Hyperthermia Induced by 3,4-Methylenedioxymethamphetamine in Unrestrained Rhesus Monkeys

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Abstract

Background—Exposure to (±)3,4-methylenedioxymethamphetamine ((±)MDMA) results in lasting reductions of many markers for serotonin terminals in a range of species. In rodents, the severity of insult depends in large part on the generation of hyperthermia in the subject. (±)MDMA can produce either hyperthermia or hypothermia in rodents depending on the ambient temperature and these effects may be limited to the S(+) enantiomer. Limited prior evidence suggests (±)MDMA does not produce hyperthermia in chair-restrained monkeys [Bowyer et al., 2003, Neurotoxicology 24(3):379–390]. This study was therefore conducted to determine if racemic MDMA and its enantiomers induce hyperthermia and increase spontaneous locomotor activity in unrestrained rhesus monkeys.

Methods—Body temperature and spontaneous home cage activity were monitored continuously in four monkeys via radiotelemetric devices. The subjects were challenged with 1.7 mg/kg, i.m., (±) MDMA, S(+)MDMA and R(−)MDMA in pseudorandomized order.

Results—Maximum and average temperature in the four hour interval post-dosing was elevated 0.7–0.9°C by (±)MDMA and each enantiomer. Reductions in locomotor activity following dosing did not reliably differ from vehicle effects.

Conclusions—MDMA produces an acute hyperthermia in unrestrained rhesus monkeys, much as it does with rats, mice, pigs, rabbits and humans. Hyperthermia occurs despite no increase in locomotor activity thus the effect does not depend on motor activation. Each enantiomer appears to be equivalently active thus primates may differ from rodents in thermoregulatory sensitivity to the R(−) enantiomer. Significant differences in outcome between this and a prior study in monkeys indicate a need for additional study of the thermoregulatory impact of MDMA in nonhuman primates.

Keywords

MDMA; Macaca mulatta; circadian; thermoregulation; serotonin

1. Introduction

The Drug Abuse Warning Network estimates some 4,000 annual emergency department (ED) visits in which Ecstasy/MDMA is involved (Ball et al. 2003; Ball et al. 2004). ED surveys often report significant and malignant elevations in body temperature (Dams et al. 2003; Gillman 1997; Greene et al. 2003; Mallick and Bodenham 1997) but likely underrepresent the true prevalence of thermoregulatory distress. Many incidents may not appear serious enough to invoke emergency medical services, particularly given that MDMA use is illegal in most jurisdictions. It is challenging to identify the critical contributing factors to the relatively rare

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Ecstasy fatality from ED reports. In fatal cases, tissue levels of MDMA are usually quite high, but not exclusively so since case reports associate fatalities with a wide range of plasma levels of MDMA, i.e., 40–7000 ng/ml (Brown and Osterloh 1987; Dowling et al. 1987; Garcia-Repetto et al. 2003; Greene et al. 2003; Karlovsek 2004; Karlovsek et al. 2005). A survey of 102 medical examiner death reports (Patel et al. 2004) reported a mean peripheral blood level of 1120 ng/ml (SD= 1230) of MDMA. Furthermore, although the majority of street "Ecstasy" pills contain some MDMA (Parrott 2004), they are often contaminated with other psychoactive compounds with thermomodulatory properties (Baggott et al. 2000; Cheng et al. 2003; Palhol et al. 2002), making it difficult to determine the specific contribution of MDMA to thermoregulation. Thus, animal models are required to determine the circumstances under which MDMA can disrupt thermoregulation to further understanding of how such disruption may result in ED visits (and potential fatality) for the recreational user.

MDMA intake results in an acute elevation of body temperature in human laboratory studies following doses (1.5–2.0 mg/kg, p.o.) described as within the range of common recreational doses (Freedman et al. 2005; Liechti et al. 2000). MDMA also produces an acute hyperthermia in rats (Brown and Kiyatkin 2004; Dafters 1994; Malberg and Seiden 1998), mice (Carvalho et al. 2002; Fantegrossi et al. 2003), guinea pigs (Saadat et al. 2004), pigs (Fiege et al. 2003; Rosa-Neto et al. 2004) and rabbits (Pedersen and Blessing 2001). Body temperature data have not generally been included in monkey studies of lasting serotonergic alterations (Insel et al. 1989; Ricaurte et al. 1988; Taffe et al. 2002a; Taffe et al. 2001). It is surprising that MDMA apparently reduced body temperature in chair-restrained rhesus monkeys (Bowyer et al. 2003) and therefore the present study was undertaken to test the hypothesis that MDMA elevates temperature in unrestrained rhesus monkeys. A second goal was to determine if MDMA stimulates locomotor activity in monkeys as it does in rodents (Dafters 1994; Fantegrossi et al. 2003; Gold and Koob 1988). Increases in locomotor activity would complicate the comparison with the human laboratory studies in which volunteers were not engaging in significant levels of activity (Freedman et al. 2005; Liechti et al. 2000).

The enantiomers of MDMA may differ in effect with the *S* or (+) enantiomer reported to be more potent in terms of human subjective response (Shulgin and Shulgin 2000) and in producing stereotyped behaviors in rats (Hiramatsu et al. 1989). The S(+)-MDMA enantiomer produces hyperthermia with equivalent efficacy as the racemate in mice, while R(−)MDMA appears ineffective in elevating temperature (Fantegrossi et al. 2003). Thus the final goal was to test the hypothesis that racemic and S(+)-MDMA would stimulate hyperthermia in monkeys whereas R(−)-MDMA would not.

2. Methods

2.1 Animals

Four male rhesus monkeys (Macaca mulatta; Chinese origin) were employed in this study. Animals were 6–7 years of age, weighed 8.5–12.5 kg at the start of the study and exhibited body condition scores (Clingerman and Summers 2005) of 2.5 (N=2) or 3.5 (N=2) out of 5 at the nearest quarterly exam. Daily chow (Lab Diet 5038, PMI Nutrition International; 3.22 kcal of metabolizable energy (ME) per gram) allocations were determined by a power function (Taffe 2004a; 2004b) fit to data provided in a National Research Council recommendation (NRC/NAS 2003) and modified individually by the veterinary weight management plan. Daily chow ranged from 140 to 224 g per day for the animals in this study. Animals were individually housed in a controlled temperature environment (23.5°C) and fed in the home cage. The animals' normal diet was supplemented with fruit or vegetables seven days per week and water was available *ad libitum* in the home cage at all times. The United States National Institutes of Health guidelines for laboratory animal care (Clark et al. 1996) were followed and all

protocols were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute.

2.2 Apparatus

Radio telemetric transmitters (TA10TA-D70; Transoma/Data Sciences International; "DSI") were implanted subcutaneously in the flank by, or under supervision of, the TSRI veterinary staff using sterile techniques. Animals were allowed to recover for 6 weeks prior to initiating the drug studies. Temperature and gross locomotor activity recordings were recorded every 10 minutes. The raw data were collected as a single temperature value every 10 minutes and a per-minute average of activity over each 10 minute interval. An activity "count" requires a movement across approximately half of the cage in any direction in this system. Ambient room temperature (T_A) was also recorded every 10 minutes by the system.

2.3 Drug challenge studies

($\pm$)3,4-methylenedioxymethamphetamine HCl, S(+)3,4-methylenedioxymethamphetamine HCl and R($-$)3,4-methylenedioxymethamphetamine HCl were administered intramuscularly with a constant dose of 1.7 mg/kg and an injection volume of 0.1 ml/kg. Drugs were provided by the National Institute on Drug Abuse. Challenges were administered at 1030 with active doses separated by 1–2 weeks in a pseudorandomized order. Vehicle challenges were performed the day prior to active challenge. Ambient temperature averaged 23.5°C with a daily range of 23–24°C throughout the study. The room temperature range in the four hour interval post-dosing was 23.25–23.75°C.

Animals were monitored directly by the investigators for a minimum of two hours post-challenge via remote video feed. Animals were housed normally with 4 monkeys directly across from them and 6 additional animals within sight to their left. No personnel entered the room for 2 hrs post-injection on vehicle and active days in variation from the usual M-F routine in which staff move monkeys in and out of the room for behavioral testing purposes (e.g., (Taffe et al. 2002b; 2004; Weed et al. 1999) throughout the day.

2.4 Data Analysis

Temperature and activity data were averaged over 30 minute bins (i.e., average of 3 sequential samples). Two way randomized block analysis of variance (ANOVA) was employed to evaluate acute treatment related effects starting 30 min prior to injection and continuing a total of 480 min post-injection. This interval was selected because the lights were turned off for the evening at the conclusion of this interval. The circadian temperature pattern is sensitive to this, as can be observed in Figure 1. Thus the two within subjects factors for ANOVA were time relative to injection (-30 to 450) and drug treatment condition (Vehicle, MDMA) for ($\pm$) MDMA, S(+)MDMA and R($-$)MDMA. In addition, the average and maximum (of all 10-min samples) temperature observed in the interval 4 hrs post-injection following all three compounds (and related vehicle challenges) was analyzed in a two way randomized block ANOVA. Average and maximum activity were derived from the summed activity in each 10-minute interval. For all ANOVAs, significant main effects were followed up with Fisher's LSD posthoc test. All statistical analyses were conducted using GB-STAT v7.0 for Windows (Dynamic Microsystems, Inc., Silver Spring MD) and the criterion for significance in all tests was $p < 0.05$.

3. Results

The temperature and activity measures exhibited a diurnal circadian pattern in which activity and temperature increased when the lights were turned on and decreased noticeably once lights were turned off (Figure 1). Mean temperature varied about 2°C across the day, consistent with

a similar daily temperature pattern for intraperitoneal temperature in Japanese macaques or subcutaneous temperature in cynomolgous and rhesus macaques (Almirall et al. 2001;Horn et al. 1998;Takasu et al. 2002). Temperature dropped significantly across the 4 hour analysis period, as confirmed by main effects of time post-injection for each of the (±)MDMA [$F_{16,48}$ = 14.93; p < 0.0001], S(+)MDMA [$F_{16,48}$ = 10.16; p < 0.0001] and R(−)MDMA [$F_{16,48}$ = 10.76; p < 0.0001] studies.

The administration of (±)MDMA, S(+)MDMA or R(−)MDMA resulted in a significant elevation of temperature as is shown in Figure 1. Statistically reliable main effects of drug treatment condition were confirmed for the (±)MDMA [$F_{1,3}$ = 19.88; p < 0.05] and R(−) MDMA [$F_{1,3}$ = 8.4; p < 0.05] studies but not the S(+)MDMA [$F_{1,3}$ = 4.75; p = 0.11] study. Reliable time × drug condition interactions were also confirmed in the (±)MDMA [$F_{16,48}$ = 4.03; p < 0.0001], S(+)MDMA [$F_{16,48}$ = 10.91; p < 0.0001] and R(−)MDMA [$F_{16,48}$ = 2.43; p < 0.01] studies.

The posthoc analyses confirmed that temperature was significantly increased relative to the 30-min interval prior to injection 30–180 min after (±)MDMA, 0–210 min after S(+)MDMA and 30–150 min after R(−)MDMA. No differences were confirmed for these intervals following the respective vehicle conditions. Consistent with the main effect of time post-injection for all studies, multiple timepoints from ~300–450 min post-injection were significantly lower than pretreatment in all (drug or vehicle) conditions consistent with a circadian cooling that is typically observed at that time of day.

Locomotor activity was significantly reduced in the interval post-injection for the (±)MDMA [$F_{16,48}$ = 4.77; p < 0.0001], S(+)MDMA [$F_{16,48}$ = 2.63; p < 0.01] and R(−)MDMA [$F_{16,48}$ = 2.94; p < 0.01] studies however no significant differences attributable to drug treatment condition, nor the interaction of factors were confirmed in any of the analyses.

The average temperature increase observed after (±)MDMA did not differ significantly from that observed after either enantiomer in the four hours following injection (Table 1). The ANOVA confirmed a significant effect of drug challenge over vehicle (main effect of treatment condition [$F_{1,3}$ = 23.59; p < 0.05] and the posthoc test confirmed that average temperature was higher than the respective vehicle challenge day for each test compound. No differences were observed between active treatment conditions, nor between the three vehicle conditions. The maximum temperature following drug challenge was also significantly elevated relative to vehicle [$F_{1,3}$ = 10.29; p < 0.05] and post hoc evaluation of this effect confirmed a significant increase for racemic MDMA and each enantiomer over the respective vehicle conditions. In addition, the maximum temperature observed after (±)MDMA was significantly higher than that observed after S(+)MDMA. Although both average and maximum 10-minute activity counts (Table 1) were lower relative to vehicle in the four hour interval post-MDMA, these effects were not statistically reliable, nor were any differences observed between the enantiomers and racemic MDMA.

4. Discussion

This study demonstrates that rhesus monkeys develop elevated body temperature following an intramuscular injection of a moderate dose (1.7 mg/kg) of MDMA under normal (23.5°C) ambient temperature conditions. The finding is consistent with prior reports of MDMA-associated temperature increases in most species, including humans. Effects of (±)MDMA lasted about 4 hours after injection and resulted in a peak subcutaneous temperature 0.9°C higher than the maximum temperature observed after vehicle injection. The average temperatures in the 4-hour interval after injection also differed by about 0.9°C from the vehicle

condition. These results suggest that a prior finding of decreased colonic temperature in chaired monkeys (Bowyer et al. 2003) was possibly a consequence of the experimental preparation.

Differences between the Bowyer et al. (2003) results and the present data are unlikely to be due to ambient temperature (T_A). The Bowyer et al. studies were conducted under T_A of 20.8–21.7°C (J. Bowyer, M. Paule, personal communication) which is close to the present 23.5°C and in both cases T_A was below the wide thermoneutral range (24.7–30.6°C) estimated for rhesus monkeys (Johnson and Elizondo 1979). Thus the position of the T_A relative to thermoneutral conditions cannot explain the discrepancy. In any case, primates likely differ considerably from rodents in thermoregulatory tolerance to MDMA since a recent study of humans exposed to 2 mg/kg (±)MDMA orally showed that core temperature is *increased* under both 18°C and 30°C T_A conditions (Freedman et al. 2005). This is unlike rodents that become *hypo*thermic following MDMA under sufficiently low T_A conditions (Malberg and Seiden 1998).

Circadian factors are unlikely to explain the differences with the Bowyer et al. (2003) results either. Although body temperature declines in the late afternoon (e.g., Figure 1) the injections from which the temperature data derives in the Bowyer study were conducted 0800–0900 (J. Bowyer, M. Paule, personal communication) thus normal circadian effects would be to increase or maintain stable temperatures. One possible explanation is that the temperatures of the Bowyer animals were artificially elevated during the single pre-MDMA baseline observation due to the stress of the chairing procedure; however there are plausible alternative hypotheses. The present study used subcutaneous placement of the temperature probes that would theoretically make the measure more sensitive to hemodynamic effects of MDMA. However MDMA produces vasoconstriction (Mills et al. 2004; Ootsuka et al. 2004) that would be predicted to result in less pronounced elevation or even a reduction in a subcutaneous temperature measurement relative to "core" body temperature. Indeed, rat skin temperature can be unchanged following MDMA despite increases in core temperature (Mechan et al. 2002) at least under 20°C T_A. Evidence from the Freedman et al. (2005) study is equivocal since apparent trends for MDMA-associated increases in skin temperature under both 18°C and 30°C T_A were not found to be statistically reliable (Freedman et al. 2005). Interpretation of these findings is also facilitated by a body of work from Elizondo and colleagues suggesting skin and core temperatures are highly correlated in rhesus monkeys under a variety of manipulations (Elizondo et al. 1976; Johnson and Elizondo 1979; Oddershede and Elizondo 1980; Smiles et al. 1976). In total such considerations predict that subcutaneous temperature *changes* induced by MDMA should be equivalent to, or underpredict, core temperature changes and do not explain the discrepancy of the present data from Bowyer et al. 2003.

Exposure to racemic MDMA or either enantiomer was not associated with increases in spontaneous locomotion. This is unlike rodent studies in which MDMA appears to stimulate locomotor activity across a range of doses. The telemetry activity "counts" constitute a full-body movement across approximately half of the cage in any direction and may thus be insensitive to smaller movements. However, on direct observation the monkeys appeared clearly drug intoxicated but otherwise quietly resting and almost normally responsive to other animals in the room without evidence of repetitive stereotyped movement. Therefore with respect to potential confounds from motor activity, the present temperature data would appear to be most similar to temperature results from human studies (Freedman et al. 2005; Liechti et al. 2000). While locomotor activity increases (such as dancing at nightclubs or "rave" parties) may interact with MDMA to increase body temperature in some recreational consumption settings, reliable hyperthermia can occur independently of increased muscular activity, likely because of increases in metabolism (Freedman et al. 2005). Thus individuals who prefer to consume MDMA in a quiet environment are likely still at some risk for thermodysregulatory events.

The fact that (±)MDMA and S(+)MDMA were equipotent in producing hyperthermia is consistent with a report that S(+)MDMA and (±)MDMA have equipotent effects on temperature in mice (Fantegrossi et al. 2003). Interestingly, Fantegrossi and colleagues (2003) report no impact of R(−)MDMA on temperature in mice, even following doses close to the LD_{50}. In a similar enantiomeric dissociation 10 or 20 mg/kg R(−)MDMA has no lasting impact on brain tissue serotonin (5HT) content, where similar doses of S(+)MDMA result in dose-dependent decreases of 5HT in brain of up to 50% (Schmidt 1987). The R(−) enantiomer is, however, active in rodents in other assays. Either S(+)MDMA or R(−)MDMA produces conditioned place preference (CPP) similar to twice the dose of (±)MDMA (Meyer et al. 2002). In addition, S(+)MDMA and R(−)MDMA have equipotent effects on head twitch in mice (Fantegrossi et al. 2005) where, surprisingly, (±)MDMA is inactive. Finally, Schmidt (1987) reports that the acute depletion of 5HT from brain is equivalent following S(+)MDMA and R(−)MDMA. Clearly a simple formulation of "active" versus "inactive" enantiomer is incorrect for MDMA since the effects of its enantiomers appear to depend on outcome assay (temperature, behavior, neurotoxicity, etc). The present results suggest that the impact of MDMA enantiomers on a given assay such as body temperature may depend on species differences as well. Therefore this study cautions that primate responses to MDMA may differ from that of rodents or other species on additional outcome measures, potentially in ways that are critical for translating information to the human condition.

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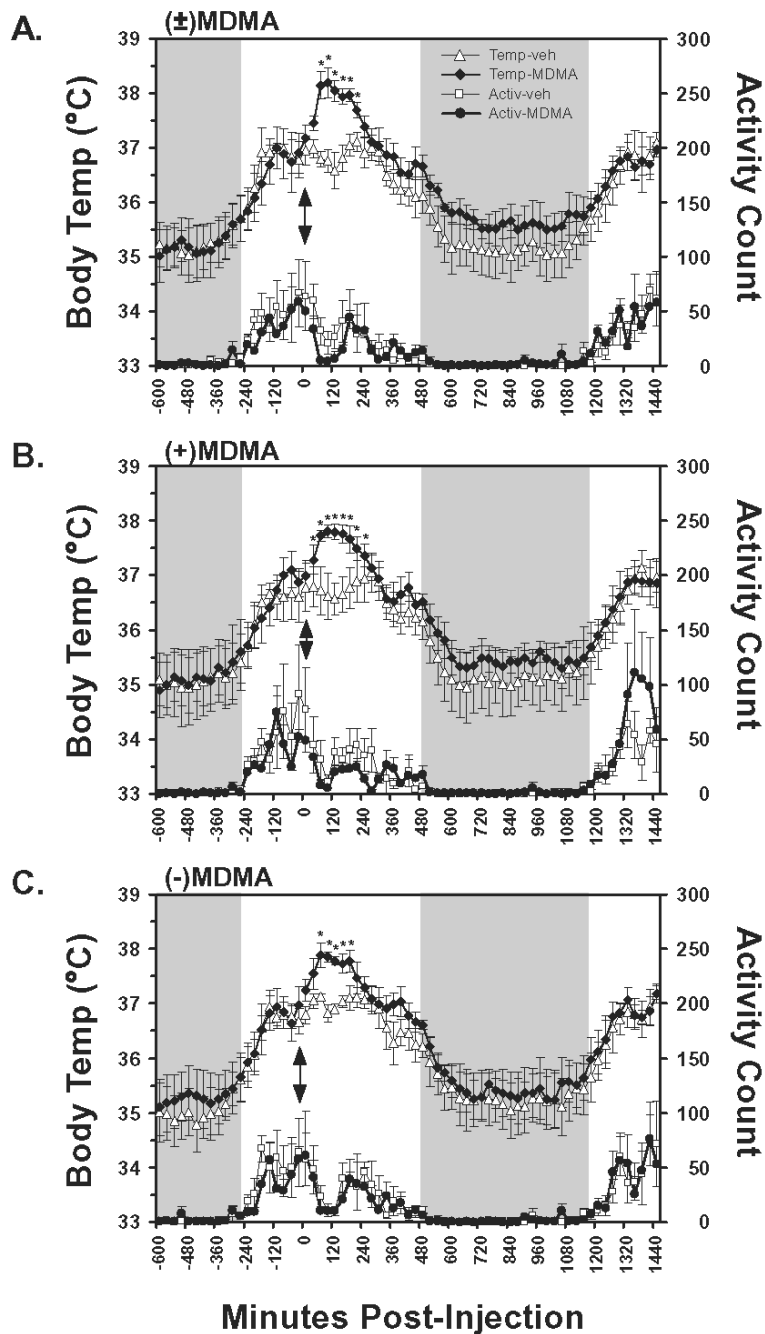
Figure 1.
The mean (N=4, bars indicate SEM) subcutaneous temperature and activity values following A) racemic MDMA, B) S(+)MDMA and C) R(−)MDMA, as well as the respective vehicle challenges, are presented. Temperature values are an average of three sequential 10-min interval samples and activity data represent the average of summed activity counts across three sequential 10-min intervals. Injections were made at 1030 for all conditions, thus the data represent the interval from midnight prior to injection to 1030 the following day. Shaded regions indicate the night period during which the room lights are off and arrows indicate the time of injection. A significant increase from both the 30-min timepoint preceding injection

and the corresponding vehicle timepoint is indicated by *. Additional differences of significance are detailed in the Results.

Table 1

Average and Maximum Temperature in Four Hours Post-Injection

	Temperature			Activity		
	(±)-MDMA	(+)-MDMA	(−)-MDMA	(±)-MDMA	(+)-MDMA	(−)-MDMA
Average (vehicle)	36.9 (± 0.21)	36.8 (± 0.38)	37.0 (± 0.13)	115 (± 29.6)	119 (± 39.0)	104 (± 21.2)
Average (MDMA)	*37.8 (± 0.07)	*37.6 (± 0.15)	*37.7 (± 0.12)	73 (± 28.1)	62 (± 9.8)	83 (± 20.5)
Maximum (vehicle)	37.2 (± 0.17)	37.1 (± 0.42)	37.4 (± 0.10)	393 (± 69.7)	410 (± 55.9)	402 (± 72.3)
Maximum (MDMA)	*38.3 (± 0.28)	*§37.9 (± 0.10)	*38.1 (± 0.13)	307 (± 96.4)	278 (± 44.3)	354 (± 75.9)

A significant difference from the respective vehicle condition is indicated by * and a significant difference from the (±)MDMA active drug condition is indicated by §.