sychopharmacology (1994) 114:505–508

Psychopharmacology

Effect of ambient temperature on hyperthermia and hyperkinesis induced by 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") in rats

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Received 12 July 1993 / Final version 27 August 1993

Abstract. A stress-free, biotelemetric monitoring technique was used to investigate the effects of ambient temperature (T_a) on the hyperthermic and hyperkinetic effects of 3,4-methylenedioxymethamphetamine. In the first experiment a single injection of 5.0 or 7.5 mg/kg MDMA produced hyperthermia in rats maintained at a T_a of 24° C but hypothermia in rats maintained at a T_a of 11° C for 24 h prior to the injection. In contrast, hyperkinesis was induced at both T_as. In the second experiment, the effects of acute MDMA administration was compared in rats maintained at a standard T_a of 24° C and in rats which were placed in a cool (11° C) room for a brief (90-min) period commencing 30 min after the injection. The brief exposure to the cool environment produced significant attenuation of MDMA-induced hyperthermia but did not affect the magnitude of hyperkinesis. The implications of the results for the understanding of the thermotoxic effects of MDMA in human drug users are discussed.

Key words: MDMA – Hyperthermia – Hyperkinesis – Ambient temperature

Recent deaths from "heatstroke" in humans following the use of MDMA at dance clubs or "raves" may reflect a lethal interaction of drug-induced hyperthermia, high ambient temperature and sustained physical activity (Henry et al. 1992; Screaton et al. 1992; Tehan 1993). Although previous studies on rats have shown that MDMA, like amphetamine, produces stimulant effects (hyperthermia, hyperkinesis, and increased metabolic rate) which are related to its effects on 5-HT release (Yehuda and Kahn 1977; Nash et al. 1988), only one study has provided data relating drug effect to ambient temperature which is of direct relevance to the possible interactive effects referred to above (Gordon et al. 1991), and this is flawed by the facts that a) very high doses were used (20–30 mg/kg MDMA), producing mortility rates of between 30 and 100 %, b) activity levels were not measured, and c) in all but one of the experiments reported, body temperature was sampled only once following drug administration and using a measurement procedure (rectal thermometer probing) which produces a significant stress-related hyperthermia itself (Eikelboom 1986; Peris and Cunningham 1986).

In the experiments to be described here, the thermic and kinetic responses of rats injected with different doses of MDMA were continuously monitored using a computerised, remote biotelemetry system. The advantages of this technique in psychopharmacological research have been emphasized elsewhere (Dafters and Taggart 1990, 1992) but include: the elimination of confounding effects of stress induced by handling and other experimental procedures, the ability to time doses coincident with a particular phase of the circadian rhythm which reduces the confounding effects of such rhythms, and the capacity to monitor responses for a continuous extended period following drug administration which allows the detection of complex effects (such as biphasic response patterns) which may be missed with traditional techniques.

The purpose of this study was to examine the relationship between MDMA-induced hyperthermia, ambient temperature and activity level. In particular, it sought to confirm, but using a stress-free measurement procedure and sub-lethal dose levels, the dependency of MDMA's thermic response on ambient temperature (T_a). In addition, it sought to clarify the nature of the interaction between thermic and kinetic effects of the drug. The facility to describe the detailed profile and time-course of drug responses which biotelemetry provides may allow us to rule out certain alternative hypotheses about drug effects. For example, it is possible that the hyperthermia is secondary to the generation of body heat caused by MDMA-induced hyperkinesis rather than to the direct serotonergic and/or dopaminergic effects which have been previously postulated (Yamamoto and Spanos 1988; Spanos and Yamamoto 1989). Substantial differences in the time-course and/or direction of thermic and kinetic responses of the drug would be incompatible with such an explanation.

Materials and methods

Animals

Male Wistar rats (B & K Supplies Ltd, Hull, UK) were housed individually in plastic cages (40 × 25 × 20 cm) with free access to food and water, maintained on a standard 12:12 h light:dark cycle and weighed 250–300 g at the start of the experiments. The temperature of the holding rooms was normally maintained at 24° C but could be changed when appropriate to any value (± 1° C).

Drugs

3,4-Methylenedioxymethamphetamine (MDMA) purchased from Sigma, Poole, Dorset, UK was dissolved in 0.9% physiological saline and injected subcutaneously in the neck. Saline injections (1 ml kg body weight) were administered by the same route.

Apparatus

Temperature and activity were monitored continuously by means of a computer-controlled biotelemetry system (Dataquest III, Mini-Mitter Co Inc, Ore. USA). This system has been described fully elsewhere (Cunningham and Peris 1983) but briefly, wax-coated transmitters (Mini-Mitter model VM-FH) implanted under anaesthesia (Hypnorm/Hypnovel) in the rats' abdominal cavity emit radiofrequency pulses (range 300–600 cps), the frequency of which varies linearly with temperature in the physiological range. Receivers located beneath each rat cage transmit the frequency information to an IBM-compatible computer which records and analyzes the data. The receivers also detect moment-to-moment changes in position and orientation of the transmitters caused by body movements which are translated into activity counts. In the present experiments the system was configured for 24 h per day monitoring with recording of temperature and activity counts every 20 min.

Procedures

Pre-drug treatment. Fourteen days prior to drug treatments, transmitters were surgically implanted and temperature and activity levels were subsequently monitored at 20-min intervals, 24 h per day to establish normal circadian rhythms. During this familiarization phase the rats were routinely weighed, handled for a few minutes and given a single saline injection each day.

Drug treatment: experiment 1. On postoperative day 15 the rats were arbitrarily assigned to one of four groups ($n = 12$) which received a single control injection of saline or 2.5, 5.0 or 7.5 mg/kg MDMA. Half of the rats in each group were maintained at the standard ambient temperature ($T_a = 24°$ C); half were maintained at $T_a = 11°$ C for a period of 48 h commencing 24 h before the drug administration. Because drug-induced hyperthermic effects may be significantly masked if the drug is administered during the high or ascending phase of the diurnal temperature cycle (Dafters and Taggart 1990), rats were injected at 1400 hours, midway through the low (light) phase of their activity and temperature cycles.

Drug treatment: experiment 2. The first experiment investigated the effects of different doses of MDMA administered at two different steady-state ambient temperatures. In experiment 2 an attempt was made to examine the effects on MDMA-induced hyperthermia of a sudden and temporary reduction in ambient temperature in a way which simulates the use of "chill-out" facilities by human MDMA abusers at dance clubs. Thus, following the standard 14-day handling and injection familiarization phase described above (at $T_a = 24°$ C) one half of the subjects in each of four groups [saline and 2.5, 5.0 or 7.5 mg/kg MDMA ($n = 16$)] received a single injection 30 min before being transferred to a "cool" room ($T_a = 11°$ C) for 90 min. The other half of each group remained in the standard "warm" room ($T_a = 24°$ C). At the end of the 90-min period the "cooled" rats were moved back into the standard 24° C environment for the remainder of the monitoring period. Data were analysed using multivariate analysis of variance and subsequent Scheffé tests to examine individual group differences.

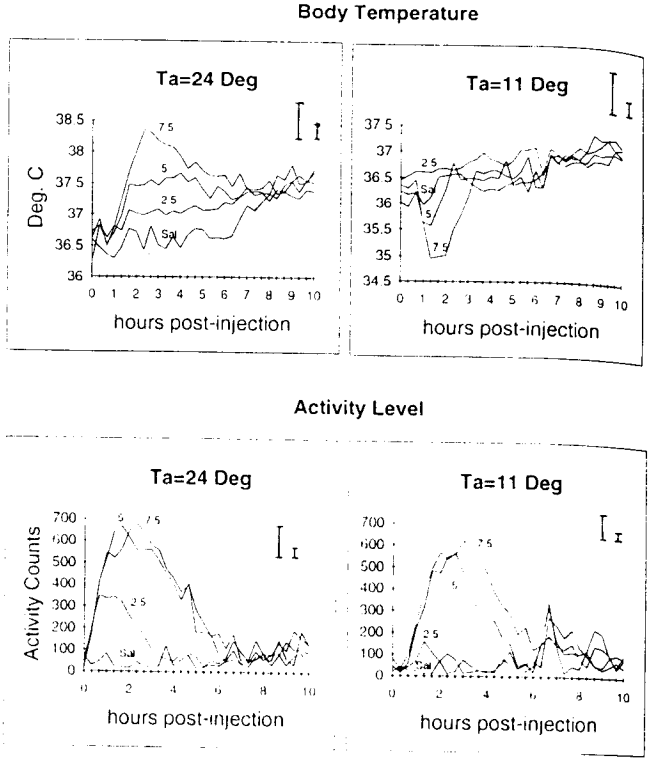

Fig. 1. Mean temperature (*upper*) and activity (*lower*) scores in experiment 1, plotted at 20-min intervals over a 10-h post-injection period. Numbers on graphs represent dose of MDMA (mg/kg). SEMs have been omitted from graphs for clarity but *vertical lines* and *bars* represent maximum and minimum SEM values for each graph

Results

Experiment 1

Figure 1 shows the group mean body temperatures (upper) and activity scores (lower) at ambient temperatures of 24° C and 11° C over a 10-h period following drug administration. MDMA produced dose-related changes in body temperature and activity. The body temperature changes were highly dependent on ambient temperature, with the two highest doses producing hyperthermia at $T_a = 24°$ C and hypothermia at $T_a = 11°$ C. This was not the case for activity which increased with dose at both T_as.

Statistical analysis was performed on the peak temperature and activity response data summarised in Table 1.

Analysis of the temperature change data revealed significant main effects of Dose [$F(3,40) = 2.926$, $P < 0.05$] and Ambient temperature [$F(1,40) = 48.99$, $P < 0.0001$] and a significant interaction of the factors [$F(3,40) = 24.31$, $P < 0.0001$]. Post-hoc tests on the interaction using the Scheffé test confirmed the suggestion

Table 1. Peak temperature and activity responses (± SEM) in experiments 1 and 2, calculated as the difference score between the maximum (or minimum) reading in the 5-h post-injection period and the last pre-injection reading

	Body temp (°C)		Activity (counts)	
Experiment 1	$T_a = 11°$	$T_a = 24°$	$T_a = 11°$	$T_a = 24°$
Saline	0.75 ± 0.46	− 0.12 ± 0.39	143 ± 24	62 ± 66
MDMA (2.5 mg/kg)	0.66 ± 0.15	1.11 ± 0.19	178 ± 72	400 ± 56
MDMA (5.0 mg/kg)	− 1.23 ± 0.17	1.31 ± 0.22	545 ± 53	657 ± 64
MDMA (7.5 mg/kg)	− 1.65 ± 0.27	2.15 ± 0.37	658 ± 84	824 ± 98
Experiment 2				
Saline	− 0.24 ± 0.26	− 0.13 ± 0.21	89 ± 36	102 ± 43
MDMA (2.5 mg/kg)	0.41 ± 0.44	0.72 ± 0.31	625 ± 69	440 ± 54
MDMA (5.0 mg/kg)	0.64 ± 0.41	1.33 ± 0.24	889 ± 90	833 ± 88
MDMA (7.5 mg/kg)	1.05 ± 0.66	2.47 ± 0.20	767 ± 91	870 ± 72

from Table 1 that ambient temperature significantly affected the magnitude and direction of thermic response in the 5.0 and 7.5 mg dose groups ($P < 0.005$ and $P < 0.0001$, respectively) but not in the saline or 2.5 mg groups ($P > 0.05$). A similar analysis of the activity change data revealed a highly significant main effect of Dose [$F(3,40) = 36.67$, $P < 0.0001$] and a slightly significant main effect of Ambient temperature [$F(1,40) = 4.77$, $P < 0.05$]. The interaction of effects was not significant ($P > 0.05$), and, in contrast to the temperature data, Scheffé tests did not find any differences in the direction of kinetic response at the two T_as ($P > 0.05$ in each dose group).

Experiment 2

The first experiment clearly showed that prolonged exposure to a cool environment has a marked effect on the strength and direction of the effects of MDMA effects. Experiment 2 sought to discover whether a brief (90-min) exposure to a cool (11° C) environment shortly following administration of MDMA could also affect thermic and/or kinetic responses. The peak temperature and activity changes are shown in Table 1 (lower). Examining the temperature changes, there were significant main effects of Dose [$F(3,56) = 9.56$, $P < 0.0001$] and Ambient temperature [$F(1,56) = 5.8$, $P < 0.05$] showing that exposure to the cool environment had reduced MDMA-induced hyperthermia. The interaction of main effects was not significant ($P > 0.05$). Analysis of the peak activity data found a highly significant Dose effect [$F(3,55) = 47.08$, $P < 0.0001$] but no effect of Ambient temperature ($P > 0.05$).

Discussion

The results of the experiments confirm and extend the previous findings of Gordon et al. (1991) in showing that, under stress-free monitoring conditions and employing sub-lethal doses, acute MDMA administration produces dose-related changes in body temperature which are strongly dependent on T_a. Experiment 1 showed that a single injection of 5.0 or 7.5 mg/kg MDMA, which at a temperature of 24° C resulted in hyperthermia, produced a marked hypothermia in rats pre-exposed to a cool (11° C) environment for a prolonged period commencing 24 h before the injection. However, MDMA produced dose-related hyperkinesis at both ambient temperatures. The results of experiment 2 established the efficacy of even a relatively short exposure to a cool environment in reducing the hyperthermic response and again, it is significant that marked differences in hyperthermic response between the standard and cooled groups were not mirrored in the hyperkinetic response - T_a had no effect on the magnitude of the drug-induced hyperkinesis. Thus, in both experiments there was evidence for a dissociation of thermic and kinetic effects. Ambient temperature produced changes in thermic response which were either absent (experiment 2) or opposite in direction (experiment 1) in the kinetic response.

Taken together these results provide no support for the notion that hyperthermia is secondary to drug-induced hyperkinesis. In addition, the fact that the same dose of drug can produce a simultaneous decrease in body temperature and an increase in activity level suggests that the degree of physical activity per se is not a major factor in the aetiology of the toxic heatstroke syndrome experienced by some human MDMA users. However, the profound effects of T_a do suggest that the use of "chill-out" to reduce MDMA-induced hyperthermia may be an effective treatment.

The differences in the profiles of thermic and kinetic responses shown here may partly reflect differences between serotonergic and dopaminergic properties of MDMA. Serotonergic pathways play a crucial role in thermoregulation. MDMA administration causes release of 5-HT in both in vitro and in vivo preparations with subsequent stimulation of central serotonergic pathways (Johnson et al. 1986; Schmidt et al. 1987). In addition, microinjections of 5-HT into the anterior hypothalamus results in heat producing/conserving responses which result in hyperthermia (Jacob and Girault 1979; Myers 1980). However, there is evidence that the hyperkinetic effects of MDMA are more closely associated with the dopaminergic effects of the drug (Robinson and Becker 1986). For example, the time course of in vivo MDMA-induced dopamine release has been shown to closely parallel the time-course of induced hyperkinesis (Yamamoto and Spanos 1988), and in addition, it is reported that whereas serotonergic syndrome behaviors (low body posture, forepaw treading, headweaving) show dose-related increases in both intensity and duration, locomotor

activity varied only in intensity (Spanos and Yamamoto 1989). The dual action of MDMA on serotonergic and dopaminergic systems and the complex interplay between the two systems (Ugedo et al. 1989) certainly complicates the interpretation and the possibilities of pharmacological intervention in the thermotoxic effects of the drug.

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