Physiological and Subjective Responses to Controlled Oral 3,4-Methylenedioxymethamphetamine Administration

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Abstract: A randomized, within-subject, double-blind, inpatient study of the physiological and subjective effects of oral 3,4-methylenedioxymethamphetamine (MDMA) was conducted in human volunteers with previous MDMA experience. Placebo, low (1.0 mg/kg), and high (1.6 mg/kg) doses of oral MDMA were administered in a controlled inpatient setting at least 7 days apart to 6 African American (4 male, 2 female) and 2 white (both male) volunteers (mean [SE] age, 21.1 [0.8] years; weight, 77.2 [7.7] kg). 3,4-Methylenedioxymethamphetamine doses were 46 to 150 mg, in the range of typical recreational doses. Participants completed all sessions without clinically significant adverse events. 3,4-Methylenedioxymethamphetamine produced significant dose-dependent increases in heart rate (highest, 132 bpm), systolic (highest, 171 mm Hg) and diastolic (highest, 102 mm Hg) blood pressure, and subjective responses for energy level, closeness to others, mind racing, heightened senses, and high (evaluated by visual analog scales). Peak effects occurred 1 to 2 hours after dose, with no secondary peak. There were no significant effects on body temperature (measured at tympanic membrane), respiratory rate, or blood oxygen saturation (by pulse oximetry). Although most physiological and subjective parameters were significantly correlated with MDMA plasma concentrations, correlation coefficients were low and clinically insignificant, eliminating the ability to predict effects from single plasma concentrations. These findings suggest that oral MDMA in typical recreational doses produces short-term effects on cardiovascular function and subjective state but that temperature effects may result from interaction with environmental and subject factors.

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3,4-Methylenedioxymethamphetamine (MDMA, ecstasy), a ring-substituted phenethylamine structurally similar to methamphetamine and mescaline, has gained worldwide popularity as a drug of abuse. The *S*-MDMA enantiomer is primarily responsible for stimulation and *R*-MDMA for hallucinogenic effects.[1] Therapeutic use of MDMA in conjunction with psychotherapy is based on its entactogenic ("touching within") properties to lower psychological defenses, increase insightfulness, and enhance communication.[2,3] Usual recreational doses are 30 to 150 mg/pill, although purity of the street drug is notoriously poor.[4]

Previous human laboratory studies of controlled MDMA administration have demonstrated marked increases in cardiovascular parameters, pupil dilation, dry mouth, and loss of appetite due to sympathetic nervous system stimulation.[5–8] Common subjective effects reported in multiple studies include euphoric or loving feelings, greater self-confidence, self-acceptance, and enhanced empathy and understanding.[3,6,8–12] Commonly reported acute adverse effects include jaw clenching, grinding of the teeth, nausea, tremor, and feelings of tension. Previous studies generally included predominantly male white subjects and monitored subjective and physiological effects for less than 24 hours. Documentation of drug abstinence before MDMA administration varied from requesting subjects to abstain to housing subjects on a research unit before dosing.

After oral administration, MDMA is absorbed rapidly into the bloodstream.[13–19] Maximum plasma MDMA concentrations are achieved at approximately 2 h; the terminal elimination half-life is 7 to 9 h.[1,8,15,18,20] The major metabolic route involves conversion by CYP2D6 and to a lesser extent CYP1A2 and CYP3A4[14,21] to 3,4-dihydroxymethamphetamine, an unstable intermediate, and then by catechol-*O*-methyltransferase[16] to 4-hydroxy-3-methoxymethamphetamine. In the minor metabolic pathway, MDMA is *N*-demethylated by CYP1A2 and to a lesser extent CYP2D6 to 3,4-methylenedioxyamphetamine.

The primary objective of this controlled oral MDMA administration study was evaluation of physiological and subjective effects after typical recreational doses in a gender and racially varied subject population using rigorous design features, for example, objective confirmation of recent MDMA use, subjects not under the acute influence of MDMA or other drugs (urine testing and monitored 12-hour abstinence), and assessment in a controlled environment for up to 167 hours. We hypothesized that MDMA would produce dose-dependent changes in physiological and subjective variables with this study design similar to those reported in prior less rigorously controlled studies. A secondary objective was elucidating the relationship between MDMA plasma concentrations and physiological and subjective effects.

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METHODS

Human Participants

The protocol was approved by the Institutional Review Board of the Intramural Research Program, National Institute on Drug Abuse. Individuals were recruited by television, radio, and newspaper advertisements, flyers, and word of mouth. All participants provided written informed consent and were paid for their participation. Inclusion criteria required individuals to be 18 to 40 years, with a lifetime consumption of at least 5 tablets of ecstasy and at least 1 tablet in the 90 days before screening. History of MDMA use was confirmed by a positive urine amphetamines (cross-reacts with MDMA, methamphetamine, and amphetamine) or hair MDMA test within 90 days before study entrance. Female subjects were required to use a reliable method of birth control or abstain from sexual intercourse throughout study participation. Serum and urine pregnancy tests were administered at the screening visit and on the morning of each dosing session, respectively.

All potential subjects received a comprehensive medical and psychological evaluation, including medical and drug use history and physical examination, clinical laboratory tests, 12-lead electrocardiogram (ECG) with 3-minute rhythm strip, SCL-90R, and computer-administered version of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Individuals meeting any of the following criteria were excluded: nursing or pregnant women; current medical condition or history of neurologic illness; Axis I psychiatric diagnosis other than abuse or dependence on nicotine, cannabis, or MDMA; recent (within 30 days of MDMA administration) prescription of a CYP2D6 or CYP3A4 inhibitor or a CYP3A4 inducer (with reconsideration 30 days after the individual voluntarily stopped use); systolic blood pressure (SBP) more than 135, diastolic blood pressure (DBP) more than 85, or heart rate more than 100 bpm after 5 minutes of rest; total cholesterol more than 250 mg/dL if older than 30 years; hemoglobin less than 12.5 g/100 mL (male) or less than 12 g/100 mL (female); clinically significant abnormal ECG; and serum transaminase levels more than 3 times normal.

Eight healthy volunteers (4 African American males, 2 African American females, and 2 white males) met study eligibility criteria. Participants' mean ± SE age was 21.1 ± 0.8 years (range, 18–24 years) and weight was 77.2 ± 7.7 kg (range, 46.4–103.5 kg). Current self-reported MDMA use ranged from 3 pills/wk to 2 pills/mo for less than 1 to 5 years. Pupil measurements, participant dose identification, and duration of effect data included 1 additional participant (African American male, 18 years old, 73.3 kg). Other physiological and subjective data from this participant were collected within a functional magnetic resonance imaging scanner environment and thus could not be combined with other subjects' data.

Study Design

All participants resided on the closed research unit of the Intramural Research Program, National Institute on Drug Abuse. One participant completed all 3 drug administration sessions in 1 stay, with 7 days between sessions. Seven participants were discharged after each session and readmitted later for the other 2 sessions. The interval, mean ± SE (range), between unit discharge and readmission was 15.8 ± 3.5 days (3–46 days); all 3 sessions were completed within 42.9 ± 8.4 days (14–81 days).

Separate stay participants were reevaluated at each readmission to confirm continued study eligibility. Urine was screened for benzodiazepines, cocaine, amphetamines (cross-reacting with MDMA, methamphetamine, and amphetamine), cannabis, opiates, PCP, and barbiturates with a Triage 7 Drugs of Abuse panel (Biosite, Inc, San Diego, Calif). Negative results were required for all drug classes except amphetamines (includes cross-reaction with MDMA) and cannabis (many MDMA users also use cannabis) for the dosing session to proceed. Participants entered the inpatient unit at least 12 hours before controlled dosing to ensure dissipation of effects from any previously self-administered drug. Participants ate a light breakfast approximately 2 hours before MDMA dosing. Females were administered a urine pregnancy test. After obtaining baseline measures, biological specimens and a 12-lead ECG, participants ingested 1 of 3 doses: 0 (placebo), 1.0 mg/kg (low), or 1.6 mg/kg (high) MDMA (Lipomed, Arlesheim, Switzerland) while seated in a quiet room maintained at approximately 21°C. Active drug was prepared as the hydrochloride salt; placebo contained only lactose. For safety purposes, there was a maximum absolute dose limit of 150 mg MDMA. One male participant whose weight exceeded 93.75 kg received this maximum dose. Participants remained on the unit for 3 to 7 days after dosing.

Physiological Monitoring

After a double-blind MDMA or placebo administration, participants remained seated during monitoring by medical staff for 3 hours or until SBP, DBP, and heart rate returned to within 20% of predose levels (or heart rate to <95 bpm), whichever occurred later. Physiological measurements and biological specimen collection continued throughout the stay on the unit. Heart rate, SBP, DBP, blood oxygen saturation, and respiratory rate were recorded at −0.25, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 13, 23, 29, 47, 71, 95, 119, 143, and 167 h using a Datascope-Passport Model El (Datascope Corporation, Paramus, NJ). Tympanic temperature was measured at these same times using a ThermoScan Instant Thermometer HM2 (Braun, Lynnfield, Mass). Pupil diameter was measured before drug administration and 1.25 and 6 hours after dose using a Coolpix 3200 digital camera (Nikon Corporation, Tokyo, Japan). Participants held a ruler under their eye during the photograph to provide a scale for later caliper measurement of pupil diameter.

Subjective Evaluations

Participants completed visual analog scales (VAS) for subjective response for 29 hours after dosing. Six subjective effects were evaluated: high, energy level, feelings of closeness to others, mind racing, heightened senses, and ability

to concentrate. Participants were seated at a computer monitor while VAS were individually presented on the screen as 265-mm lines with the following anchors at each end: "not at all" to "most ever" (high, mind racing, heightened senses) or "least ever" to "most ever" (feelings of closeness to others, energy level, ability to concentrate). Subjects used a joystick to move the cursor on the screen to indicate which point on the scale best described how they felt in the past 5 minutes. Responses were scored as distance (in millimeters) from the left end of the line.

Participants were asked by a research nurse on the day after dosing if they believed they received a placebo, low, or high MDMA dose and also indicated on a questionnaire the duration (in hours) of their MDMA experience.

Analysis of MDMA in Plasma

3,4-Methylenedioxymethamphetamine was quantified in human plasma according to a previously published method.[22] Briefly, MDMA-*d5* as internal standard was added to 1 mL participant plasma, calibrator, or quality-control sample. Acidic hydrolysis was performed to release conjugated metabolites for assay as part of a detailed pharmacokinetic study (data presented elsewhere).[20] 3,4-Methylenedioxymethamphetamine concentrations were unaffected by acidic hydrolysis.[22] Derivatization was accomplished with 10 μL of heptafluorobutyric acid anhydride and heating at 60°C for 20 minutes. Two-dimensional gas chromatography/electron impact mass spectrometry operated in selected ion monitoring mode was used to quantify MDMA from 2.5 to 400 ng/mL. Method accuracy was greater than 80%. The greatest coefficient of variation (CV) for an intraassay batch was 8.4%, whereas CV for interassay imprecision was 6.7% or less. Plasma concentration data are presented as mean ± SE.

Statistical Analysis

The primary statistical analysis evaluated the joint effects of MDMA dose and time after MDMA administration on a battery of physiological and subjective parameters. Raw data were used for analysis. For each MDMA response, repeated-measures regression (SAS Proc Mixed; SAS Institute Inc, Cary, NC) was used to assess the main effects of dose and time and dose-by-time interaction. If the main effect of dose was significant, post hoc paired comparisons were achieved to determine which doses differed from each other. Tukey test was used to constrain the overall type I error rate to less than 0.05. If the main effect of time was significant, a Dunnett test was performed separately by dose to determine if effects at specific times differed from baseline and to constrain the overall type I error rate to less than 0.05. The time frame evaluated was limited to times for which an effect was apparent in time course graphs: 0 to 4 hours after administration for physiological measures (Fig. 1) and 0 to 5 hours after administration for all subjective measures except heightened senses and high (0–9 h; Fig. 2).

A secondary analysis examined the effects of MDMA dose on measures that summarized the time course for each dose within subject: the effect's maximum increase from baseline (decrease for blood oxygen saturation and ability to concentrate), the time corresponding to the maximum effect (T_{max}), and the area under the time-effect curve (AUC). Change scores were used to control for inter- and intrasubject variability between sessions. If the maximum response occurred at multiple time points, the first such time point was considered T_{max}. The same parameters and time frame were used as for the primary analysis. Repeated-measures linear regression (SAS Proc Mixed; SAS Institute Inc) was used to assess the effect of dose. If this was significant, post hoc paired comparisons were done to determine which doses differed from each other; Tukey test was used to constrain the overall type I error rate to less than 0.05.

Pearson correlation coefficient, coefficient of determination, and the equation for the line (using least squares linear regression) assessed the degree of association between MDMA plasma concentrations (achieved by both active doses) and each physiological or subjective effect over the entire time course. Correlation with pupil diameter was evaluated at 1.25 hours after dose.

All analyses used SAS version 9.1 (SAS Institute Inc) with a 2-tailed $P < 0.05$ indicating statistical significance. Descriptive statistics are mean ± SE unless otherwise noted.

RESULTS

Physiological Response

3,4-Methylenedioxymethamphetamine had a significant dose-dependent stimulatory effect on heart rate and blood

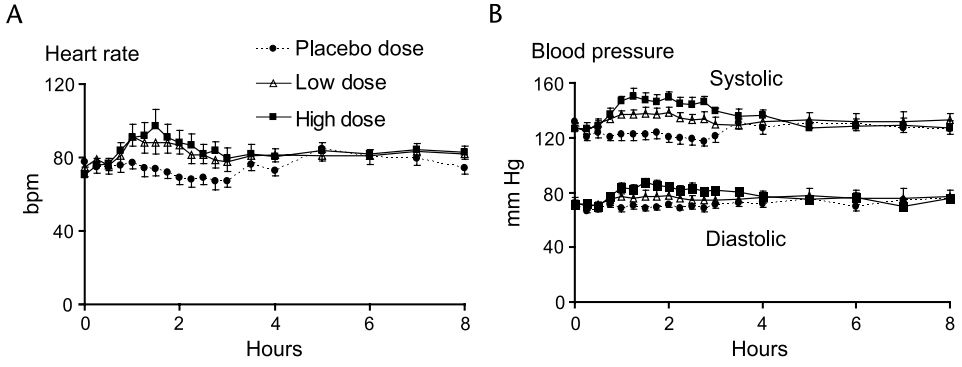

FIGURE 1. Heart rate (A) and SBP and DBP (B) responses after double-blind, randomized controlled oral administration of placebo, low (1.0 mg/kg), and high (1.6 mg/kg) doses of MDMA (N = 8). Data presented as mean ± SE.

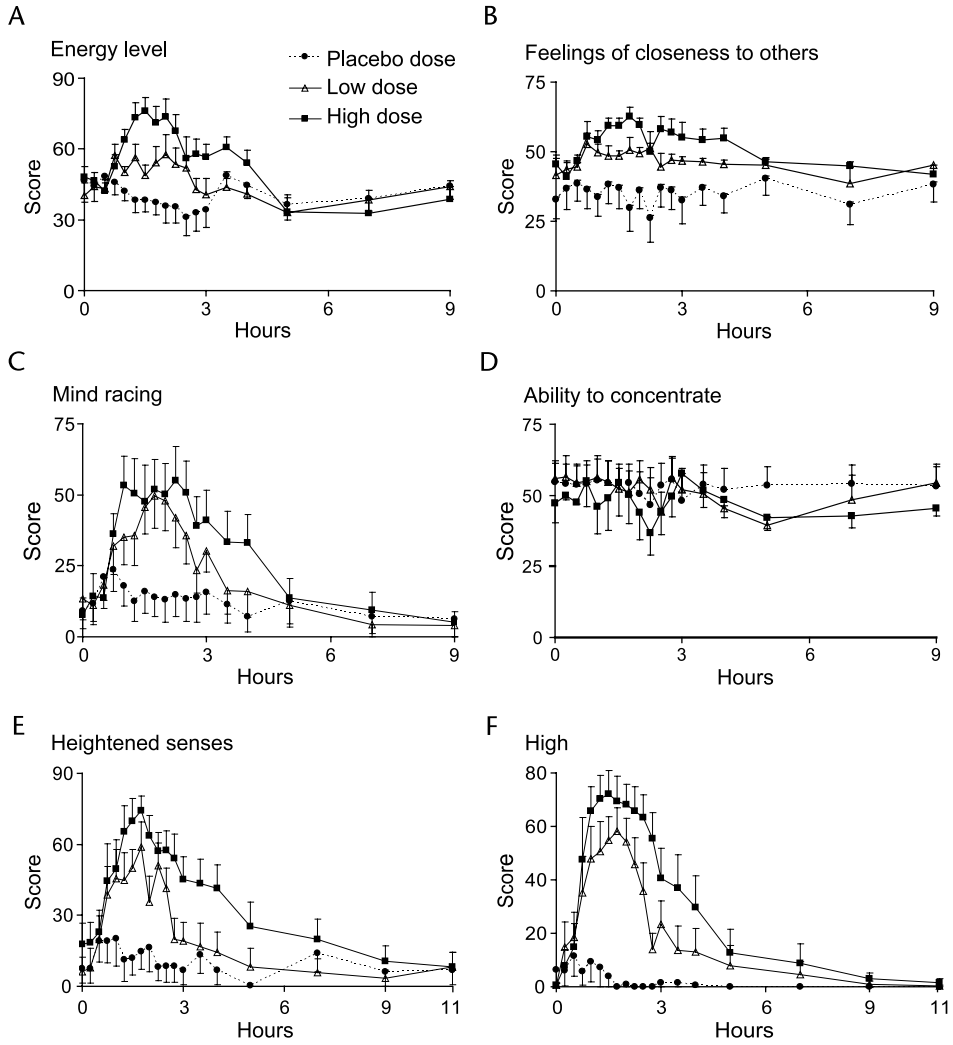

FIGURE 2. Subjective responses after a double-blind, randomized controlled oral administration of placebo, low (1.0 mg/kg), and high (1.6 mg/kg) doses of MDMA (N = 8). Data presented as mean ± SE. Subjective responses measured by 265-mm VAS.

pressure. Peak effects occurred 1 to 2 hours after administration, with no secondary or delayed peaks (Fig. 1, Tables 1 and 2). The response to high-dose MDMA often lasted significantly longer than after the low dose (Fig. 1). 3,4-Methylenedioxymethamphetamine had no significant overall effect on tympanic temperature (maximum increase of 1.9°C in a single participant after the high dose), respiratory rate, or blood oxygen saturation (Tables 1 and 2). Participants completed all dosing sessions with no clinically significant adverse events.

Only high-dose MDMA produced a maximum heart rate increase from baseline significantly greater than placebo (P = 0.0009; Table 2). There was no significant dose effect on $AUC_{0–4h}$ or T_{max} (Table 2). The fastest individual heart rate was 132 bpm, occurring after a high MDMA dose. Increases from baseline ranged from 11 to 58 and from 15 to 59 bpm after the 1.0- and 1.6-mg/kg doses, respectively.

Both MDMA doses produced maximum increases in SBP significantly different from placebo and each other (Table 2): low > placebo (P = 0.0016), high > placebo (P = 0.0001), and high > low (P = 0.0066). Maximum increases from baseline ranged from 13 to 27 mm Hg after the low dose and from 13 to 43 mm Hg after the high dose. The highest recorded SBP was 171 mm Hg. Mean $AUC_{0–4h}$ showed a similar dose response to maximum increase: low > placebo (P = 0.0002), high > placebo (P < 0.0001), and high > low (P = 0.0021). There was no significant dose effect on T_{max}, which ranged from 1 to 4 h.

High-dose MDMA produced significantly greater maximum increases from baseline in DBP compared with placebo (P = 0.0014) and low dose (P = 0.0127; Table 2). Peak increases from baseline of 0 to 28 and from 17 to 31 mm Hg were recorded after the low and high doses, respectively. The highest observed DBP of 102 mm Hg occurred in 2 subjects after the 1.6 mg/kg dose. There was a significant dose effect on $AUC_{0–4h}$: low > placebo (P = 0.023), high > placebo (P < 0.0001), and high > low doses (P = 0.0053). T_{max} occurred 1 to 2 hours after dose.

TABLE 1. Physiological and Subjective Effects of MDMA by Dose (Placebo, Low [1.0 mg/kg], High [1.6 mg/kg]) and Time After Double Blind, Randomized Controlled Oral Administration to 8 Healthy Adults

Parameter	Main Effects	Post Hoc Dose Effects*
Physiological		
Heart rate	Dose ($F_{2,14}$ = 3.90, P = 0.045) Time ($F_{14,98}$ = 3.08, P = 0.0006)	NS
SBP	Dose ($F_{2,14}$ = 11.92, P = 0.0009) Time ($F_{14,98}$ = 2.38, P = 0.0067) Dose × Time ($F_{28,196}$ = 2.10, P = 0.0019)	Placebo and low (P = 0.022); placebo and high (P = 0.0007)
DBP	Dose ($F_{2,14}$ = 35.57, P < 0.0001) Time ($F_{14,98}$ = 2.65, P = 0.0026)	Placebo and low (P = 0.0018); placebo and high (P < 0.0001); low and high (P = 0.0023)
Tympanic temperature	NS	—
Respiration rate	NS	—
Blood oxygen saturation†	NS	—
Pupil diameter	Dose ($F_{2,16}$ = 8.30, P = 0.0034) Time ($F_{2,16}$ = 29.01, P < 0.0001) Dose × Time ($F_{4,32}$ = 9.94, P < 0.0001)	Placebo and low (P = 0.0327); placebo and high (P = 0.0028)
Subjective‡		
Energy level	Dose ($F_{2,14}$ = 10.07, P = 0.002) Time ($F_{15,105}$ = 2.92, P = 0.0007)	Placebo and high (P = 0.0015); low and high (P = 0.0383)
Feelings of closeness to others	Dose ($F_{2,14}$ = 18.0, P = 0.0001)	Placebo and low (P = 0.0044); placebo and high (P = 0.0001)
Mind racing	Dose ($F_{2,14}$ = 4.17, P = 0.038) Time ($F_{15,105}$ = 2.37, P = 0.0055)	Placebo and high (P = 0.0327)
Ability to concentrate	NS	—
Heightened senses	Dose ($F_{2,14}$ = 15.48, P = 0.0003) Time ($F_{17,119}$ = 3.67, P < 0.0001)	Placebo and low (P = 0.0343); placebo and high (P = 0.0002); low and high (P = 0.0294)
High	Dose ($F_{2,14}$ = 20.63, P < 0.0001) Time ($F_{17,119}$ = 5.87, P < 0.0001) Dose × Time ($F_{34,231}$ = 2.64, P < 0.0001)	Placebo and low (P = 0.002); placebo and high (P < 0.0001)

Analysis performed on raw data.
*Tukey post hoc analysis.
†Measured by peripheral pulse oximetry.
‡Measured with VAS.
NS indicates not significant.

3,4-Methylenedioxymethamphetamine significantly increased pupil diameter 1.25 hours after dose (Tables 1 and 2), with diameters increased by up to 4 mm.

High-dose MDMA significantly increased the maximum change from baseline in respiratory rate (P = 0.0223) and shortened the T_{max} (P = 0.0495) but had no effect on $AUC_{0–4h}$ (Table 2). T_{max} ranged from 0.25 to 2.25. All peak respiratory rates were between 17 and 28 breaths/min.

3,4-Methylenedioxymethamphetamine had no significant effect on maximum decrease from baseline in blood oxygen saturation, T_{max}, or $AUC_{0–4h}$ (Table 1). All measurements were between 95% and 100%.

Subjective Effects

3,4-Methylenedioxymethamphetamine produced significant dose-dependent subjective responses (Fig. 2, Table 1) in all variables except ability to concentrate (Fig. 2, Tables 1 and 2). Significant increases from baseline in subjective responses always were observed after the high dose (Table 1). After the low dose, only increases in mind racing, heightened senses, and high significantly differed from baseline. All significant increases from baseline occurred between 0.75 and 3 hours after dosing (Fig. 2).

Subjective responses showing the strongest effects, that is, high and heightened senses, also had the most robust increases from baseline and $AUC_{0–9h}$ (Table 2). For high, maximum increase from baseline comparisons were low dose > placebo (P = 0.008), high dose > placebo (P = 0.0002), and high dose > low dose (P = 0.03); $AUC_{0–9h}$ comparisons were low dose > placebo (P = 0.05), high dose > placebo (P = 0.006), and high dose > low dose (P = 0.05). For heightened senses, maximum increase from baseline comparison was high dose > placebo (P = 0.002); $AUC_{0–9h}$ comparisons were high dose > placebo (P = 0.03) and high dose > low

TABLE 2. Physiological and Subjective Effects in 8 Healthy Adults After Double Blind, Randomized Controlled Oral Administration of 0, 1.0, and 1.6 mg/kg Doses of MDMA

Physiological*	0 mg/kg	1.0 mg/kg	1.6 mg/kg	Subjective†,‡	0 mg/kg	1.0 mg/kg	1.6 mg/kg
Heart rate				Energy level			
Maximum positive change, bpm	7 ± 2	24 ± 6	35 ± 5	Maximum positive change, score	13 ± 5	32 ± 10	35 ± 8
T_{max}, h	1.0 ± 0.4	1.7 ± 0.3	1.5 ± 0.3	T_{max}, h	1.3 ± 0.5	1.7 ± 0.3	1.3 ± 0.3
$AUC_{0–4h}$	290 ± 13	329 ± 16	337 ± 19	$AUC_{0–5h}$	203 ± 21	230 ± 11	286 ± 16
SBP				Feelings of closeness to others			
Maximum positive change, mm Hg	5 ± 2	19 ± 2	32 ± 3	Maximum positive change, score	17 ± 6	19 ± 5	26 ± 6
T_{max}, h	2.4 ± 0.5	2.1 ± 0.3	1.6 ± 0.2	T_{max}, h	2.2 ± 0.5	1.7 ± 0.2	1.9 ± 0.4
$AUC_{0–4h}$	492 ± 14	531 ± 13	562 ± 14	$AUC_{0–5h}$	177 ± 30	235 ± 6	268 ± 11
DBP				Mind racing			
Maximum positive change, mm Hg	5 ± 1	11 ± 3	24 ± 2	Maximum positive change, score	27 ± 8	44 ± 14	57 ± 12
T_{max}, h	2.4 ± 0.4	1.5 ± 0.3	2.0 ± 0.2	T_{max}, h	1.3 ± 0.6	1.1 ± 0.3	1.2 ± 0.3
$AUC_{0–4h}$	280 ± 7	300 ± 4	320 ± 4	$AUC_{0–5h}$	68 ± 28	133 ± 36	181 ± 44
Tympanic Temperature				Ability to concentrate			
Maximum positive change, °C	0.4 ± 0.1	0.7 ± 0.1	0.8 ± 0.2	Maximum negative change, score	−18 ± 7	−21 ± 7	−28 ± 6
T_{max}, h	2.4 ± 0.6	2.4 ± 0.4	1.5 ± 0.4	T_{max}, h	2.4 ± 0.4	2.8 ± 0.6	1.8 ± 0.5
$AUC_{0–4h}$	146 ± 1	146 ± 0	147 ± 1	$AUC_{0–5h}$	263 ± 34	252 ± 26	242 ± 21
Respiration rate				Heightened senses			
Maximum positive change, breaths/min	2 ± 1	5 ± 1	5 ± 1	Maximum positive change, score	24 ± 10	61 ± 13	66 ± 10
T_{max}, h	1.5 ± 0.6	1.6 ± 0.3	0.9 ± 0.2	T_{max}, h	0.5 ± 0.2	1.6 ± 0.3	1.6 ± 0.3
$AUC_{0–4h}$	70 ± 3	75 ± 4	74 ± 3	$AUC_{0–9h}$	87 ± 48	159 ± 53	305 ± 60
Blood oxygen saturation§				High			
Maximum negative change, %	−1 ± 0	−2 ± 1	−2 ± 0	Maximum positive change, score	15 ± 8	64 ± 11	84 ± 5
T_{max}, h	0.5 ± 0.2	1.4 ± 0.4	1.5 ± 0.5	T_{max}, h	0.7 ± 0.4	1.4 ± 0.3	1.7 ± 0.3
$AUC_{0–4h}$	394 ± 2	393 ± 2	394 ± 1	$AUC_{0–9h}$	13 ± 7	156 ± 48	247 ± 55
Pupil diameter							
Change at 1.25 h, mm	−0.2 ± 0.2	1.6 ± 0.3	2.3 ± 0.4				

Data analyzed as change from baseline and presented as mean ± SE.

*All evaluations up to 4 hours after dose.

†All evaluations up to 5 hours after dose, except heightened senses and high (9 h).

‡Measured with VAS.

§Measured by peripheral pulse oximetry.

dose ($P = 0.04$). Four of 9 participants correctly guessed their dosing. Three participants identified both the 1.0- and the 1.6-mg/kg MDMA doses as low doses. One participant identified both placebo and low dose as placebo and considered the high dose to be low. The ninth participant identified placebo as a low dose and both low and high doses as high doses. Subjects reported MDMA effects as lasting 0 to 1 hour after placebo, 0 to 4 hours after the low, and 1.5 to 7 hours after the high dose. Duration of low-dose experience was always less than or equal to the duration of high-dose experience, regardless of how participants identified a dose.

Correlation With Plasma MDMA Concentrations

Mean MDMA plasma concentrations (n = 8) after administration of 1.0 and 1.6 mg/kg MDMA are shown in Figure 3. The time course is displayed for 47 hours after dosing, the period when most participants' plasma remained MDMA positive. Mean peak MDMA plasma concentrations of 161.4 ± 11.5 and 305.7 ± 16.9 ng/mL were achieved after the low and high doses, respectively. Mean plasma MDMA concentrations (n = 8) at 47 hours were 0.6 ± 0.6 ng/mL after the low dose and 6.8 ± 1.7 ng/mL after the high dose; although only 1 participant's plasma remained MDMA positive 47 hours after the low dose, 7 participants' plasma specimens were positive at this time after the high dose. Statistically significant correlations were observed between plasma concentrations of MDMA and physiological parameters of heart rate, SBP, DBP, and temperature and subjective responses of energy level, feelings of closeness to others, mind racing, heightened senses, and high (correlation coefficients, 0.23–0.50; all P values <0.0001). The highest correlations were observed between MDMA plasma concentration and high ($r = 0.50$), heightened senses ($r = 0.48$), and SBP ($r = 0.45$). There were no significant correlations with respiratory rate, blood oxygen concentration, pupil diameter, or ability to concentrate.

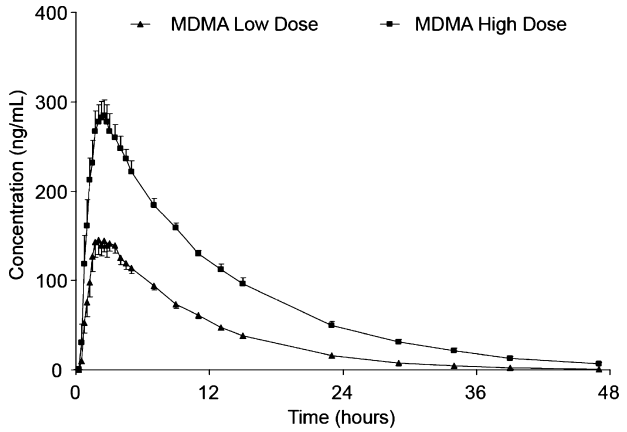

FIGURE 3. Mean MDMA plasma concentrations (N = 8) for 47 hours after a double-blind, randomized controlled oral administration of low (1.0 mg/kg) and high (1.6 mg/kg) doses of MDMA. Data presented as mean ± SE.

DISCUSSION

This double-blind, placebo-controlled study evaluated subjective effects for 29 hours and physiological effects for 167 hours after 1.0 and 1.6 mg/kg oral MDMA administration in 8 healthy men and women with prior MDMA experience. Doses were chosen to reflect typical recreational doses taken in the community; all but 1 participant identified both doses as active MDMA.

3,4-Methylenedioxymethamphetamine produced dose-dependent increases in heart rate and blood pressure, similar to those previously reported.[8,23,24] Peak effects occurred within the first 1 to 2 hours after drug administration, with no delayed or secondary peaks (Fig. 1). These effects are presumably due to MDMA's activation of the sympathetic nervous system.[25] No acute cardiotoxic effects were observed in this controlled laboratory setting, similar to previous reports.[5,6,18,26]

This finding cannot necessarily be generalized to the community setting. Participants were rigorously screened to meet stringent medical eligibility criteria. 3,4-Methylenedioxymethamphetamine could have more pronounced effects in individuals with compromised health, genetic predisposition, or other unknown vulnerability factors. This study administered pure MDMA alone. In the community, MDMA is of unknown purity and may be taken with other substances. In this study, subjects were seated calmly in a cool room and kept well hydrated throughout the period of MDMA administration. It is likely that vigorous exercise, high ambient temperatures, and dehydration, such as often occur at raves,[27] are contributory factors in any acute cardiotoxic response experienced after recreational MDMA use.

Hyperthermia has been observed in hospital admissions after recreational MDMA ingestion.[25,28–30] In the present study, MDMA had no significant effect on tympanic temperature; temperatures were always 38.2°C or less, and individual increases never exceeded 1.9°C. In prior studies, comparable doses produced significant increases in mean oral or core body temperature of 0.6°C or less in the first 4 hours after dosing.[8,26,31] One study noted that temperatures never exceeded 38°C.[11] Different sites of measurement or different ambient temperatures could partially explain differences between studies. A higher ambient temperature of 30°C was associated with greater temperature response to controlled MDMA administration.[31] Research participants do not experience the increased motor activity experienced by many recreational users. In addition, inadequate hydration is not an issue in a laboratory setting. These findings point to the effects of high environmental temperature, decreased fluid intake, increased physical activity, and/or coingestion of other illicit and licit substances, often experienced by recreational users at dance clubs and raves, as possible factors in MDMA-associated hyperthermia. Another possibility is that MDMA does not directly cause hyperthermia but reregulates the hypothalamus, responsible for intrinsic temperature control,[32] to prevent heat dissipation and to maintain temperature when challenged by external factors.

Mydriasis was observed in the current study, with pupil diameter increases of up to 4 mm. Dilated pupils can negatively affect driving ability in daylight[33] by increasing glare sensitivity and by decreasing contrast sensitivity and at night when, despite improved light sensitivity, headlight glare can be distracting. When these deficits are combined with MDMA's subjective effects, including mind racing and high, it is likely that driving skills could be further impaired. Pupil size is routinely evaluated by drug recognition experts, including police officers specially trained in recognizing signs and symptoms of drugs in drivers. Our data support increased pupil size as a marker for ingestion of MDMA.[34]

The ability to concentrate was the only subjective variable not affected by MDMA in this study. The literature presents mixed results on the effects of MDMA on concentration that may be due to differences in dosing environment, prior illicit drug use, or method of assessment. Our finding of no effect using VAS is consistent with other VAS results noted after 75 and 125 mg MDMA.[10] However, studies using the Subjective Drug Effects Questionnaire,[7] the List of Complaints,[6] and the Vegetative Lability Scale[26] reported impaired concentration after MDMA doses of 1.5 to 1.7 mg/kg. Two studies that observed significant responses included subjects with limited or no experience with recreational drugs,[6,26] whereas the current and previous studies administering VAS included experienced illicit drug users.[10] It is possible that, compared with past self-administered illicit drug experiences, the laboratory setting produced less of an effect on concentration.

The stimulatory effect of MDMA (increased energy level and mind racing) is consistent with previous studies administering 1.1 to 2.1 mg/kg MDMA.[10,11,23,24,35–37] Although the current study was the first to explicitly measure mind racing, this parameter was previously reported by a single subject as an undesirable side effect of use.[3] Subjective high also is consistent with other investigations after 0.9 to 2.1 mg/kg MDMA[7,10,23,24,35–37]; a lower dose (0.5 mg/kg) did not produce a significant high.[7]

The increased feeling of closeness to others observed in this study is consistent with the putative entactogenic effect of MDMA. In contrast, a previous investigation found no

significant change in this variable (also assessed with VAS) after 0.5 and 1.5 mg/kg, although there was a trend toward significance after the higher dose.[7] Participants' comfort in the dosing environment and familiarity with research staff could contribute to this difference.

The predominantly positive subjective effects of MDMA observed in this study are consistent with its appeal to recreational users. Prolonged effects of high, heightened senses, and feelings of closeness to others presumably contribute to MDMA's abuse potential. Motivation for treatment may be hindered by the relatively few immediately undesirable sequelae.[26]

3,4-Methylenedioxymethamphetamine's psychoactive effects had a longer duration than its physiological effects. This is consistent with the longer elimination half-life of *R*-MDMA,[17] thought to be responsible for its subjective effects, as compared with *S*-MDMA, which reportedly is more amphetamine-like[38] and therefore likely the cause of the physiological effects.

Dose also influenced duration of effects. Some physiological (Fig. 1) and subjective (Fig. 2) parameters returned to predose levels earlier after the low dose than after the high dose (Table 1). Further support for the influence of dose comes from participants' responses regarding the duration of their MDMA experience. More than 75% of participants reported that effects lasted longer after the high dose, even in situations where they reported both the 1.0- and the 1.6-mg/kg doses as high doses.

Although MDMA plasma concentrations were significantly correlated with heart rate, SBP, DBP, temperature, energy level, feelings of closeness to others, mind racing, heightened senses, and high, correlation coefficients were low and clinically insignificant, eliminating the ability to predict effects from single plasma concentrations.

This study has several strengths compared with previously published human experimental studies of MDMA administration. First, our protocol included African American and female participants, groups not well represented in prior studies. Although the sample sizes were not large enough to allow subgroup analyses, their inclusion does improve the external validity (generalizability) of the study. Second, all participants were abstinent from MDMA and other psychoactive substances for at least 12 hours before dosing, ensuring that there were no residual drug effects during study sessions. Many prior studies either did not report abstinence status of subjects or relied on self-report. Third, all subjects were required to have a positive biological test documenting MDMA use before inclusion. Fourth, data collection continued for 29 hours (subjective effects) and 167 hours (physiological effects) after dosing, allowing evaluation for possible delayed or secondary effects. Finally, dosing sessions occurred with subjects in a calm, quiet environment with controlled ambient temperature and limits on motor activity, permitting determination of MDMA's influence alone on sympathomimetic and hyperthermic effects. Although previous studies have included some of these design features, this study incorporated all of these features to provide maximum scientific rigor.

In conclusion, this placebo-controlled, double-blind human laboratory study found that oral MDMA, when administered in typical recreational doses (1.0 and 1.6 mg/kg) to experienced MDMA users free of acute MDMA or other drug effects (due to ≥12 hours abstinence), produced dose-dependent increases in heart rate and SBP and DBP and subjective responses of high, heightened senses, and mind racing. All effects resolved within 4 to 6 hours, with no delayed or secondary peaks. There were no significant effects on tympanic temperature, respiratory rate, or blood oxygenation. These findings suggest that oral MDMA produces short-term effects on cardiovascular function and psychological state but that its temperature effects may depend on environmental and subject factors such as ambient temperature and levels of hydration and motor activity. This rigorous characterization of the physiological and subjective responses to MDMA provides data on possible mechanisms involved in its toxicity and reasons for abuse and may contribute to drug abuse prevention and treatment efforts.

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