findings. Use of other psychostimulants and hallucinogens as comparison drugs would be useful in future studies.

In conclusion, 1.5 mg/kg MDMA produced robust cardiovascular changes but ones likely to be well tolerated by most healthy individuals. MDMA significantly increased cortisol, prolactin, and DHEA plasma levels that may be related to mechanisms of some of its effects. Although a few volunteers reported mild hallucinogen-like effects, in general subjective effects of 1.5 mg/kg MDMA were more similar to those of a psychostimulant than a hallucinogen. Although not inconsistent with reported effects of entactogens, the overall MDMA effect profile did not support a need for that new drug classification.

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