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ORIGINAL INVESTIGATION

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Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans

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Abstract *Rationale:* Although 3,4-methylenedioxymethamphetamine (MDMA; Ecstasy) has been reported to cause fatal hyperthermia, few studies of the effects of MDMA on core body temperature in humans have been conducted demonstrating increased body temperature. In rats, MDMA causes hyperthermia at warm ambient temperatures but hypothermia at cold ones. *Objectives:* In this study, the physiological and subjective effects of MDMA in humans were determined at cold (18°C) and warm (30°C) ambient temperatures in a temperature and humidity-controlled laboratory. *Methods:* Ten healthy volunteers who were recreational users of MDMA were recruited. Four laboratory sessions were conducted in a 2×2 design [i.e., two sessions at 30°C and two at 18°C, two during MDMA (2 mg/kg, p.o.) and two during placebo, in double-blind fashion]. Core body temperature (ingested radiotelemetry pill), skin temperature (four weighted sites), heart rate, blood pressure, metabolic rate (indirect calorimetry), shivering (electromyogram levels), and sweat rate (capacitance hygrometry) were measured as well as subjective effects for several time periods following capsule ingestion. *Results:* MDMA produced significant elevations in core body temperature and metabolic rate in both warm and cold conditions. MDMA also produced significant elevations in blood pressure and heart rate and significantly increased several ratings of subjective effects similar to those previously reported. There were no differences related to ambient temperature for any of the subjective effects, except that ratings of cold and warm were appropriate to the ambient temperature and were not influenced by MDMA. *Conclusions:* Unlike findings in rats, MDMA increased core body temperature regardless of ambient temperature in humans. These increases appeared related to increases in metabolic rate, which were substantial. These findings warrant further investigations on the role of MDMA and other stimulants in altering metabolism and thermogenesis.

Keywords MDMA · Body temperature · Hyperthermia · Metabolic rate · Subjective effects

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Introduction

One of the most commonly reported clinical consequences of 3,4-methylenedioxymethamphetamine (MDMA) use has been hyperthermia and/or hyperpyrexia. In humans, MDMA use has been associated with flushing, sympathetic activation, increased metabolic rate, as well as clinical hyperthermia, with Green et al. (2004) noting that temperatures as high as 43°C have been reported. Confounding the direct effect of MDMA on body temperature is the fact that MDMA is most often consumed at dances. Exercise alone increases core body temperature (Gleeson 1998; Fisher et al. 1999), so it is possible that MDMA plus exercise (vigorous dancing) will have a greater effect than either exercise alone or MDMA alone. The mechanism by which MDMA causes increases in body temperature has not been elucidated in humans, but it is likely that elevated body temperatures can lead to even fatal outcomes (Green et al. 2004).

There are compelling data in rats that MDMA administration is associated with hyperthermia and may actually disrupt thermoregulation (Malberg and Seiden 1998; Schmidt et al. 1990). In rats, MDMA and other psychostimulants such as cocaine and methamphetamine cause an increase in core temperature (Dafters and Lynch 1998; Dafters 1995; Gonzales 1993; Gordon et al. 1991). Furthermore, Malberg and Seiden (1998) have reported that the effect of MDMA on core body temperature was influenced by ambient temperature. In fact, rats given

MDMA at 20°C developed hypothermia, whereas those given MDMA at 26–30°C developed hyperthermia, suggesting a general disruption in thermoregulation. The hyperthermic response following MDMA administration is not limited to rats. Both mice (Fantegrossi et al. 2003) and rabbits (Pedersen and Blessing 2001) also demonstrate increased body temperature following MDMA exposure.

Given that MDMA is usually consumed in the context of crowded environments and prolonged physical exertion, it is not surprising that hyperthermia occurs in humans (Dar and McBrien 1996; Mallick and Bodenham 1997; Ferrie and Loveland 2000; Green et al. 2004) and has been implicated in some deaths (Henry 2000). Unfortunately, the extent of the problem is not known, as only a small fraction of individuals seek medical care. When MDMA has been administered in laboratory settings, increases in body temperature have been seen, but not only was the magnitude small but in no study was it statistically significant (Grob et al. 1996; Vollenweider et al. 1998; Mas et al. 1999). If, in fact, humans lose the ability to regulate body temperature following MDMA use, this would have profound public health implications regarding controlling ambient temperature and trying to decrease the physical activity at the dances. In the present study, the effects of MDMA on temperature regulation as well as subjective experience was assessed in humans at cold and warm ambient temperatures under well-controlled laboratory conditions. Because only a single dose of MDMA could be tested, the highest dose, 2 mg/kg, safely tested in our previous studies, was selected for evaluation (Tancer and Johanson 2003).

Materials and methods

Participants

Participants who were recruited were between 18 and 35 years of age, had a minimum of a high school education or general education diploma (GED), and had no psychiatric or medical conditions that precluded participation. In addition, they had to have a history of using MDMA at least three times, once in the last 6 months. No candidate with a current or past Axis I diagnosis, including drug or alcohol dependence disorder, other than nicotine dependence was eligible. The exception was that drug or alcohol abuse disorder was not exclusionary if at least a year had passed since remission. Candidates were excluded if lifetime recreational use of psychomotor stimulants, opiates, phencyclidine, or sedatives exceeded 50 times. Females could not be pregnant or lactating, and no participant could weigh over 200 lbs. Cognitive ability was assessed with the revised Shipley Institute of Living Scale (Zachary 1986), and only individuals with an estimated IQ over 85 could participate. The study was approved by the Wayne State University Human Investigation Committee, and participants were reimbursed for their time and inconvenience.

Potential participants attended a screening interview to determine eligibility, explain the study, and obtain written informed consent. To determine eligibility, participants had a physical, submitted a blood and urine sample, received an electrocardiogram (EKG), and filled out several questionnaires about their medical and drug use history. To evaluate psychiatric status, a masters' level psychologist administered the Semi-structured Clinical Interview for Diagnostic and Statistical Manual IV (SCID; First et al. 1996). The study purpose was explained, and participants were told that they would receive either MDMA or a placebo each session, but they would not be told which drug they received until after the study. After asking any questions and passing a true–false quiz to assess their understanding of the protocol, the candidate and investigator signed the consent form in the presence of a witness.

Participants were instructed not to take any drugs, including recreational drugs, between sessions and no alcohol for 12 h before a session. Urine drug and breathalyzer tests were conducted prior to every session to assure that these restrictions had been followed. The exception was marijuana because it is retained in the body for such a long period, and most MDMA users also smoke marijuana. However, participants were assessed for intoxication. Any evidence of drug or alcohol use resulted in a rescheduling of the session. A pregnancy test was also administered to female participants prior to every session. Participants were allowed to consume their usual amounts of caffeine and nicotine.

Physiological measures

Core body temperature (T_c) was measured with a radiotelemetry pill (CorTemp; HTI Technologies, Inc., St. Petersburg, FL). The pill was ingested 90 min before each session to allow egress from the stomach. Skin temperature was recorded with Yellow Springs 729 thermistor probes taped to the chest (T_1), upper arm (T_2), thigh (T_3), and lower leg (T_4). Mean skin temperature (T_{sk}) was calculated as follows (Freedman and Krell 1999):

$$T_{sk} = 0.3\,(T_1 + T_2) + 0.2\,(T_3 + T_4).$$

The telemetry pills were calibrated in a circulating water bath against a National Bureau of Standards certified glass thermometer with an absolute accuracy of 0.05°C. If any telemetry pill deviated from the standard by more than 0.1°C, it was recalibrated.

Electrical muscle activity [electromyogram (EMG)] to detect shivering was recorded with Meditrace silver–silver chloride electrodes placed 3 cm apart over the pectoralis major and rectus femoris muscles. The skin sites were cleaned with alcohol and gauze to an impedance of less than 10 kΩ. The signals were recorded with Grass (Grass Instrument Division, AstroMed, Inc., West Warwick, RI) alternating-current preamplifiers with a bandpass filter of 10–30 kHz and then full-wave-rectified and integrated with a time constant of 0.25 s (Freedman and Krell 1999).

Sweating activity was recorded by means of a capacitive humidity sensor within a plastic chamber 3.5 cm in diameter attached over the sternum with adhesive skin barriers. Dry compressed air was passed through the chamber at a rate of 200 ml/min. The minimum level of sweat detection with this system was 0.001 mg cm^{-2} min^{-1} (Freedman and Krell 1999).

Temperature, shivering, sweating, and integrated EMG signals were sampled at 100 Hz by a PC (IBM Corporation, White Plains, NY) computer with an Analog Devices (Analog Devices, Inc., Norwood, MA) A/D board and were stored on a disk in 15-s blocks. All data were continuously displayed in numeric form on the computer screen and in analog form on a Grass model 7D polygraph.

Heart rate and blood pressure were measured every 4 min with an Ohio Medical Products (Madison, WI) 2105 automatic recorder. Metabolic rate was continuously measured by indirect calorimetry using a MedGraphics CPX/D (St. Paul, MN) metabolic cart and is shown as oxygen consumption.

Subjective effects measures

Subjective effects were assessed using the Addiction Research Center Inventory (ARCI; Martin et al. 1971), a modified version of the Profile of Moods States (POMS; McNair et al. 1971; Johanson and Uhlenhuth 1980), the Hallucinogenic Rating Scale (HRS; Strassman et al. 1994), and visual analog scales (VAS). The ARCI and POMS were administered to the participant three times, prior to the change in room temperature, prior to drug ingestion (see Procedures below), and at the end of the session. The HRS was only administered at the end of the session. The VAS consists of a series of eight horizontal 100-mm lines, each labeled with an adjective (Alert, Anxious, Bad Drug Effect, Good Drug Effect, Liking, Sedated, Warm, and Cold). These measures were obtained prior to the change in temperature, prior to drug ingestion (see Procedures below) and every hour until the end of the session (4 h post-ingestion). All of these subjective effects measures have been described in greater detail in Tancer and Johanson (2003).

Procedures

There were four separate sessions at least 1 week apart. Participants received either MDMA (2 mg kg^{-1}, p.o.) or placebo, double blind, in warm (30°C) or cold (18°C) ambient temperatures. The order of sessions was randomized. Participants refrained from all food, beverages, and nicotine for 4 h before the study. The experiments were conducted in a specially constructed environmental room at a relative humidity of 50% and a wind speed of 0.1 m/s. Recording equipment was kept in a separate room. The rooms were connected by closed-circuit television and audio linkages so that the participants and experimenters could always communicate. Participants wore cotton hospital scrub suits and were in the seated position.

The telemetry pill was swallowed at approximately 0830 hours. All data collection began at 1000 hours, with the room temperature at 23°C. After 30 min, the room temperature was changed to 18°C or 30°C, which took about 2 min. The drug or placebo capsule was given with a small amount of water 30 minutes later (1100 hours). Physiological recording continued for 4 h, after which the session ended (1500 hours).

Statistical analyses of physiological measures

To facilitate analysis, all physiological data were averaged in 10-min blocks. These were analyzed with three-way (Drug×Temperature×Time) repeated-measures analyses of variance (ANOVAs). Violations of sphericity were addressed using the Huynh-Feldt adjustment factor. Significant interactions were further analyzed by the lower-order simple effects. Analyses were done using SPSS 12.1.

The T_c sweating threshold was indicated by the first detection of any sweating ≥0.001 mg cm^{-2} min^{-1}. The T_c shivering threshold was defined as the point at which the average of the two EMG levels first exceeded the final baseline value by more than 50%. These algorithms have been used previously (Freedman and Krell 1999). The T_c thresholds were analyzed with paired *t* tests. The minimum level of statistical significance for all analyses was $p<0.05$. All data are shown as means±SE.

Statistical analyses of subjective effects

Profile of Moods States, VAS, ARCI, and HRS scales were analyzed using repeated measures univariate analysis of variance, with temperature condition (2), drug condition (2), and session time (1, 3, or 6, depending on measure) as repeated factors using SPSS 11.0. Violations of sphericity were addressed using the Huynh-Feldt adjustment factor. The minimum level of statistical significance for all analyses was $p<0.05$. Significant interactions between condition and time were explored with simple effects analyses. Relationships between VAS ratings of feelings of cold and warm and body temperatures were tested with Pearson product-moment correlation coefficients.

Drug supplies

Racemic MDMA HCl was obtained from David Nichols (Purdue University) in powder form, so that it was possible to administer doses on a milligram per kilogram basis. The measured powder was placed in gelatin capsules and filled with dextrose. Placebo capsules were filled with dextrose. All capsules were identical in color and size. Dosages were based on the salt weight.

Results

Participants

Ten participants completed the study: four white males, one black male, one multirace male, two white females, and two black females with an average age of 22.9 (range 18–35). The average number of uses of MDMA was 14.9 (range 3–30). All but three were current cigarette smokers, eight also used marijuana currently, and all drank alcohol, with six using less than once a month. Other drugs were used recreationally but rarely.

Physiological measures

MDMA increased core body temperature (T_c) relative to placebo in a time-related manner as indicated by a significant condition × time interaction [$F(29,261)=7.4$; $p<0.003$] in the three-way analysis (Fig. 1). In addition, there was a significant temperature × time effect [$F(29,261)=5.6$; $p<0.0001$], indicating that core temperatures were higher in the warm environment. The simple effect analyses indicated that the increase in temperature following MDMA was significant under both the warm [$F(29,261)=6.3$; $p<0.001$] and cold [$F(29,261)=4.4$; $p<0.02$] environments. Simple effects analyses also indicated that there were significant temperature × time effects for both placebo [$F(29,261)=2.5$; $p<0.05$] and MDMA [$F(29,261)=3.5$; $p<0.02$]. However, there is no statistical evidence (temperature × condition interaction) demonstrating that the increase in core temperature as a result of MDMA administration was greater in magnitude in the warm environment because under the placebo condition, core temperature was also greater in magnitude under the warm condition.

Skin temperature was significantly [$F(29,261)=38.3$; $p<0.0001$] greater in the warm than in the cold room and changed in a time-related manner (Fig. 2). Simple effects analyses revealed that this temperature × time interaction was significant under both MDMA [$F(29,261)=14.1$; $p<0.0001$] and placebo [$F(29,261)=29.4$; $p<0.0001$] conditions. There was also a significant condition × time interaction [$F(29,261)=4.5$; $p<0.02$] in the three-way analyses. However, in the simple effects analyses, MDMA did not significantly increase skin temperature relative to placebo in either the cold [$F(29,261)=3.0$; $p<0.062$] or warm [$F(29,261)=2.6$; $p<0.104$] environment, although these both approached statistical significance.

Although there was not a significant difference in the time at which sweating occurred (see Figs. 1 and 2) in the warm environment across drug conditions, there was a difference in core temperature at the time sweating occurred under both conditions. Following placebo, sweating began at a mean T_c of 36.9±0.13°C, whereas following MDMA, sweating began at a mean T_c of 37.5±0.09°C [$t(3)=9.5$; $p<0.002$]. For skin temperature, the differences were not significant ($p<0.07$).

MDMA significantly elevated metabolic rate (oxygen consumption) in a time-related manner as indicated by a significant condition × time interaction in the three-way analyses [$F(29,261)=5.3$; $p<0.001$, Fig. 3]. These increases

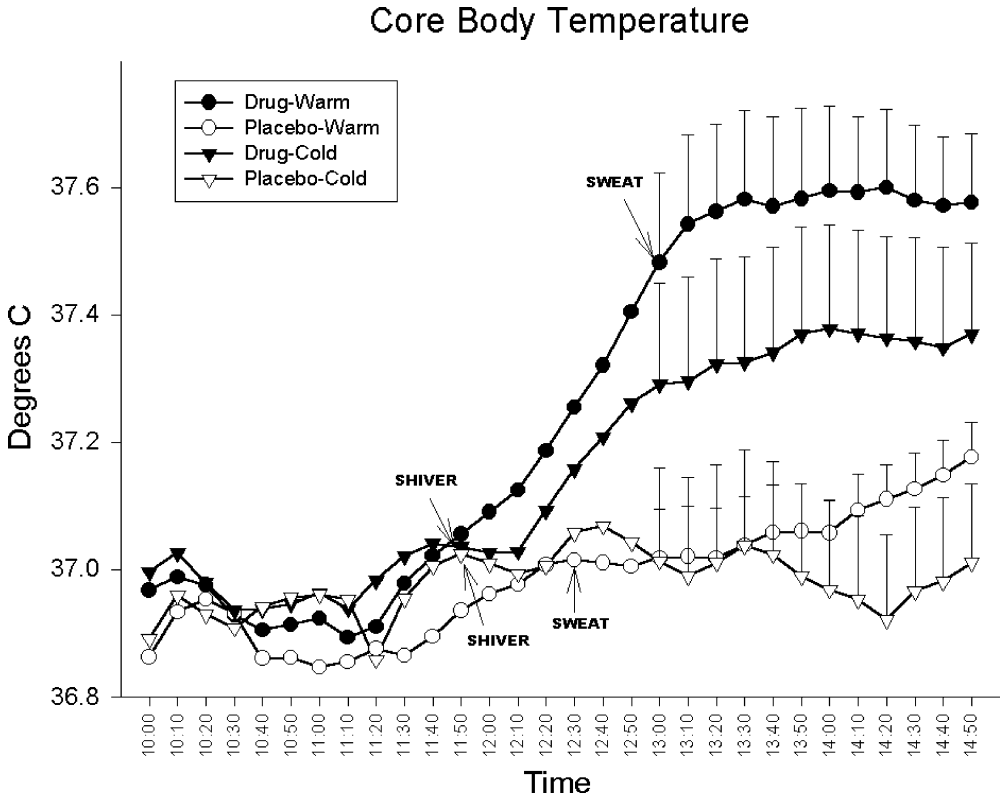

Fig. 1 Core body temperature following the administration of MDMA and placebo under high-temperature (30°C) and low-temperature (18°C) conditions (means±SE) across the session

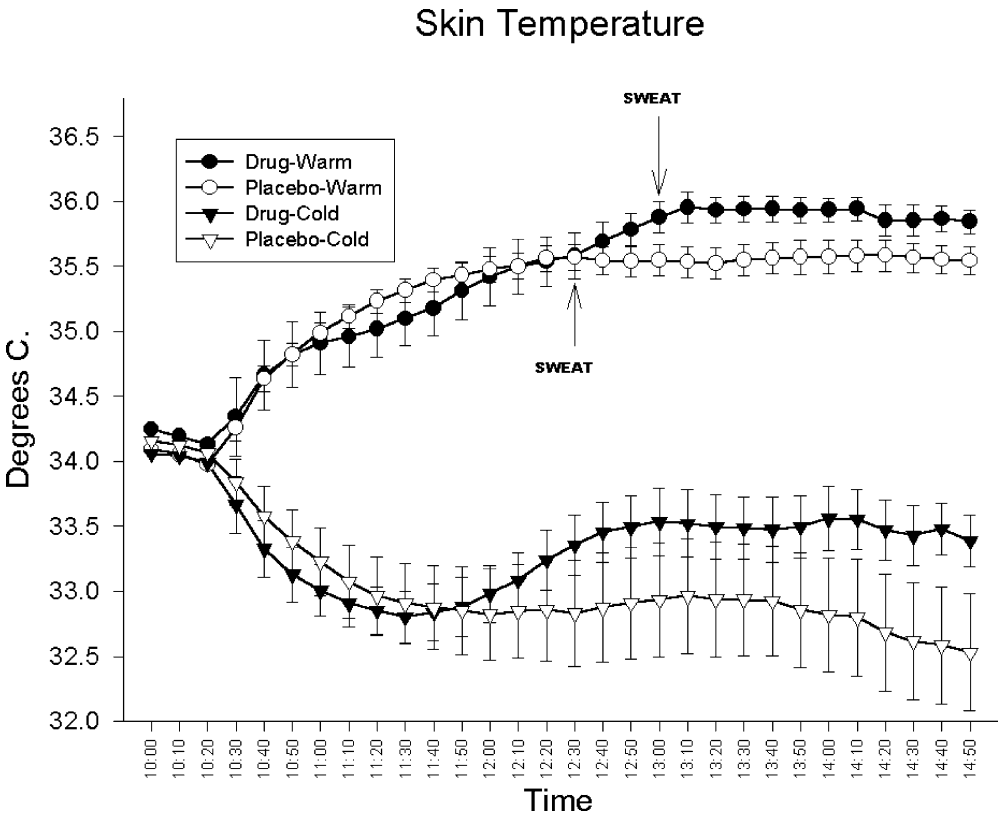

Fig. 2 Average skin temperature following the administration of MDMA and placebo under high-temperature (30°C) or low-temperature (18°C) conditions (means±SE) across the session. *Arrows* indicate approximate point where sweating began

remained significant in the simple effects analyses under both the warm [$F(29,261)=3.3$; $p<0.014$] and cold [$F(29,261)=3.5$; $p<0.004$] conditions. There was also a significant temperature × time effect in the main analyses [$F(29,261)=12.1$; $p<0.0001$] demonstrating that metabolic rate was higher in the cold environment. This was true as

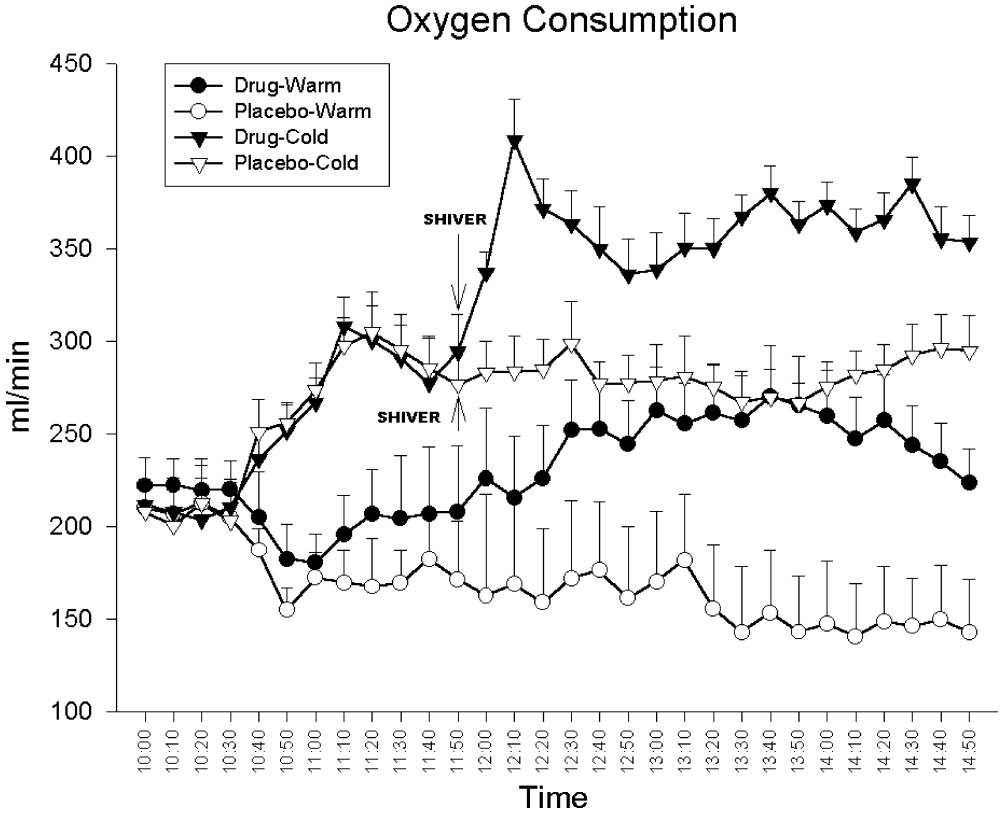

Fig. 3 Oxygen consumption following the administration of MDMA and placebo under high-temperature (30°C) and low-temperature (18°C) conditions (means±SE) across the session. *Arrows* indicate approximate point of shivering onset

well in the simple effects analyses with both MDMA [$F(29,261)=4.8$; $p<0.001$] and placebo [$F(29,261)=8.6$; $p<0.0001$]. Although there were no differences in time of onset of shivering or the core body temperature at which shivering occurred, metabolic rate, which was already increased under both drug conditions, increased considerably more following the onset of shivering in the cold room when MDMA had been administered (Fig. 3).

For systolic and diastolic blood pressure as well as heart rate, there were statistically significant increases following the administration of MDMA compared to placebo (all p's<0.0001). There were no significant temperature × time effects. There were no statistically significant effects related to respiratory quotient (RQ) and respiration rate.

Subjective effects measures

3,4-Methylenedioxymethamphetamine produced significant increases in VAS measures of Drug Liking [$F(5,45)=10.44$, $p<0.0001$], Good Drug Effect [$F(5,45)=9.51$, $p<0.0001$], and Anxious [$F(5,45)=3.11$, $p<0.05$]; ARCI scales of lysergic acid diethylamide LSD [a measure of somatic complaints and dysphoria; $F(2,18)=7.35$, $p<0.02$] and mor-

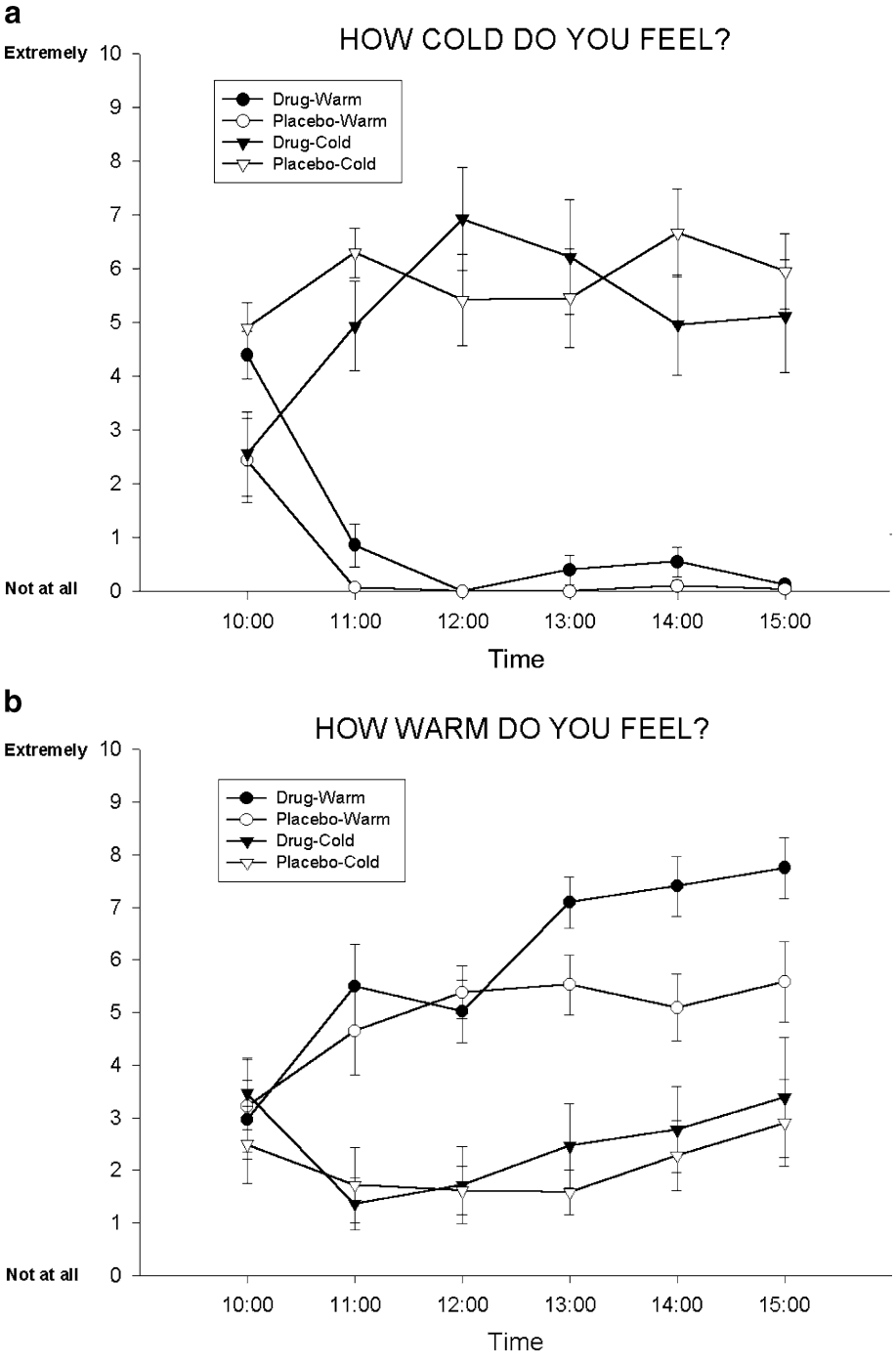

Fig. 4 Effects on feelings of warmness and coldness following the administration of MDMA and placebo under high-temperature [(HT) 30°C] and low-temperature [(LT)18°C] conditions (means±SE) across the session

Table 1 Correlations between VAS ratings of cold and warm and body temperatures (Pearson *r*)

Condition	Feelings of warmth		Feelings of coldness	
	Core	Skin	Core	Skin
Placebo/HT	0.40**	0.48***	−0.21	−0.38*
MDMA/HT	0.42**	0.56***	−0.30†	−0.67***
Placebo/LT	0.00	−0.18	−0.16	−0.15
MDMA/LT	0.35*	0.20	−0.14	−0.05

HT High temperature, *LT* low temperature
***$p<0.0001$; **$p<0.001$; *$p<0.005$; †$p<0.05$

phine benzedrine group (MBG) [a measure of euphoria; $F(2,18)=3.93$, $p<0.04$]; and five of the six scales of the HRS (all related to hallucinogenic-like effects; F values from 8.1 to 22.2, $p<0.001$–0.02). Simple effects analyses of the VAS, POMS, and ARCI indicated that for most of these scales, MDMA produced these effects under both temperature conditions. There were no significant temperature × time effects indicating that the temperature condition did not alter subjective effects. For feelings of Cold [$F(5,45)=11.54$, $p<0.0001$] and Warm [$F(5,45)=26.12$, $p<0.0001$], there were significant temperature × time effects (Fig. 4), and MDMA did not alter these ratings.

Table 1 shows the correlations between feelings of warm and cold measured with the VAS and core and skin temperatures. Under the high-temperature condition, there were positive correlations of both core and skin temperature with feelings of warm and negative correlations of skin temperature with feelings of cold. The correlations were somewhat greater under MDMA than placebo. With one exception, there were no significant correlations under the low-temperature condition.

Discussion

MDMA at a dose of 2 mg kg^{-1} produced statistically significant elevations in core body temperature under both warm and cold conditions, with increases in the range of 0.6–0.3°C, respectively. In previous laboratory studies in humans using slightly smaller doses (1.0–1.7 mg kg^{-1}), body temperature was reported to increase about 0.2–0.3°C, but these increases were not statistically significant (Grob et al. 1996; Mas et al. 1999). In addition, absolute core temperatures were higher following MDMA in the warm environment compared to the cold environment. However, core temperature was also higher in the warm environment compared to the cold environment following the administration of placebo. The interpretation of these findings is that both ambient temperature and MDMA influenced core body temperature, and although the increases appeared greater under the warm environment, there was no statistical evidence of an interaction. The elevations were most likely due to increases in metabolic rate following MDMA, which increased an average of approximately 50–100%. This increase was comparable to or greater than that achieved by sympathomimetics and direct adrenergic agonists, which are thought to mediate nonshivering thermogenesis (Hoeks et al. 2003). It is noteworthy in this regard that the MDMA-induced elevation of metabolism occurred independently of demands for thermoregulatory thermogenesis. Thus, although the MDMA-induced elevation of metabolism was comparable to that induced by mild cold stress alone, the drug-induced thermogenesis did not mitigate the need for shivering and nonshivering thermoregulatory thermogenenesis. These observations suggest that heat generated by MDMA is not registered by the same physiological mechanisms that maintain body temperature. Finally, unlike adrenergic agonists, thermogenesis induced by MDMA was not associated with changes in RQ. This observation suggests that MDMA and sympathomimetics induce thermogenesis by distinct metabolic mechanisms (Schiffelers et al. 2001).

The results at warm ambient temperature are in partial agreement with those in rats. Gordon et al. (1991) found increased T_c and metabolic rate at ambient temperatures at 30°C. This study and that of Malberg and Seiden (1998) also found decreased T_c at cooler ambient temperatures in contrast to our results. This discrepancy may be due to species differences in thermoregulation, in MDMA pharmacology, or both (see Green et al. 2003). Nevertheless, the rat studies suggest that MDMA causes a complete loss of thermoregulatory function. Two aspects of the present study argue against this. First, the T_c shivering threshold was unchanged by MDMA. Second, perceptions of warmth and cold were not modified by the drug.

The finding of intact thermal perception is in contrast to that of a recent study of cocaine-induced hyperthermia in humans (Crandall et al. 2002). That investigation found that cocaine impaired the perception of heat stress but also found a reduction in sweating. This reduction is similar to the finding in the present study that sweating following MDMA in the warm environment occurred at a significantly higher core body temperature. The difference in temperature perceptions likely reflects differences in the central mechanisms of cocaine and MDMA.

Although we found statistically significant hyperthermia in warm and cold conditions, the magnitude of T_c elevation was modest, about 0.6°C. How can the fatal hyperthermia of MDMA, with average T_c of 41.6°C (Henry 2000) be explained? First, T_c will also be elevated by vigorous physical activity such as dancing. Second, the concurrent use of other hyperthermic drugs such as cocaine (Crandall et al. 2002) and methamphetamine (Gouzoulis-Mayfrank et al. 1999) can also exert an independent but additive influence. Finally, it has been proposed that some cases of MDMA hyperthermia are caused by a mutation in the CYP2D6 gene (Tucker et al. 1994) that reduces metabolism, thus possibly increasing duration of action resulting in drug accumulation following multiple drug exposures.

In addition to the temperature-related effects, MDMA also significantly increased heart rate and blood pressure, in agreement with previous findings (Vollenweider et al. 1998; Lester et al. 2000; Tancer and Johanson 2003), and these changes were similar under both temperature conditions. Likewise, the subjective effects of MDMA were similar to those previously reported (Tancer and Johanson 2003), although they were generally of a smaller magnitude. Furthermore, they were completely unaffected by ambient temperature.

While these findings are provocative, there are several limitations in the present study. Only a single dose of MDMA was administered, whereas in the natural environment, individuals may take higher doses repeatedly in combination with other drugs such as cocaine and methamphetamine, and thus, the effects may be even greater. Unfortunately both federal and local agencies have required that the maximum number of ingestions in laboratory studies be limited to two or three, making it impossible to test additional doses or temperatures with the present design.

In conclusion, MDMA produced hyperthermia at warm and cold ambient temperatures most likely due to increased metabolic rate and also to inhibition of sweating. However, a complete loss of thermoregulation did not occur, as core body temperature also increased in the cold environment, and shivering and thermal perceptions were not impaired. Given that neurotoxicity may be related to core body temperature (Malberg and Seiden 1998), these findings should be of some concern, particularly given the recent initiation of investigations of MDMA's putative therapeutic effects. Furthermore, unlike rats, moving to a cold environment does not protect completely against increases in core body temperature, although it is true that the absolute core temperature is greater in the warm environment. Finally, there is evidence that the increases are actually mediated by increases in metabolism that may involve mechanisms related to thermogenesis. Because of the recent increase in abuse of methamphetamine, future studies comparing MDMA and methamphetamine are warranted, particularly those designed to investigate neurochemical mechanisms of action.

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