Available online at www.sciencedirect.com
ScienceDirect
Pharmacology, Biochemistry and Behavior 87 (2007) 11 – 19
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Oral administration of (±)3,4-methylenedioxymethamphetamine and (+)methamphetamine alters temperature and activity in rhesus macaques

Rebecca D. Crean, Sophia A. Davis, Michael A. Taffe *

Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, La Jolla, CA, USA

Received 7 February 2007; received in revised form 16 March 2007; accepted 23 March 2007
Available online 3 April 2007

Abstract

Rationale: Emergency Department visits and fatalities in which (±)3,4-methylenedioxymethamphetamine (MDMA) or (+)methamphetamine (METH) are involved frequently feature unregulated hyperthermia. MDMA and METH significantly elevate body temperature in multiple laboratory species and, most importantly, can also produce unregulated and threatening hyperthermia in nonhuman primates. A majority of prior animal studies have administered drugs by injection whereas human consumption of "Ecstasy" is typically oral, an important difference in route of administration which may complicate the translation of animal data to the human condition.
Objective: To determine if MDMA and METH produce hyperthermia in monkeys following oral administration as they do when administered intramuscularly.
Methods: Adult male rhesus monkeys were challenged intramuscularly (i.m.) and *per os* (p.o.) with 1.78 or 5 mg/kg (±)MDMA and with 0.1 or 0.32 mg/kg (+)METH. Temperature and activity were monitored with a radiotelemetry system.
Results: Oral administration of either MDMA or METH produced significant increases in body temperature. Locomotor activity was suppressed by MDMA and increased by METH following either route of administration.
Conclusions: The data show that the oral route of administration is not likely to qualitatively reduce the temperature increase associated with MDMA or METH although oral administration did slow the rate of temperature increase. It is further established that MDMA reduces activity in monkeys even after relatively high doses and oral administration.

Keywords: Ecstasy; Neurotoxicity; *Macaca mulatta*; Circadian; Thermoregulation; Serotonin; Amphetamine

1. Introduction

Many of the adverse clinical symptoms reported in Emergency Department (ED) visits in which 3,4-methylenedioxymethamphetamine (MDMA) or methamphetamine are involved (Ball et al., 2003, 2004) such as rhabdomyolysis, disseminated intravenous coagulation and acute renal failure (Henry et al., 1992; White, 2002) may result from hyperthermia (Buffum and Shulgin, 2001; Dams et al., 2003; Gillman, 1997; Green et al., 2003; Mallick and Bodenham, 1997; Prosser et al., 2006; Zhu et al., 2005). It is now well established that MDMA (considered the authentic compound in street "Ecstasy" tablets) can elevate temperature in humans (Freedman et al., 2005) and many other species (Brown and Kiyatkin, 2004; Carvalho et al., 2002; Dafters, 1994; Fantegrossi et al., 2003; Fiege et al., 2003; Pedersen and Blessing, 2001; Rosa-Neto et al., 2004; Saadat et al., 2004; Taffe et al., 2006). Methamphetamine (METH), which is often substituted for MDMA intentionally (Kelly et al., 2006; Levy et al., 2005; Wu et al., 2006) or otherwise (Baggott et al., 2000; Tanner-Smith, 2006) in the nightclub setting, likewise produces hyperthermia (Bowyer et al., 1994, 1992; Crean et al., 2006), in some cases to an unregulated and fatal degree (Madden et al., 2005; Ricaurte et al., 2003, 2002; Yuan et al., 2006). Animal models have been highly useful in identifying possible neurochemical and physiological mechanisms which may contribute

* Corresponding author. Committee on the Neurobiology of Addictive Disorders, SP30-2400, 10550 North Torrey Pines Road, The Scripps Research Institute, La Jolla, CA 92037, USA. Tel.: +1 858 784 7228; fax: +1 858 784 7405.
E-mail address: mtaffe@scripps.edu (M.A. Taffe).

0091-3057/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2007.03.015

to unregulated hyperthermia (see Green et al., 2004; Rusyniak and Sprague, 2005, for review). One question which has not been explored to a significant extent is the influence of the route of drug administration on thermoregulatory responses to MDMA. This is potentially a critical issue since Ecstasy is overwhelmingly consumed orally by human users; one recent survey confirms that only about 8% of *regular* Ecstasy users have injected Ecstasy in the past 6 months (White et al., 2006). In contrast MDMA, METH and other amphetamines have been administered by intramuscular, subcutaneous or intraperitoneal injection in most animal studies.

Studies on the risks posed by orally administered MDMA are also increasingly important because of proposed therapeutic applications. For example trials have recently been planned or initiated in the US, Switzerland and Israel to use MDMA in the treatment of Post-Traumatic Stress Disorder and for anxiety in late stage cancer (Doblin, 2006; Mithoefer, 2006a; Mojeiko, 2006; Oehen, 2006). Furthermore, some recent findings from animal models suggest that MDMA may be therapeutically useful in Parkinson's Disease (Bishop et al., 2006; Iravani et al., 2003; Sotnikova et al., 2005) thereby increasing the potential for additional human trials and eventual clinical use of MDMA. Other amphetamines are already in current clinical use, for example METH is marketed as Desoxyn® for indications such as ADHD and obesity. The METH metabolite (+)amphetamine (which produces subjective and physiological effects in humans and other species that are highly similar to METH) is marketed for ADHD therapy (Adderall®). Perhaps unsurprisingly, amphetamines formulated for oral therapeutic use are frequently diverted for recreational use (McCabe et al., 2006, 2004; Upadhyaya et al., 2005; Wilens et al., 2006; Wu et al., in press).

Recent studies have shown that rhesus monkeys develop elevated temperature after intramuscular administration of racemic MDMA or either enantiomer (Taffe et al., 2006) and that the magnitude of the effect is invariant across ambient temperatures from 18 to 30 °C (Von Huben et al., 2007). In contrast rodent temperature responses are highly sensitive to ambient temperature and enantiomer (Fantegrossi et al., 2003; Malberg and Seiden, 1998). Interestingly, MDMA appears to produce a greater magnitude of peak hyperthermia in rats in comparison with METH administered at an equal dose (Clemens et al., 2005, 2004) whereas METH produces a similar peak temperature response in monkeys at equivalent or slightly lower doses compared with MDMA (Crean et al., 2006). Such observations suggest that monkey thermoregulatory responses to amphetamines may differ somewhat from rodents and at least in the case of ambient temperature be more similar to human responses (Freedman et al., 2005). It therefore continues to be important to examine thermoregulatory responses to MDMA in nonhuman primate models.

The present study was conducted to determine if the acute thermoregulatory effects of MDMA and METH in rhesus monkeys are qualitatively different when administered orally or by intramuscular injection. Although primarily motivated to explore thermoregulatory risks associated with *recreational* consumption of these compounds, the studies also contribute to understanding risks associated with current and proposed *medical* use of METH and MDMA.

2. Materials and methods

2.1. Animals

Ten individually housed male rhesus monkeys (*Macaca mulatta*) were used in these experiments. Animals were 6–10 years of age, weighed 8.5–15 kg at the start of the study and exhibited body condition scores (Clingerman and Summers, 2005) of 2.0–3.75 out of 5 at the nearest quarterly exam. Daily chow (160–248 g; LabDiet® 5038, PMI Nutrition International, Richmond, IN, USA; 3.22 kcal of metabolizable energy (ME) per gram) allocations were determined by a power function (Taffe, 2004a,b) fit to data provided in a National Research Council recommendation (NRC/NAS, 2003) and modified individually by the veterinary weight management plan. The animals' normal diet was supplemented with fruit or vegetables 7 days per week and water was available *ad libitum* in the home cage at all times. Animals on this study had previously been immobilized with ketamine (5–20 mg/kg) no less than semi-annually for purposes of routine care and some experimental procedures. Animals also had various acute exposure to raclopride, SCH23390 (Von Huben et al., 2006), methylphenidate, Δ^9-THC, nicotine, mecamylamine (Katner et al., 2004a) and scopolamine in behavioral pharmacological studies and 4 had been exposed to an oral ethanol induction procedure (Katner et al., 2004b). Experimental drug treatments had been last administered a minimum of 1 year prior to the start of thermoregulation studies. These animals had been participating in temperature/activity studies related to this one and had received prior doses of delta9-tetrahydrocannabinol (0.1–0.3 mg/kg), MDMA (0.56–5 mg/kg), METH (0.1–1 mg/kg) and/or 3,4-methylenedioxyamphetamine (0.56–5 mg/kg) in acute studies no more frequently than once per week. The precise history of each animal was not identical but was highly similar within groups of six (Crean et al., 2006) and four monkeys (Taffe et al., 2006). 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 (La Jolla).

2.2. Apparatus

Radio telemetric transmitters (TA10TA-D70; Transoma/Data Sciences International, St. Paul, MN, USA) were implanted subcutaneously in the flank. The surgical protocol was adapted from the manufacturer's surgical manual and implantation was conducted by, or under supervision of, the TSRI veterinary staff using sterile techniques under isoflurane anesthesia. Temperature and gross locomotor activity recordings were obtained from the transmitters implanted in the monkeys *via* in-cage receivers (RMC-1; Transoma/Data Sciences International, St. Paul, MN, USA). Data were recorded on a 5 min sample interval basis by the controlling computer and represented as a moving average of three samples (−5 min, current, +5 min) for each 10 min. Ambient room temperature was also recorded by the system *via* a probe mounted near the top of the housing room.

2.3. Drug challenge studies

For these studies doses of (±)3,4-methylenedioxymethamphetamine HCl (1.78, 5 mg/kg) or (+)methamphetamine HCl (0.1, 0.32 mg/kg) were administered intramuscularly (i.m.) in a volume of 0.1 ml/kg saline and *per os* (p.o.) in a volume of 1–2 ml/kg. Oral administration was conducted by training animals to drink flavored vehicle solutions (Tang®, KoolAid®, *etc.*) from a 10 ml syringe. Drugs were provided by the National Institute on Drug Abuse (Bethesda, MD, USA). All challenges were administered in the middle of the light cycle, either at 1030 or 1300 h, with active doses separated by not less than 1 week. The ambient room temperature averaged 23–27 °C for these studies. The intramuscular 1.78 mg/kg MDMA and intramuscular METH data (and respective i.m. vehicles) were reported previously (Crean et al., 2006) and are employed here as a comparison with the p.o. data. The 5 mg/kg MDMA i.m. and p.o. challenges were conducted in the original group of six subjects used in Crean et al. (2006), however the remaining p.o. studies were subsequently conducted with 5 of this original group due to transmitter battery expiration in one of the original six animals. The ongoing studies, including the present, were conducted over an interval of about 5–14 months in a given monkey. In general, the 5 mg/kg MDMA studies were conducted within a month of the conclusion of the intramuscular studies (which were conducted over about 5 months) and the oral studies were initiated about 2 months later. For each active drug challenge the relevant vehicle data were collected within about 3 weeks of the active dose day. The rectal/telemetry comparison was conducted in a different group of 4 animals which participated in an earlier study (Taffe et al., 2006). Rectal temperatures were recorded under ketamine immobilization (10 mg/kg) with the probe inserted ~ 5 cm.

2.4. Data analysis

Randomized block (repeated measures) analysis of variance (ANOVA) was employed to evaluate acute treatment-related effects on temperature and activity. In general, two repeated measures factors were included to determine the effects of drug treatment condition and time relative to drug administration. The analyses were designed based on results from our prior studies. The temperature analysis for the lower dose MDMA challenges started 10 min prior to injection (referred to as "baseline") and continued for 2 h post-injection (sample "+120 min"). This interval was designed into the study as the interval in which normal, potentially disruptive, daily room activities were suspended, similar to our prior MDMA studies (Crean et al., 2006; Taffe et al., 2006; Von Huben et al., 2007), because original pilot work suggested this was the duration of acute MDMA effects at this dose. Analysis of the 5 mg/kg MDMA and oral METH data was extended to 300 min after dosing to permit a more direct comparison with our prior study (Crean et al., 2006) in which the acute temperature changes lasted at least 5 h after intramuscular METH administration. Analysis was limited to 5 h after dosing as this was the shortest interval between dosing and the beginning of the dark period. The figures represent the temperature data as changes from baseline within individual as the most intuitive representation of both the dosing and analytic (*i.e.*, repeated measures) designs. The statistical analysis of activity was similar to that for temperature except the time factor used 1 h bins for total activity counts. *Post-hoc* analyses of all significant effects were conducted with the Fisher's LSD procedure. 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

3.1. Temperature effects of MDMA

MDMA significantly increased body temperature following either oral (*per os*; p.o.) or intramuscular (i.m.) routes of administration and at either dose (Figs. 1 and 2). A significant increase in temperature (Fig. 1) was observed after 1.78 mg/kg MDMA as was confirmed by a significant main effect of drug treatment condition [$F_{1,5}=7.47$; $p<0.05$] and of time post-

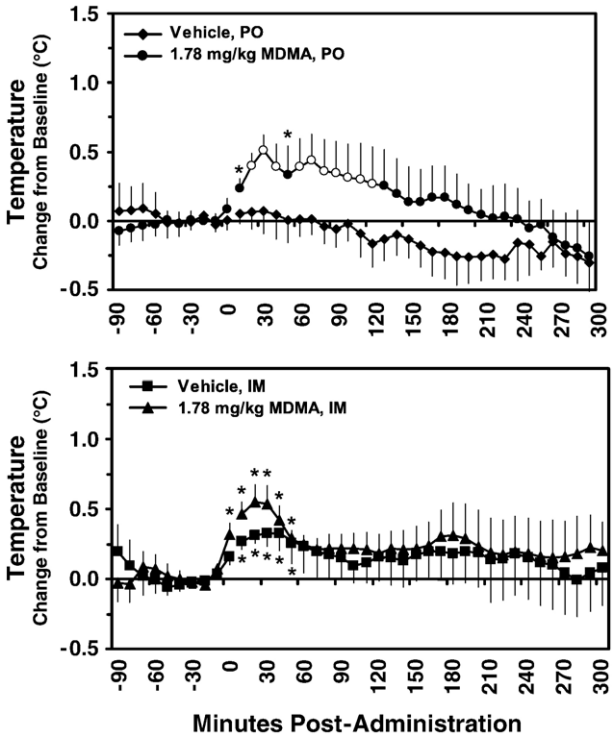

Fig. 1. Mean ($N=5$–6, bars indicate SEM) temperature for animals treated with 1.78 mg/kg MDMA *per os* (upper panels) or intramuscularly (lower panels). Temperature data are represented as changes from the average of three samples prior to administration for each animal to appropriately reflect the repeated measures analysis of the absolute temperature data. The break in each series indicates the time of injection; the slight change in temperature at time "0" in part reflects variation in administration to all 6 subjects relative to the computer sampling schedule and the moving average procedure, see Materials and methods. The intramuscular data were previously reported (Crean et al., 2006) and are reused with permission from Elsevier. The open symbols indicate a significant difference from both baseline (the sample immediately prior to drug administration) and the respective vehicle condition and the * indicates a significant difference from the baseline (only).

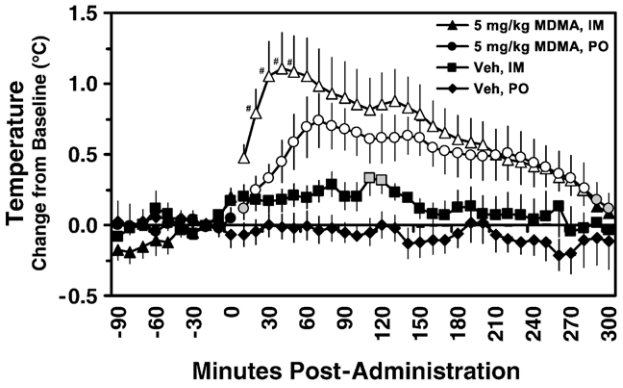

Fig. 2. Mean (N=6, bars indicate SEM) temperature for animals treated with 5.0 mg/kg MDMA *per os* or intramuscularly. Temperature data are represented as changes from the average of three samples prior to administration for each animal to appropriately reflect the repeated measures analysis of the absolute temperature data. The open symbols indicate a significant difference from both baseline (the sample immediately prior to drug administration) and the respective vehicle condition and shaded symbols indicate a significant difference from the vehicle condition at a given timepoint (only). A significant difference between MDMA administered i.m. and p.o. is indicated by #.

administration [$F_{13,65}$=13.19; p<0.0001]. The *post-hoc* test confirmed that after 1.78 mg/kg MDMA p.o., temperature was significantly elevated over baseline (10–120 min post-administration) and over the oral vehicle condition (20–40, 60–120 min). The *post-hoc* test also confirmed that temperature was significantly elevated over baseline after i.m. injection of 1.78 mg/kg MDMA (0–50 min). Temperature was also significantly elevated over baseline after i.m. vehicle injection (10–60 min) however did not differ significantly between i.m. vehicle and i.m. drug at any timepoint. *Post-hoc* analysis also confirmed a significant difference in temperature between i.m. and p.o. vehicle treatments and between i.m. and p.o. 1.78 mg/kg MDMA conditions for most timepoints; temperature was consistently higher by about 0.2 °C.

The 5 mg/kg dose of MDMA also significantly increased temperature (Fig. 2; significant main effects of drug treatment condition [$F_{3,15}$=3.68; p<0.05], time post-administration [$F_{31,155}$=6.44; p<0.0001] and an interaction of factors [$F_{93,465}$=3.38; p<0.0001]). The *post-hoc* test confirmed that temperature was significantly elevated over baseline from 10 to 270 min after i.m. injection and from 20 to 280 min after p.o. administration. Temperature was also elevated over baseline 110–120 min after vehicle, i.m. Similarly, 5 mg/kg MDMA elevated temperature relative to the respective vehicle control condition after i.m. (10–280 min) and p.o. (10–300 min) administration. Finally, temperature was significantly different between 5 mg/kg MDMA i.m. and p.o. conditions 20–50 min after administration thus indicating a slowed rate of increase associated with oral administration.

3.2. Temperature effects of METH

The administration of METH by oral or intramuscular routes of administration significantly increased temperature (Fig. 3; significant main effects of drug condition [$F_{2,10}$=42.13; p<0.0001] and time post-administration [$F_{31,155}$=10.72; p<0.0001] as well as the interactions between route of administration and time post-administration [$F_{31,155}$=5.01; p<0.0001] and between drug condition and time post-administration [$F_{62,310}$=4.47; p<0.0001]). The *post-hoc* test confirmed that temperature was significantly elevated from baseline after 0.1 mg/kg METH, p.o. (30–300 min post-administration) and after 0.32 mg/kg METH, p.o. (30–300 min), but not after oral vehicle. Temperature was also significantly elevated relative to oral vehicle after 0.1 mg/kg METH, p.o. (40–300 min post-administration) and after 0.32 mg/kg METH, p.o. (30–300 min). The *post-hoc* evaluation further confirmed that temperature was elevated over baseline by the intramuscular vehicle (10–100 min post-administration), 0.1 mg/kg METH, i.m. (10–220 min post-administration) and by 0.32 mg/kg METH, i.m. (10–290 min). Furthermore, temperature was elevated relative to the intramuscular vehicle condition after 0.1 mg/kg METH, i.m. (60–230, 270–300 min post-administration) and by 0.32 mg/kg METH, i.m. (all timepoints).

Temperature both increased and decreased more quickly after i.m. injection of either dose of METH relative to p.o. administration. The *post-hoc* test confirmed that temperature was both significantly higher (10–20 min) and lower (130, 200–290 min) after 0.1 mg/kg METH i.m., relative to the same

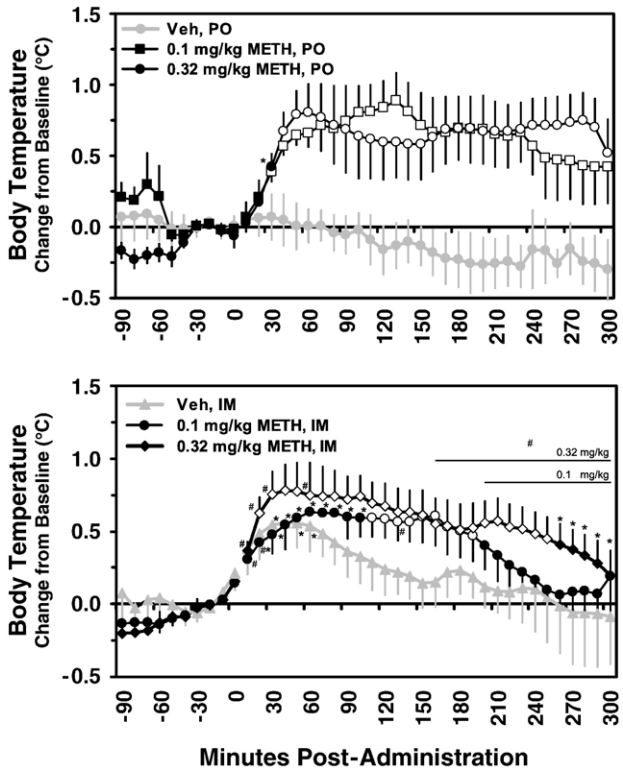

Fig. 3. Mean (N=5–6, bars indicate SEM) temperature values for animals treated with 0.1 or 0.32 mg/kg METH *per os* or intramuscularly are presented. Temperature data are represented as changes from the average of three samples prior to administration for each animal to appropriately reflect the repeated measures analysis of the absolute temperature data. The intramuscular data were previously reported (Crean et al., 2006) and are reused with permission from Elsevier. The open symbols indicate a significant difference from both baseline (the sample immediately prior to drug administration) and the respective vehicle condition. The * indicates a significant difference from the baseline (only) and a significant difference between METH administered i.m. and p.o. is indicated by #.

dose p.o. Similarly, temperature was higher (10–30 min) and lower (60, 160–300 min) after 0.32 mg/kg METH i.m. relative to the same dose p.o. No significant differences in temperature between the oral and the i.m. vehicles were confirmed.

3.3. Activity effects of MDMA and METH

Activity was significantly changed after the administration of 1.78 mg/kg MDMA (effects of the interaction of drug condition with time post-administration [$F_{5,25}=3.06$; $p<0.05$] and the interaction of all factors [$F_{5,25}=3.74$; $p<0.05$]) as is shown in Fig. 4A. *Post-hoc* evaluation confirmed that activity was lower than baseline (the hour preceding administration) and the respective vehicle timepoint in the first hour after 1.78 mg/kg MDMA i.m. In addition, activity was lower 1–2 h after 1.78 mg/kg MDMA i.m. and 1 h after i.m. vehicle in comparison with the activity after the same treatments administered p.o. Thus the low dose of MDMA initially decreased activity after i.m., but not after oral, administration. Activity was also lower than the baseline 5 h (p.o.) and 2–5 h (i.m.) after vehicle consistent with typical circadian changes across the day under normal circumstances.

Activity was also significantly decreased (Fig. 4B) after the administration of 5 mg/kg MDMA (main effects of route of administration [$F_{1,5}=21.34$; $p<0.01$]; drug treatment condition [$F_{1,5}=8.17$; $p<0.05$], time post-administration [$F_{5,25}=2.88$; $p<0.05$] and the interaction of drug condition with time [$F_{5,25}=5.93$; $p<0.001$]). The *post-hoc* test confirmed that activity was significantly lower after 5 mg/kg MDMA in comparison with both the pre-treatment baseline and the respective vehicle timepoint 1–2 h after i.m. administration and in the second hour after p.o. administration. In total, activity was significantly lower than the baseline for intervals 1–5 h after 5 mg/kg MDMA i.m. and from 2 to 5 h after p.o. administration. Activity was never significantly different from baseline after the i.m. vehicle and was lower than baseline only 4–5 h after p.o. vehicle. Finally, activity was lower 1, 2 and 4 h after i.m. administration of 5 mg/kg MDMA in comparison with similar timepoints after p.o. administration. Thus activity was significantly reduced by 5 mg/kg MDMA by either route, albeit to a greater extent when administered i.m. in comparison with oral dosing.

Activity was significantly increased (Fig. 4C) after the administration of METH (main time post-administration [$F_{5,25}=2.82$; $p<0.05$]) in contrast to the effects of MDMA. The *post-hoc* test confirmed that activity was significantly increased over baseline 1 h after either oral dose of METH and increased relative to the corresponding vehicle timepoints after 0.1 mg/kg METH, i.m. (1, 3–4 h) or 0.32 mg/kg METH, i.m. (1–4 h). Activity was also higher 1–4 h after 0.1 mg/kg METH, p.o. in comparison with the same dose administered i.m. Finally, activity was significantly higher after 0.32 mg/kg METH, i.m. in comparison with the corresponding timepoints following vehicle (1–4 h) or 0.1 mg/kg METH, i.m. (2–4 h).

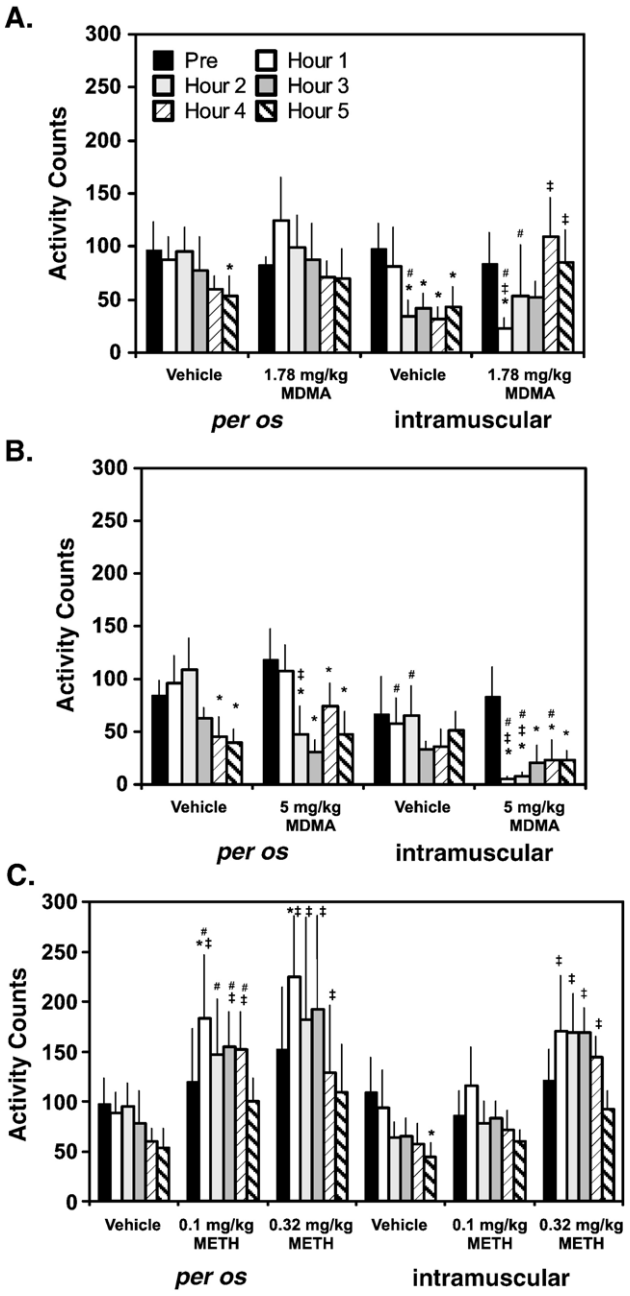

Fig. 4. The mean ($N=5$–6, bars indicate SEM) of hourly activity counts for animals treated with A) 1.78 mg/kg MDMA; B) 5.0 mg/kg MDMA; or C) METH (0.1, 0.32 mg/kg) by oral or intramuscular routes are presented. The intramuscular data (except 5 mg/kg MDMA) were previously reported (Crean et al., 2006) and are reused with permission from Elsevier. A significant difference from baseline is indicated by *, a significant difference from the respective vehicle timepoint by ‡ and a significant difference between doses administered i.m. and p.o. is indicated by #.

3.4. Telemetered versus colonic temperature

Four animals employed in a prior study (Taffe et al., 2006) were challenged with 5 mg/kg MDMA, i.m. and immobilized with 10 mg/kg ketamine, i.m., for rectal temperature evaluation 60 ($N=3$) or 30 ($N=1$) min after dosing. Rectal temperature was measured in the home cage and a simultaneous reading of the telemetered temperature was obtained *via* the real-time tracing feature of the data acquisition system (Fig. 5). These data were compared with a baseline rectal temperature obtained during a prior immobilization for routine health exam; in this case the

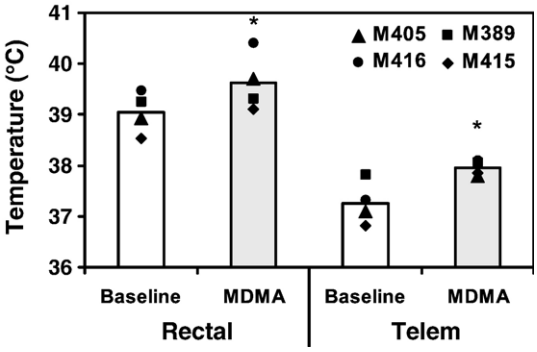

Fig. 5. Mean (N=4) and individual temperatures derived from the subcutaneous telemetry implant and with a rectal thermometer are presented in the upper panel. Animals were immobilized with ketamine either without pre-treatment (baseline) or following administration of 5 mg/kg MDMA. Significant differences between baseline and MDMA conditions are indicated by *.

comparison baseline telemetered value was the sample collected just prior to the animal being removed from the cage. Statistical analysis with randomized block ANOVA confirmed a main effect of both drug condition [$F_{1,3}$=14.59; p<0.05] and the source of temperature measurement [$F_{1,3}$=74.24; p<0.01]. *Post-hoc* exploration confirmed that all four measurements differed significantly from the three remaining conditions. There was no interaction between the main factors; in other words the *difference* between rectal and telemetered temperature was identical between baseline and MDMA conditions. Alternately, the difference in temperature attributable to 5 mg/kg MDMA was the same magnitude whether rectal (0.58 °C; SEM=0.22) or telemetered (0.69 °C; SEM=0.19) temperature was considered.

4. Discussion

This study demonstrates that the body temperature of rhesus monkeys is increased after oral administration of either MDMA or METH, much as it is increased by intramuscular injection of either compound. The results also show that MDMA suppresses activity in monkeys following both intramuscular (i.m.) and oral (*per os*; p.o.) administration. In contrast, activity was increased by METH whether administered i.m. or p.o. Thus *qualitative* differences in thermoregulatory or activity responses to MDMA or METH in monkeys are not produced by oral administration which enhances confidence in applying preclinical results to the human condition.

This study extends our recent findings in three ways. First it is demonstrated that the oral administration of either MDMA or METH leads to an elevation in body temperature in macaque monkeys. As a methodological matter the oral administration may lead to more interpretable outcome since intramuscular vehicle injection frequently (Crean et al., 2006; Von Huben et al., 2007), although not exclusively (Taffe et al., 2006), results in a brief elevation of temperature; thus oral administration may be more a more sensitive preparation. Second, activity levels are either reduced (MDMA) or increased (METH), irrespective of route of administration. These findings are very consistent with prior reports on the effects of these drugs in monkeys after intramuscular administration (Crean et al., 2006; Taffe et al., 2006). Thirdly, the temperature response to MDMA in this study shows a dose dependency not previously observed, likely because the dose range was here extended to 5 mg/kg. The present results are also consistent with both general pharmacological principles respecting oral versus intramuscular administration and available pharmacokinetic data from monkeys. Specifically, the i.m. administration of 5 mg/kg MDMA resulted in a more rapid onset and higher peak temperature response (Fig. 2) in comparison with p.o. administration of the same dose. Available data show that peak plasma MDMA levels are achieved 30 min after 7.4 mg/kg MDMA s.c. in squirrel monkeys (Mechan et al., 2006) and 20–30 min after 10 mg/kg MDMA i.m. in rhesus monkeys (Bowyer et al., 2003). When administered orally in squirrel monkeys, a 7.4 mg/kg dose of MDMA produced peak plasma levels 37% lower and 30 min later in comparison with subcutaneous administration (Mechan et al., 2006); in contrast the halflife was not significantly different. Similarly the intramuscular administration of either METH dose also increased temperature more rapidly compared with p.o. administration (Fig. 3) however the peak change in temperature was similar for this compound. In total the data suggest that oral administration delays the peak of the temperature response to MDMA or METH by about 20–30 min and may attenuate the magnitude of the peak temperature response to MDMA but not METH.

The comparison of the effects of route of administration on activity identified differences of interest. First it is notable that the i.m. administration of 5 mg/kg MDMA suppressed activity in monkeys, much as we have previously reported for lower doses of MDMA administered i.m. (Crean et al., 2006; Taffe et al., 2006; Von Huben et al., 2007) and observed (unpublished) for a 10 mg/kg i.m. dose administered in a repeated dosing study (Taffe et al., 2002, 2001). In this regard the monkey response clearly differs from the consistent hyperlocomotion produced by MDMA in rats (Clemens et al., 2007; Frith et al., 1987; Gold and Koob, 1988) and mice (Fantegrossi et al., 2004; Risbrough et al., 2006). The oral administration of 5 mg/kg MDMA also suppressed activity in monkeys although to a lesser extent than after 5 mg/kg i.m.; there was no effect after 1.78 mg/kg p.o. Interestingly, the lower dose of MDMA resulted in a much delayed increase in activity observed as a change compared with vehicle treatment (i.m.) or a failure to observe normal circadian reductions (p.o.). It should nevertheless be appreciated that such effects appear modest in comparison with elevations in activity induced by MDMA in rodent models.

The oral administration of METH increased the activity of monkeys relative to vehicle treatment conditions, in clear contrast with the effects of MDMA. In this case activity was elevated for several hours after either METH dose (Fig. 4C) administered p.o. suggesting that oral administration may broaden the peak of the dose–response function. As in our prior studies (Crean et al., 2006; Taffe et al., 2006; Von Huben et al., 2007) there was no evidence of repetitive, in-place stereotyped behavior consistently observed in any of the MDMA or METH treatment conditions. The most important part of the (expected) finding that METH

increased activity in this model is that it functions as a positive control for our ongoing, relatively unexpected MDMA findings. It shows that that the relative insensitivity of the telemetered activity measure (requiring ~3/4 of a cage crossing for a "count") and other design features do not prevent the expression of increased activity in this model. Thus the clear observation, replicated in three independent groups of monkeys (Crean et al., 2006; Taffe et al., 2006; Von Huben et al., 2007), that MDMA suppresses activity in monkeys is further bolstered. This outcome in monkeys underscores the fact that temperature responses to MDMA are not integrally coupled to increases in activity, similar to the report of effects in humans quietly resting in the laboratory (Freedman et al., 2005). Thus this finding is also important for the translation of information to the human condition. While situational factors such as the "rave" party/danceclub environment are important in MDMA users, it is often overlooked that substantial amounts of MDMA use takes place in more restricted social settings in which high levels of physical activity are not present. It is also clear that some cases of medical emergency arise from the quiet/nonactive MDMA episode (Libiseller et al., 2005; Melian et al., 2004; Patel et al., 2005). The fact that MDMA does not cause an increase in activity in monkeys means that this species can model the nonactive category of human risk.

This study also highlights another important consideration in generating cross-species comparisons or inferences. The source of a "body temperature" measurement can be highly critical in smaller laboratory species. The skin temperatures of rat tail or rabbit ear pinnae are unchanged or even reduced following MDMA administration, while core or rectal temperatures are increased (Blessing et al., 2003; Pedersen and Blessing, 2001). Such findings indicate that MDMA-induced peripheral vasoconstriction impairs heat shedding and contributes to increased body temperature in these species. Peripheral heat shedding in rodents is also affected by additional environmental factors since rats in metal cages fail to develop rectal temperature increases after MDMA under conditions in which rats in acrylic cages exhibit 2.5 °C rectal temperature increases (Gordon and Fogelson, 1994) and sufficiently low ambient temperature can block or reverse MDMA-induced hyperthermia (Dafters, 1994; Malberg and Seiden, 1998). Yet Freedman et al. (2005) have shown that oral MDMA increases gastric and *skin* temperature to a similar degree in humans under high or low ambient temperatures. We have shown that ambient temperature is similarly irrelevant to MDMA-induced changes in monkeys' subcutaneous temperature (Von Huben et al., 2007). The direct comparison of rectal temperature with the subcutaneous telemetry measure in the present study further demonstrates that the rhesus monkey is more similar to humans than is the rat, because the magnitude of the MDMA effect on temperature does not vary due to source of the temperature measure. This is perhaps unsurprising since the telemetered subcutaneous temperature in rhesus differed from rectal by only about 1.8 °C under ambient temperature conditions in which skin temperature differs from rectal by about 4–5 °C (Johnson and Elizondo, 1979). Together this evidence suggests that temperature effects of MDMA in the larger bodied species (or at least primates) are more consistent from core to periphery in comparison with rodents or rabbits. This suggests that caution should be employed when translating data regarding the physiology and pharmacology of peripheral vasoconstriction induced by MDMA in small animal models to understanding the etiology of MDMA-induced thermoregulatory distress in humans.

A critically important consideration in the present study is that the effects observed occurred well within a dose range that is relevant to drug exposure in both recreational and therapeutic contexts. User dose statistics (Fox et al., 2001) and Ecstasy tablet analyses (Cole et al., 2002; Schifano, 2000; Teng et al., 2006) suggest that a 50 kg (110 lb) "novice user" would be exposed to a 3 mg/kg MDMA dose frequently and a 4.5–6 mg/kg oral dose at least once. Currently running clinical trial for Post-Traumatic Stress Disorder administer a cumulative dose of 3.75 mg/kg in a 50 kg individual (Mithoefer, 2006a,b). The tablets tested by harm reduction organizations suggest that in most "Ecstasy" tablets containing both METH and MDMA, METH content ranges ~20%–100% of the MDMA content (EcstasyData.org, 2006). Although absolute METH levels in such tablets are not available, the relative content suggests that the present doses are highly relevant to the Ecstasy user. In therapeutic use, the treatment target for ADHD children (FDA, 2004, 2001) is 10 mg of METH (Desoxyn®) or amphetamine (or an equivalent plasma profile produced with extended-release formulations). One clinical study of "mixed-salts amphetamines" (Adderall®) reported a mean amphetamine dose of 0.16–0.63 mg/kg (Greenhill et al., 2003). Although Adderall® and Desoxyn® are approved drugs which permit titration of dose by the physician, it should be clear that the METH doses for the present study are similar to the most common therapeutic doses.

In conclusion, this study confirmed the hypothesis that oral administration of either MDMA or METH increases the body temperature of rhesus monkeys. It was further demonstrated that the maximum extent of temperature increase following oral administration was only moderately different from effects of intramuscular injection. Thus the oral administration of MDMA or METH, in doses that are highly relevant to both recreational and therapeutic exposure can disrupt critical thermoregulatory functions. It is therefore concluded that while route of administration may make a *quantitative* difference it does not introduce a *qualitative* change in thermoregulatory disruption associated with MDMA or METH in nonhuman primates. These data further support the validity of translating data arising from injected MDMA or METH in nonhuman primate models to the human condition.

Acknowledgements

The authors gratefully acknowledge contributions made to this work by Stefani N. Von Huben, Christopher C. Lay and Simon N. Katner, Ph.D. Portions of this work were presented in preliminary form at the 2006 annual meeting of the College on Problems of Drug Dependence and at the 2006 annual meeting of the Society for Neuroscience. This work was supported by USPHS grant DA018418. This is publication #18222-MIND from The Scripps Research Institute.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pbb.2007.03.015.

References

Baggott M, Heifets B, Jones RT, Mendelson J, Sferios E, Zehnder J. Chemical analysis of ecstasy pills. JAMA 2000;284:2190.

Ball J, Garfield T, Morin C, Steele D. Emergency Department Trends from the Drug Abuse Warning Network, Final Estimates 1995–2002. DAWN Series D-24, DHHS Publication No. (SMA) 03-3780. Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies; 2003.

Ball J, Morin C, Cover E, Green J, Sonnefeld J, Steele D, et al. Drug Abuse Warning Network, 2003: Interim National Estimates of Drug-Related Emergency Department Visits. DAWN Series D-26, DHHS Publication No. (SMA) 04-3972. Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies; 2004.

Bishop C, Taylor JL, Kuhn DM, Eskow KL, Park JY, Walker PD. MDMA and fenfluramine reduce L-DOPA-induced dyskinesia via indirect 5-HT1A receptor stimulation. Eur J Neurosci 2006;23:2669–76.

Blessing WW, Seaman B, Pedersen NP, Ootsuka Y. Clozapine reverses hyperthermia and sympathetically mediated cutaneous vasoconstriction induced by 3,4-methylenedioxymethamphetamine (ecstasy) in rabbits and rats. J Neurosci 2003;23:6385–91.

Bowyer JF, Tank AW, Newport GD, Slikker Jr W, Ali SF, Holson RR. The influence of environmental temperature on the transient effects of methamphetamine on dopamine levels and dopamine release in rat striatum. J Pharmacol Exp Ther 1992;260:817–24.

Bowyer JF, Davies DL, Schmued L, Broening HW, Newport GD, Slikker Jr W, et al. Further studies of the role of hyperthermia in methamphetamine neurotoxicity. J Pharmacol Exp Ther 1994;268:1571–80.

Bowyer JF, Young JF, Slikker W, Itzak Y, Mayorga AJ, Newport GD, et al. Plasma levels of parent compound and metabolites after doses of either d-fenfluramine or d-3,4-methylenedioxymethamphetamine (MDMA) that produce long-term serotonergic alterations. Neurotoxicology 2003;24:379–90.

Brown PL, Kiyatkin EA. Brain hyperthermia induced by MDMA (ecstasy): modulation by environmental conditions. Eur J Neurosci 2004;20:51–8.

Buffum JC, Shulgin AT. Overdose of 2.3 grams of intravenous methamphetamine: case, analysis and patient perspective. J Psychoactive Drugs 2001;33:409–12.

Carvalho M, Carvalho F, Remiao F, de Lourdes Pereira M, Pires-das-Neves R, de Lourdes Bastos M. Effect of 3,4-methylenedioxymethamphetamine ("ecstasy") on body temperature and liver antioxidant status in mice: influence of ambient temperature. Arch Toxicol 2002;76:166–72.

Clark JD, Baldwin RL, Bayne KA, Brown MJ, Gebhart GF, Gonder JC, et al. Guide for the care and use of laboratory animals. Washington D.C.: Institute of Laboratory Animal Resources, National Research Council; 1996. p. 125.

Clemens KJ, Van Nieuwenhuyzen PS, Li KM, Cornish JL, Hunt GE, McGregor IS. MDMA ("ecstasy"), methamphetamine and their combination: long-term changes in social interaction and neurochemistry in the rat. Psychopharmacology (Berl) 2004;173:318–25.

Clemens KJ, Cornish JL, Li KM, Hunt GE, McGregor IS. MDMA ('Ecstasy') and methamphetamine combined: order of administration influences hyperthermic and long-term adverse effects in female rats. Neuropharmacology 2005;49:195–207.

Clemens KJ, Cornish JL, Hunt GE, McGregor IS. Repeated weekly exposure to MDMA, methamphetamine or their combination: long-term behavioural and neurochemical effects in rats. Drug Alcohol Depend 2007 Jan 12;86(2−3): 183–90. [Electronic publication ahead of print 2006 Aug 1].

Clingerman KJ, Summers L. Development of a body condition scoring system for nonhuman primates using *Macaca mulatta* as a model. Lab Anim (NY) 2005;34:31–6.

Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA. The content of ecstasy tablets: implications for the study of their long-term effects. Addiction 2002;97:1531–6.

Crean RD, Davis SA, Von Huben SN, Lay CC, Katner SN, Taffe MA. Effects of (+/−)3,4-methylenedioxymethamphetamine, (+/−)3,4-methylenedioxyamphetamine and methamphetamine on temperature and activity in rhesus macaques. Neuroscience 2006;142:515–25.

Dafters RI. Effect of ambient temperature on hyperthermia and hyperkinesis induced by 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") in rats. Psychopharmacology (Berl) 1994;114:505–8.

Dams R, De Letter EA, Mortier KA, Cordonnier JA, Lambert WE, Piette MH, et al. Fatality due to combined use of the designer drugs MDMA and PMA: a distribution study. J Anal Toxicol 2003;27:318–22.

Doblin R. MAPS-sponsored cancer anxiety research. MAPS Bull 2006;16:11.

EcstasyData.org. EcstasyData.org: Ecstasy Lab Testing & Analysis Results — Ecstasy Pill Reports. Erowid, Dancesafe, MAPS, & the Promind Foundation, 2006.

Fantegrossi WE, Godlewski T, Karabenick RL, Stephens JM, Ullrich T, Rice KC, et al. Pharmacological characterization of the effects of 3,4-methylenedioxymethamphetamine ("ecstasy") and its enantiomers on lethality, core temperature, and locomotor activity in singly housed and crowded mice. Psychopharmacology (Berl) 2003;166:202–11.

Fantegrossi WE, Kiessel CL, Leach PT, Van Martin C, Karabenick RL, Chen X, et al. Nantenine: an antagonist of the behavioral and physiological effects of MDMA in mice. Psychopharmacology (Berl) 2004;173:270–7.

FDA. Desoxyn®: Methamphetamine Hydrochloride tablets, USP. Rockville MD: U. S. Food and Drug Administration; 2001.

FDA. Adderall XR Capsules. Rockville MD: U.S. Food and Drug Administration; 2004.

Fiege M, Wappler F, Weisshorn R, Gerbershagen MU, Menge M, Schulte Am Esch J. Induction of malignant hyperthermia in susceptible swine by 3,4-methylenedioxymethamphetamine ("Ecstasy"). Anesthesiology 2003;99:1132–6.

Fox HC, Parrott AC, Turner JJ. Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. J Psychopharmacol 2001;15:273–81.

Freedman RR, Johanson CE, Tancer ME. Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl) 2005;183:248–56.

Frith CH, Chang LW, Lattin DL, Walls RC, Hamm J, Doblin R. Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat. Fundam Appl Toxicol 1987;9:110–9.

Gillman PK. Ecstasy, serotonin syndrome and the treatment of hyperpyrexia. Med J Aust 1997;167:109–11.

Gold LH, Koob GF. Methysergide potentiates the hyperactivity produced by MDMA in rats. Pharmacol Biochem Behav 1988;29:645–8.

Gordon CJ, Fogelson L. Metabolic and thermoregulatory responses of the rat maintained in acrylic or wire-screen cages: implications for pharmacological studies. Physiol Behav 1994;56:73–9.

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev 2003;55:463–508.

Green AR, O'Shea E, Colado MI. A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response. Eur J Pharmacol 2004;500:3–13.

Greenhill LL, Swanson JM, Steinhoff K, Fried J, Posner K, Lerner M, et al. A pharmacokinetic/pharmacodynamic study comparing a single morning dose of adderall to twice-daily dosing in children with ADHD. J Am Acad Child Adolesc Psychiatry 2003;42:1234–41.

Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). Lancet 1992;340:384–7.

Iravani MM, Jackson MJ, Kuoppamaki M, Smith LA, Jenner P. 3,4-methylenedioxymethamphetamine (ecstasy) inhibits dyskinesia expression and normalizes motor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates. J Neurosci 2003;23:9107–15.

Johnson GS, Elizondo RS. Thermoregulation in *Macaca mulatta*: a thermal balance study. J Appl Physiol 1979;46:268–77.

Katner SN, Davis SA, Kirsten AJ, Taffe MA. Effects of nicotine and mecamylamine on cognition in rhesus monkeys. Psychopharmacology (Berl) 2004a;175:225–40.

Katner SN, Flynn CT, Von Huben SN, Kirsten AJ, Davis SA, Lay CC, et al. Controlled and behaviorally relevant levels of oral ethanol intake in rhesus macaques using a flavorant-fade procedure. Alcohol Clin Exp Res 2004b;28: 873–83.

Kelly BC, Parsons JT, Wells BE. Prevalence and predictors of club drug use among club-going young adults in New York city. J Urban Health 2006;83: 884–95.
Levy KB, O'Grady KE, Wish ED, Arria AM. An in-depth qualitative examination of the ecstasy experience: results of a focus group with ecstasy-using college students. Subst Use Misuse 2005;40:1427–41.
Libiseller K, Pavlic M, Grubwieser P, Rabl W. Ecstasy—deadly risk even outside rave parties. Forensic Sci Int 2005;153:227–30.
Madden LJ, Flynn CT, Zandonatti MA, May M, Parsons LH, Katner SN, et al. Modeling human methamphetamine exposure in nonhuman primates: chronic dosing in the rhesus macaque leads to behavioral and physiological abnormalities. Neuropsychopharmacology 2005;30:350–9.
Malberg JE, Seiden LS. Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. J Neurosci 1998;18:5086–94.
Mallick A, Bodenham AR. MDMA induced hyperthermia: a survivor with an initial body temperature of 42.9 degrees C. J Accid Emerg Med 1997;14:336–8.
McCabe SE, Teter CJ, Boyd CJ. The use, misuse and diversion of prescription stimulants among middle and high school students. Subst Use Misuse 2004;39: 1095–116.
McCabe SE, Teter CJ, Boyd CJ. Medical use, illicit use and diversion of prescription stimulant medication. J Psychoactive Drugs 2006;38:43–56.
Mechan A, Yuan J, Hatzidimitriou G, Irvine RJ, McCann UD, Ricaurte GA. Pharmacokinetic profile of single and repeated oral doses of MDMA in squirrel monkeys: relationship to lasting effects on brain serotonin neurons. Neuropsychopharmacology 2006;31:339–50.
Melian AM, Burillo-Putze G, Campo CG, Padron AG, Ramos CO. Accidental ecstasy poisoning in a toddler. Pediatr Emerg Care 2004;20:534–5.
Mithoefer M. MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD): seventh update on study progress. MAPS Bull 2006a;16:7–8.
Mithoefer M. Study protocol: Phase II clinical trial testing the safety and efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in subjects with chronic posttraumatic stress disorder. Multidisciplinary Association for Psychedelic Studies; 2006b. http://www.maps.org/mdma/protocol/index.html.
Mojeiko V. Israel MDMA/PTSD Research Project. MAPS Bull 2006;16:10.
NRC/NAS. Nutrient requirements of nonhuman primates: second revised edition. Washington D.C.: National Research Council of The National Academy of Sciences; 2003.
Oehen P. MDMA-assisted psychotherapy pilot study in Switzerland. MAPS Bull 2006;16:9.
Patel MM, Belson MG, Longwater AB, Olson KR, Miller MA. Methylenedioxymethamphetamine (ecstasy)-related hyperthermia. J Emerg Med 2005;29: 451–4.
Pedersen NP, Blessing WW. Cutaneous vasoconstriction contributes to hyperthermia induced by 3,4-methylenedioxymethamphetamine (ecstasy) in conscious rabbits. J Neurosci 2001;21:8648–54.
Prosser JM, Naim M, Helfaer MA. A 14-year-old girl with agitation and hyperthermia. Pediatr Emerg Care 2006;22:676–9.
Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD. Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"). Science 2002;297:2260–3.
Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD. Retraction. Science 2003;301:1479.
Risbrough VB, Masten VL, Caldwell S, Paulus MP, Low MJ, Geyer MA. Differential contributions of dopamine D1, D2, and D3 receptors to MDMA-induced effects on locomotor behavior patterns in mice. Neuropsychopharmacology 2006 Nov;31(11):2349–58. [Electronic publication 2006 Jul 19].
Rosa-Neto P, Olsen AK, Gjedde A, Watanabe H, Cumming P. MDMA-evoked changes in cerebral blood flow in living porcine brain: correlation with hyperthermia. Synapse 2004;53:214–21.
Rusyniak DE, Sprague JE. Toxin-induced hyperthermic syndromes. Med Clin North Am 2005;89:1277–96.
Saadat KS, Elliott JM, Colado MI, Green AR. Hyperthermic and neurotoxic effect of 3,4-methylenedioxymethamphetamine (MDMA) in guinea pigs. Psychopharmacology (Berl) 2004;173:452–3.
Schifano F. Potential human neurotoxicity of MDMA ('Ecstasy'): subjective self-reports, evidence from an Italian drug addiction centre and clinical case studies. Neuropsychobiology 2000;42:25–33.
Sotnikova TD, Beaulieu JM, Barak LS, Wetsel WC, Caron MG, Gainetdinov RR. Dopamine-independent locomotor actions of amphetamines in a novel acute mouse model of Parkinson disease. PLoS Biol 2005;3:e271.
Taffe MA. Effects of parametric feeding manipulations on behavioral performance in macaques. Physiol Behav 2004a;81:59–70.
Taffe MA. Erratum: "Effects of parametric feeding manipulations on behavioral performance in macaques". Physiol Behav 2004b;82:589.
Taffe MA, Weed MR, Davis S, Huitron-Resendiz S, Schroeder R, Parsons LH, et al. Functional consequences of repeated (+/−)3,4-methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. Neuropsychopharmacology 2001;24:230–9.
Taffe MA, Davis SA, Yuan J, Schroeder R, Hatzidimitriou G, Parsons LH, et al. Cognitive performance of MDMA-treated rhesus monkeys: sensitivity to serotonergic challenge. Neuropsychopharmacology 2002;27:993–1005.
Taffe MA, Lay CC, Von Huben SN, Davis SA, Crean RD, Katner SN. Hyperthermia induced by 3,4-methylenedioxymethamphetamine in unrestrained rhesus monkeys. Drug Alcohol Depend 2006;82:276–81.
Tanner-Smith EE. Pharmacological content of tablets sold as "ecstasy": results from an online testing service. Drug Alcohol Depend 2006;83:247–54.
Teng SF, Wu SC, Liu C, Li JH, Chien CS. Characteristics and trends of 3,4-methylenedioxymethamphetamine (MDMA) tablets found in Taiwan from 2002 to February 2005. Forensic Sci Int 2006 Sep 12;161(2−3):202–8. [Electronic publication ahead of print 2006 Jul 13].
Upadhyaya HP, Rose K, Wang W, O'Rourke K, Sullivan B, Deas D, et al. Attention-deficit/hyperactivity disorder, medication treatment, and substance use patterns among adolescents and young adults. J Child Adolesc Psychopharmacol 2005;15:799–809.
Von Huben SN, Davis SA, Lay CC, Katner SN, Crean RD, Taffe MA. Differential contributions of dopaminergic D1- and D2-like receptors to cognitive function in rhesus monkeys. Psychopharmacology (Berl) 2006 Nov;188(4):586–96. [Electronic publication 2006 Mar 15].
Von Huben SN, Lay CC, Crean RD, Davis SA, Katner SN, Taffe MA. Impact of ambient temperature on hyperthermia induced by (+/−)3,4-methylenedioxymethamphetamine in rhesus macaques. Neuropsychopharmacology 2007;32: 673–81.
White SR. Amphetamine toxicity. Semin Respir Crit Care Med 2002;23:27–36.
White B, Day C, Degenhardt L, Kinner S, Fry C, Bruno R, et al. Prevalence of injecting drug use and associated risk behavior among regular ecstasy users in Australia. Drug Alcohol Depend 2006;83:210–7.
Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. J Am Acad Child Adolesc Psychiatry 2006;45: 408–14.
Wu LT, Schlenger WE, Galvin DM. Concurrent use of methamphetamine, MDMA, LSD, ketamine, GHB, and flunitrazepam among American youths. Drug Alcohol Depend 2006 Sep 1;84(1):102–13. [Electronic publication ahead of print 2006 Feb 17. Erratum in: Drug Alcohol Depend 2007 Jan 12;86(2–3):301].
Wu LT, Pilowsky DJ, Schlenger WE, Galvin DM. Misuse of methamphetamine and prescription stimulants among youths and young adults in the community. Drug Alcohol Depend in press. [Electronic publication ahead of print 2007 Jan 23].
Yuan J, Hatzidimitriou G, Suthar P, Mueller M, McCann U, Ricaurte G. Relationship between temperature, dopaminergic neurotoxicity, and plasma drug concentrations in methamphetamine-treated squirrel monkeys. J Pharmacol Exp Ther 2006;316:1210–8.
Zhu BL, Ishikawa T, Quan L, Li DR, Zhao D, Michiue T, Maeda H. Evaluation of postmortem serum calcium and magnesium levels in relation to the causes of death in forensic autopsy. Forensic Sci Int 2005;155:18–23.