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ORIGINAL INVESTIGATION

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Effect of ambient temperature and a prior neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA) on the hyperthermic response of rats to a single or repeated ('binge' ingestion) low dose of MDMA

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Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) administration to rats produces acute hyperthermia and long-term neurotoxic damage to 5-hydroxytryptamine (serotonin, 5-HT) neurones. *Objective:* We wished to examine MDMA-induced hyperthermia in rats housed at normal (19°C) and high (30°C) room temperatures and investigate the effect of a prior neurotoxic lesion. *Methods:* Rectal temperature was measured after administration of single or repeated doses of MDMA to rats housed at 19°C and 30°C. *Results:* MDMA (5 mg/kg IP) produced a sustained hyperthermic response in rats housed at 30°C, but not in rats housed at 19°C. A prior (5 weeks earlier) neurotoxic dose of MDMA (12.5 mg/kg IP) resulted in MDMA (5 mg/kg) producing a greater hyperthermic response in rats housed at 30°C than in non-pre-treated animals. Repeated MDMA administration (binge dosing; 2, 4 or 6 mg/kg ×3) produced dose-dependent hyperthermia in rats housed at 19°C, with MDMA (2 mg/kg ×3) having little effect. However, this dose produced significant hyperthermia (≥2°C above control values)in rats housed at 30°C following the third dose. A prior neurotoxic dose of MDMA resulted in MDMA (2 mg/kg ×3) producing marked hyperthermia (>1°C) after the first dose and severe hyperthermia (≥2°C) after the third dose. *Conclusions:* MDMA administration to rats housed at 30°C produces a more severe hyperthermic response than that seen in rats housed at 19°C. A prior neurotoxic dose enhances the response further in animals housed at 30°C. Binge dosing produces a higher final peak response than a similar non-divided dose. This effect is more marked in animals housed at high room temperature. These data may have implications for recreational users of MDMA in hot environments, particularly those who may have damaged serotoninergic neurones because of prior heavy or frequent use of the drug.

Keywords 3,4-Methylenedioxymethamphetamine · Ecstasy · MDMA · Hyperthermia · 5-Hydroxytryptamine · Neurotoxicity · Thermoregulation

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Introduction

Administration of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') to rats produces two major changes in the animals. The first is an acute hyperthermic response, which is dose dependent and occurs in the first few hours following administration of the drug (Nash et al. 1988; Dafters 1994; O'Shea et al. 1998). A recent study demonstrated that this response is primarily mediated by enhanced dopamine release and stimulation of dopamine D_1 receptors (Mechan et al. 2002), an interpretation supported by similar studies on the hyperthermic response which follows methamphetamine administration (Sugimoto et al. 2001).

The second change, which occurs some days following administration of high or repeated doses of the drug, is a selective neurotoxic loss of 5-HT content in several regions of the forebrain (Battaglia et al. 1987; Slikker et al. 1988; Colado et al. 1993; O'Shea et al. 1998). There is good evidence that this loss reflects neurodegeneration of 5-HT nerve endings (Battaglia et al. 1987; O'Hearn et al. 1988; Molliver et al. 1990; Hewitt and Green 1994).

Both of the MDMA-induced responses that have been observed in rats may also occur in human recreational users of MDMA. A hyperthermic response is a well established adverse effect of MDMA ingestion (Brown and Osterloh 1987; Henry et al. 1992; Green et al. 2003) and while it is not normally a problem in most users, when it does occur it can result in other associated major clinical events including potentially life-threatening problems such as rhabdomolysis, intravascular coagulation and acute renal failure (Brown and Osterloh 1987; Chadwick et al. 1991; Henry et al. 1992; McCann et al. 1996; Green et al. 2003). Whether MDMA also induces neurotoxic damage to 5-HT nerve endings in the brain of heavy recreational users of MDMA remains controversial, but there are sufficient clinical data now available to indicate the possibility that changes do occur (McCann et al. 1998; Ricaurte et al. 2000; Reneman et al. 2002a, 2002b).

Recent studies in rats have shown that one of the long-term consequences of MDMA-induced neurodegeneration is an impairment of thermoregulation, the animals being less able to lose body heat when exposed to high ambient temperature conditions (Dafters and Lynch 1998; Mechan et al. 2001). Since humans often take MDMA recreationally in hot crowded dance-club conditions, these data suggest that heavy recreational users of MDMA (if they have damaged serotoninergic function) may have thermoregulatory problems when taking further doses of MDMA when in a hot environment.

We have now, therefore, examined the effect of MDMA administration on body temperature in certain situations. First, we examined the effect of a single MDMA administration on rectal temperature of rats housed either in a room at a normal ambient temperature (19°C) or in a hot room (30°C). Second, the same response was examined in rats that had been given a prior neurotoxic dose of MDMA to simulate possible prior neurotoxic damage to 5-HT neurones in the brains of heavy recreational users of the drug. In a third series of experiments, we examined the rectal temperature response of rats present in normal or high ambient temperature conditions when MDMA was given three times at 3-h intervals to simulate 'binge' ingestion (several doses on a single occasion), as is sometimes practised by recreational users (Weir 2000; Parrott 2002) and which has been modelled in a recent preclinical study (Badon et al. 2002). Finally, this study was repeated in rats given a prior neurotoxic dose of MDMA.

Materials and methods

Animals and drug administration

Male Dark Agouti (DA) rats, weighing 200–260 g, were used in all experiments (Harlan UK Ltd., Bicester, Oxon, UK, and Interfauna, Barcelona, Spain). The animals were housed in groups of six, at an ambient temperature of 20±2°C and a 12-h/12-h light/dark cycle (lights on at 0730 hours). Both food and water were freely provided.

All procedures were carried out following approval by the University Experimental Ethics Committee and in accordance with United Kingdom Home Office regulations, which ensure humane and proper care of research animals.

(±)-MDMA obtained from either Dr. P. Guiry, University College, Dublin, or NIDA (Research Triangle Park, North Carolina, USA) was dissolved in 0.9% w/v saline and injected IP. The dose administered to produce neurotoxic damage was 12.5 mg/kg, which has previously been shown to produce a defined but modest (approximately 30%) loss of 5-HT in the forebrain (Mechan et al. 2001, 2002).

Studies examining the acute hyperthermic response to MDMA injection used doses of 2, 4, 5 or 6 mg/kg, as detailed in the results. All studies were conducted with rats grouped in batches of 6, both to simulate crowded dance-club conditions and because amphetamines produce more marked behavioural effects in grouped animals (Chance 1947; Morton et al. 2001; Fantegrossi et al. 2003). Animals were tested in a cohort group that had been both housed and pre-treated together. Testing was performed in polypropylene cages (50×25×15 cm) with a light floor covering of sawdust. Appropriate control (saline injected) groups were always run at the same time as the MDMA-injected experimental groups.

Ambient room temperature was maintained between either 19°C and 21°C (referred to in text as 19°C) or 30°C and 32°C (referred to as 30°C) during the studies on the hyperthermic effect of MDMA administration. Animals were housed in these conditions for 1 h before drug or vehicle administration. Rats were only ever used once in the investigations reported.

Temperature measurement

Temperature measurement was performed using an MC 8700 thermometer, with digital readout, and a H-RB3 rectal temperature probe (EXACON A/S, Roskilde, Denmark) lubricated with a lanolin hand cream. Each rat was lightly restrained by hand for approximately 20 s while the probe was inserted approximately 2.5 cm into its rectum and a steady reading was obtained.

Analysis of data

All studies measured rectal temperature in groups of six rats. Rats were injected with saline or MDMA and temperature measured at various times thereafter. Most studies were performed in groups of animals that had been injected with either saline or a neurotoxic dose of MDMA (12.5 mg/kg) ("lesioned") 5 weeks previously to allow comparison of responses to acute MDMA injections in control and lesioned animals. The rectal temperature at each time point of the MDMA-treated rat was subtracted from the mean value of the temperature of the saline-injected control group thereby providing a mean±SEM value of the MDMA-induced temperature change and most data are presented thus. Addition of the temperature change at every time point of the study for each individual animal also allowed a calculation of the overall temperature change over the observation period, an approximation of the total area under the temperature curve (AUC). This allowed a comparison of the size of the response in each group and is also presented graphically in the results section.

Data from the AUC and peak temperature results were analysed using analysis of variance (ANOVA) plus Bonferroni correction for 't'-test. Statistical analyses of the temperature measurements were performed using the statistical computer package BMDP/386 Dynamic (BMDP Statistical Solutions, Cork, Eire). Data were analysed by ANOVA with repeated measures (program 2 V). Treatment was used as the between-subjects factor and time as the repeated measure. The ANOVA values represent a main effect of treatment.

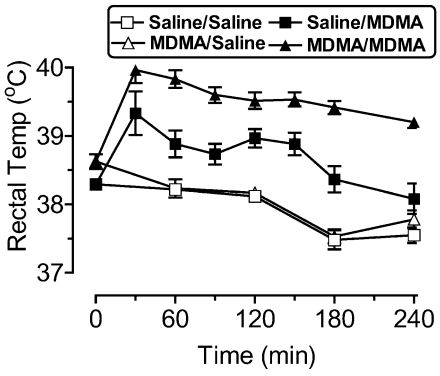

Fig. 1 The acute temperature response of rats administered a challenge injection of saline 5 weeks after a previous injection of saline (*open squares*) or 3,4-methylenedioxymethamphetamine (MDMA), 12.5 mg/kg (*open triangles*) and rats administered a challenge injection of MDMA (5 mg/kg) 5 weeks after a previous injection of saline (*closed squares*) or MDMA, 12.5 mg/kg (*closed triangles*). The challenge injections were administered after acclimatisation for 1 h at 30°C and the animals maintained at this high ambient temperature for a further 4 h. All groups were examined together, but fewer measures were made in the saline-injected groups. MDMA administration to rats previously treated with saline produced a hyperthermic response ($F_{1,10}$=21.07, P<0.01). MDMA neurotoxic pre-treatment significantly augmented this hyperthermic response ($F_{1,10}$=23.63, P<0.001). Results are shown as mean ±SEM, n=6 per group

Results

Effect of MDMA (5 mg/kg) on rectal temperature in normal and lesioned rats at normal and high ambient temperature rooms

Rats administered MDMA (5 mg/kg) when housed at high ambient temperature had a distinct hyperthermic response (Fig. 1). Rats previously treated with a neurotoxic dose of MDMA (12.5 mg/kg) 5 weeks before also had a clear hyperthermic response to MDMA (5 mg/kg) when housed at high ambient temperature, and this response was substantially greater than that seen in the rats not pre-treated with a neurotoxic dose of MDMA (Fig. 1). This neurotoxic pre-treatment had no effect on the temperature response to saline (Fig. 1).

In contrast, a dose of MDMA (5 mg/kg) administered to rats housed at 19°C failed to induce a significant increase in rectal temperature (Fig. 2a). A prior neurotoxic lesion had no effect on the size of the MDMA-induced rectal temperature response, the temperature of the rats not being significantly different from saline-injected animals (Fig. 2a). These results are in contrast with those obtained at high ambient temperature, as mentioned above, and which are also included for comparison in Fig. 2a. The difference in the temperature of the rats of MDMA (5 mg/kg) when housed at 30°C compared with those housed at 19°C and the further enhancement in rats pre-treated with a neurotoxic dose of MDMA is emphasised by the AUC data presented in Fig. 2b.

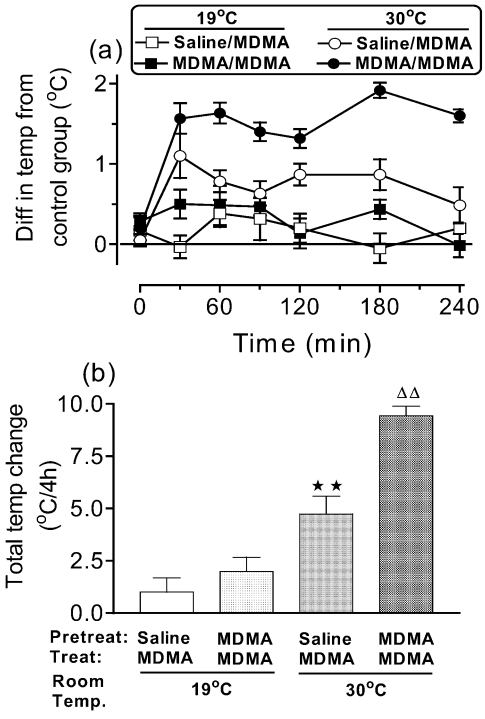

Fig. 2 **a** Effect of 3,4-methylenedioxymethamphetamine (MDMA; 5 mg/kg) administered at 19°C or 30°C on the rectal temperatures of rats pre-treated 5 weeks before with saline (*open symbols*) or MDMA, 12.5 mg/kg (*closed symbols*). Data represent the difference in rectal temperature from an appropriate control group given saline (shown as the *zero line*). There was an overall effect of treatment ($F_{1,3}$=26.57, P<0.001). There was no difference in the temperature response to MDMA given at 19°C between the saline- and MDMA-pre-treated groups ($F_{1,10}$=1.01, P=0.34). Pre-treated (lesioned) rats different from non-lesioned at high ambient temperature ($F_{1,10}$=17.40, P<0.01); non-lesioned rats at high temperature different from those at normal ambient temperature ($F_{1,10}$=8.18, P<0.05). **b** The total temperature change (AUC) over the 4 h of observation of rats administered saline or MDMA (5 mg/kg) following pre-treatment with saline or MDMA (12.5 mg/kg). Response shown of rats housed at 19°C or 30°C. **Different from similarly treated rats housed at 19°C, P<0.01. ▲▲Different from both similarly treated rats housed at 19°C and saline-pre-treated rats housed at 30°C, P<0.01. Results are shown as mean ±SEM, n=6 per group

Effect of repeated doses of MDMA when housed in a normal ambient temperature

A study was performed using three doses of MDMA (2, 4 and 6 mg/kg) given at 3-h intervals. The lowest dose produced a significant hyperthermic response following the 2nd injection (Fig. 3), while the marginal hyperthermia induced by a dose of 4 mg/kg was enhanced and sustained by the subsequent doses (Fig. 3). The highest dose of MDMA (6 mg/kg) produced a rapid clear hyperthermia following each injection (Fig. 3). The overall total temperature response was linearly dose dependent when plotted using linear regression of the mean response at each dose (r=0.95).

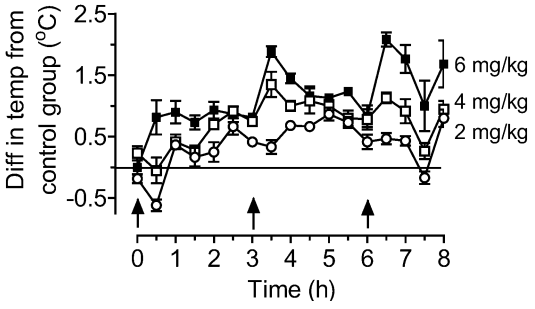

Fig. 3 The difference in rectal temperature of rats given repeated doses of 3,4-methylenedioxymethamphetamine (MDMA; 2, 4 or 6 mg/kg), as shown by *arrows*, from the temperature response of a saline-injected control group (shown as the *zero line*). There was an overall effect of treatment ($F_{1,2}$=35.62, P<0.001). MDMA at 4 mg/kg produced a hyperthermic response which was greater than that produced at 2 mg/kg ($F_{1,10}$=17.27, P<0.01). The hyperthermia following the dose of 4 mg/kg was enhanced at the dose of 6 mg/kg ($F_{1,10}$=18.27, P<0.01). Results are shown as mean ±SEM, n=6 per group

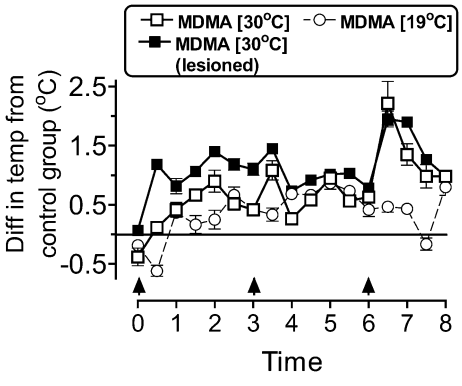

Fig. 4 The difference in rectal temperature of rats given repeated doses of 3,4-methylenedioxymethamphetamine (MDMA; 2 mg/kg, marked by the *arrows*) at 19°C or 30°C, from the temperature response of an appropriate saline-injected control group. Groups shown had been pre-treated 5 weeks earlier with either saline (*open symbols*) or MDMA, 12.5 mg/kg (*closed symbol*). There was an overall effect of treatment ($F_{1,2}$=37.41, P<0.001). MDMA at 30°C produced a greater overall hyperthermic response compared with that at 19°C ($F_{1,10}$=14.47, P<0.01), which was further enhanced by MDMA neurotoxic pre-treatment ($F_{1,10}$=16.74, P<0.01). Results are shown as mean ±SEM, n=6 per group. The data of the group examined in a 19°C environment is taken from the data presented in Fig. 3 and is added for comparison

Effect of high ambient temperature on the hyperthermic response of rats to repeated doses of MDMA in control and lesioned rats

The temperature response of rats housed at 30°C to a dose of MDMA (2 mg/kg ×3) was similar in magnitude following the first two injections to that seen in rats housed at 19°C (Fig. 4). However, the third dose produced a substantial hyperthermia in rats housed at 30°C in contrast to those housed at normal room temperature (Fig. 4). Rats with a prior MDMA-induced lesion displayed a marked hyperthermia following the first dose that was sustained by the second dose. The third dose produced a further marked increase in the hyperthermic response (Fig. 4).

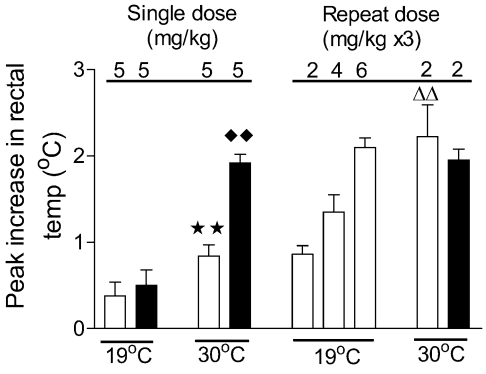

Fig. 5 The peak increase in rectal temperature after single or repeated challenge doses of 3,4-methylenedioxymethamphetamine (MDMA) following subtraction of the appropriate saline-injected control value. Rats were treated with saline (*open bars*) or MDMA (12.5 mg/kg, *closed bars*) 5 weeks earlier. Challenge doses of MDMA (5 mg/kg) were administered at 19°C or 30°C as indicated. **Different from saline injected group at 19°C; P<0.001, ◆◆Different from non-lesioned group; P<0.001, △△Different from group given 2 mg/kg when housed at 19°C; P<0.01 (all analysed by ANOVA plus Bonferroni correction for 't'-test). Results are shown as mean ±SEM, n=6 per group

Analysis of the overall AUC temperature change over 8 h (see Methods) produced the following data. In 19°C housing, MDMA (2 mg/kg ×3): 6.47±0.89, MDMA (4 mg/kg ×3): 12.15±1.21, MDMA (6 mg/kg ×3): 19.22±1.51. In 30°C housing following MDMA (2 mg/kg ×3), saline pre-treatment group: 12.48±1.32, neurotoxic MDMA lesion pre-treatment group: 18.77±0.63. In summary, therefore, a dose of 2 mg/kg ×3 produced an overall modest hyperthermic response in rats housed at 19°C, a greater response in rats housed at 30°C and the biggest response in lesioned rats housed at 30°C.

Peak rectal temperature following the various dose and administration regimes

The data collected allowed examination of the peak rectal temperature rise in every group examined, and these are shown in Fig. 5. The main observations are that the peak increase following MDMA (5 mg/kg) is greater in rats housed at 30°C than 19°C and that a prior neurotoxic lesion with MDMA induces a greater peak response than the non-lesioned group in rats housed at 30°C but not when the rats are housed at 19°C. During repeat dose administration, there is a dose-dependent peak response in rats housed at 19°C. When housed at 30°C, the animals given a repeated dose of 2 mg/kg had a greater peak response than those housed at 19°C, although this response is not further enhanced by a prior lesion.

Discussion

The current data demonstrate that when MDMA is administered to rats that are housed at high ambient temperature (30°C) the hyperthermic response that is induced is greater than that observed in rats housed in normal room temperature conditions. This confirms and re-enforces previous similar observations (Dafters 1995; Malberg and Seiden 1998). Acute MDMA administration appears to inhibit the normal heat-loss mechanisms in the rat (Mechan et al. 2002), so it is not surprising that there are increased problems in rats housed at high ambient temperature.

When rats have been given a prior neurotoxic dose of MDMA another problem can also occur, namely that the normal heat loss mechanisms that play a role when rats are exposed to high ambient temperature are compromised and less effective (Dafters and Lynch 1998; Mechan et al. 2001). This problem was previously demonstrated to occur when MDMA-lesioned rats were subjected to a thermoregulatory challenge by placing them in a room of ambient temperature 30°C and then returning them to normal ambient temperature conditions (Mechan et al. 2001). This defect in thermoregulation has now been observed when MDMA is administered to lesioned rats housed at 30°C. Not only did these animals have a bigger hyperthermic response than that seen in lesioned rats housed at 19°C, the response was also substantially greater than normal rats housed at 30°C and administered an acute dose of MDMA (Fig. 1). No such problem was encountered when lesioned rats were administered MDMA when housed at normal ambient temperature (Fig. 2b), which reinforces the view that this problem only manifests itself when the animals are present in high temperature conditions.

The current study also indicated that administering several lower doses of MDMA rather than one high dose (binge dosing) produced a more substantial hyperthermic response, since 2 mg/kg ×3 over 6 h produced a clear and increasing hyperthermic response after second and third injections that was significantly greater than that following a single injection of 5 mg/kg, a dose that had a marginal effect on body temperature.

Binge dosing of 2 mg/kg also had a much greater effect on body temperature in 30°C room conditions, and this response was further enhanced in MDMA-lesioned rats. What was of particular interest was the fact that the overall response and peak response of the control rats at 30°C following the third injection was very similar to the lesioned animals. Presumably the effect of the first two injections was to deplete cerebral 5-HT content to a value that was similar to that of the lesioned rats, thereby inducing similar impairment in thermoregulation (Fig. 4 and Fig. 5).

The dose of MDMA administered to produce neurotoxicity (12.5 mg/kg) has previously been found to produce a modest decrease (20–30%) of 5-HT in the brain (Mechan et al. 2001) and was chosen to produce a decrease that was similar to the loss in 5-HT markers reported to occur in heavy recreational users of MDMA (McCann et al. 1998). It is possible therefore that not only the studies on the effect of single and binge doses of MDMA in intact animals but also the studies in lesioned animals have clinical relevance. Primarily the data suggest that MDMA ingested in high ambient temperature conditions is more likely to produce a hyperthermic effect. The results also suggest that taking several low doses of MDMA over a period of time to an equivalent total of a single dose produces a final hyperthermic response that is greater than the single dose. Finally, the data suggest that heavy recreational users of MDMA (if this indeed does produce cerebral damage) may be more at risk of an adverse hyperthermic response if the acute dose of MDMA is taken in a hot environment. However, what constitutes a "hot" environment for humans will not be the same as that established for rats or even primates and is likely to be much higher than for these animals, since hair-covered animals have fewer mechanisms available to lose temperature—for example, the major heat-loss mechanism available to rats is vasodilatation of blood vessels in the tail (Mechan et al. 2002).

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