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ORIGINAL INVESTIGATION

**Annis O. Mechan · Esther O'Shea · J. Martin Elliott**
**Maria Isabel Colado · A. Richard Green**

# A neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) to rats results in a long term defect in thermoregulation

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**Abstract** *Rationale*: 3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") administration to rats produces damage to cerebral 5-HT nerve endings; however, the long-term functional consequences of this damage are poorly understood. *Objective*: To confirm that MDMA administration produces a long-term effect on thermoregulation and investigate the mechanisms involved. *Methods*: Male Dark Agouti rats were injected with a neurotoxic dose of MDMA (12.5 mg/kg IP). Five to 6 weeks later, they were exposed to high ambient temp (30°C) for 60 min followed by a return to normal temp (20°C), with rectal temperature being measured under both conditions. Further groups of MDMA-pretreated rats were challenged with 8-OH-DPAT and their temperature response measured. *Results*: MDMA administration produced acute hyperthermia. Rectal temperature had normalised 24 h later and was similar to saline-injected controls over the following 15 days. MDMA administration produced a 37% loss in hypothalamic 5-HT content 18 days later. When MDMA-pretreated rats were subjected to high ambient temperature 33 days post-treatment, they displayed both a faster rise in rectal temperature and sustained hyperthermia when returned to normal conditions. There was no difference in their hypothermic response to the 5-$HT_{1A}$ agonist 8-OH-DPAT. *Conclusions*: A neurotoxic dose of MDMA resulted in impaired thermoregulation when rats were exposed to high ambient temperature. 5-$HT_{1A}$ receptor mechanisms were unaltered. Impaired serotonergic function following MDMA presumably alters the neurotransmitter balance, thereby compromising thermoregulation. Heavy recreational users of MDMA may also have impaired thermoregulation and thus be at greater risk of an acute adverse response to MDMA in a hot crowded dance environment.

**Keywords** MDMA · Ecstasy · 3,4-Methylenedioxymethamphetamine · 5-HT · Thermoregulation · Hyperthermia · Neurodegeneration · 8-OH-DPAT

A.O. Mechan · J.M. Elliott · A.R. Green (✉)
Department of Pharmacology,
School of Pharmacy and Pharmaceutical Sciences,
De Montfort University, The Gateway, Leicester LE1 9BH, UK
e-mail: richard.green@astrazeneca.com

E. O'Shea
School of Biomedical Sciences,
University of Nottingham Medical School,
Queen's Medical Centre, Nottingham NG7 2UH, UK

M.I Colado
Departamento de Farmacologia, Facultad de Medicina,
Universidad Complutense, 28040 Madrid, Spain

## Introduction

There is substantial evidence that administration of 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") to several species, including primates, results in damage to 5-HT nerve endings in the forebrain (O'Hearn et al. 1988; Molliver et al. 1990). This damage is reflected in a decrease in the cerebral concentration of 5-HT and in a decrease in the density of 5-HT uptake sites labelled with [$^3$H]-paroxetine (Sharkey et al. 1991; Colado et al. 1997). There is controversy as to whether similar damage might occur in the brain following regular recreational use of MDMA by humans (see Green and Goodwin 1996; Saunders 1996). However, a recent study using positron emission tomography (PET) revealed evidence for a reduction in the 5-HT transporter in the brains of human MDMA users (McCann et al. 1998). Additionally, MDMA users have been reported to display abnormal neuroendocrine and behavioural responses to the 5-HT agonist *m*-chloro-phenylpiperazine (McCann et al. 1999).

One of the major features of acute MDMA toxicity in both rodents and humans is hyperthermia (Nash et al. 1988; Gordon et al. 1991; Colado et al. 1993; Dafters 1994) which, in humans, can be fatal (Henry et al. 1992; Green et al. 1995). Since 5-HT is intimately associated with thermoregulation (Myers 1980; Salmi and Ahlenius 1998), it seemed possible that regular MDMA use might,

by producing neurotoxic degeneration of 5-HT neurones in the brain, decrease 5-HT function and thereby alter the response of individuals to either a further dose of MDMA, or to a hot and crowded environment in which MDMA is usually ingested. In rats there is evidence that prior exposure to MDMA may alter the response to a further dose of the compound, although data are conflicting with both sensitisation (Dafters 1995) and attenuation (Shankaran and Gudelsky 1999) of the temperature response being reported.

Recently, Dafters and Lynch (1998) provided evidence that prior exposure of rats to several doses of MDMA altered their ability to thermoregulate to a high ambient temperature. These investigators used a biotelemetry system for temperature measurement and their data suggested that the MDMA-treated rats showed a sustained hyperthermic response when exposed to a 60-min period of high ambient temperature. Comparison with control animals was made in two ways. Firstly, these authors examined the areas under the curves of the responses of saline and MDMA groups. However, this measure only incorporates both magnitude and duration of response and does not allow a "picture" of the change versus the parallel control group during and following the challenge. Secondly, the investigators examined the magnitude and duration of the response versus the response of the same animals before MDMA had been administered several weeks earlier. We have now repeated the study but used conventional temperature measuring techniques and have compared the response of MDMA pretreated animals with a parallel saline-injected control group.

Dafters and Lynch (1998) did not measure the loss in 5-HT content in the brain of the MDMA-treated rats. There was therefore no indication of the magnitude of the loss of cerebral 5-HT content that had resulted in the impaired thermoregulation. We therefore examined the extent of 5-HT loss in a group of Dark Agouti rats administered MDMA. Dark Agouti (DA) rats were used in this study, as we have previously shown that a single dose of MDMA produces a reliable lesion of 5-HT nerve endings in several brain regions (e.g. Colado et al. 1995, 1998; O'Shea et al. 1998), in contrast to other strains which require several doses of MDMA (see Green et al. 1995). Furthermore, we have performed several studies on the mechanisms of neurotoxicity in this strain of rat (Colado et al. 1995, 1997, 1998).

Finally, some studies were performed to try to clarify the mechanisms involved in the altered thermoregulatory response. It is probable that any long-term alteration in thermoregulation following MDMA results from the MDMA-induced loss of 5-HT in the hypothalamus and a consequent change in the balance of monoamine function, particularly 5-HT and dopamine, both of which have been demonstrated to play a role in thermoregulation (Cox 1979; Jacob and Girault 1979). Evidence for 5-$HT_{1A}$ receptor function being altered following MDMA is, at present, conflicting. Aguirre et al. (1998) reported an enhanced 8-OH-DPAT-induced hypothermic response in animals pretreated with MDMA while McNamara et al. (1995) observed no change in this response. We therefore examined this response in the same animals in which we had demonstrated an altered thermoregulatory response.

## Materials and methods

### Animals

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

### Drugs and drug administration

Drugs were administered, either intraperitoneally (IP) or subcutaneously (SC) as detailed in results. All drugs were dissolved in normal saline (NaCl 0.9% w/v). Doses of MDMA and 8-OH-DPAT are quoted as the base weight, DOI and *m*-CPP quoted as the salt weight. All drugs were obtained from Sigma-Aldrich Company Ltd (Poole, Dorset, UK).

### Temperature measurement

Temperature measurement was performed using an MC 8700 thermometer, with digital readout, and a lubricated H-RB3 rectal temperature probe (EXACON A/S, Roskilde, Denmark). 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.

### Effects of MDMA administration

#### *Acute response*

Rats were randomly assigned to experimental and control groups (*n*=12, in each case), the former being injected with MDMA (12.5 mg/kg IP) and the latter with saline, at 1000–1100 hours. Ambient temperature ($T_a$) was maintained at 20±2°C. Rectal temperature was recorded prior to injection and at regular intervals thereafter, for a total of 3.5 h.

#### *Longer term effect*

Rectal temperature in a different group of animals was measured at regular intervals, on days preceding and succeeding MDMA administration, between 1000–1100 hours.

### Thermoregulatory challenge

Five to 6 weeks following MDMA administration, both treated and control groups (*n*=12, in each case) were subjected to a thermoregulatory challenge. Rectal temperature was recorded under "normal" ambient temperature conditions, in a thermal holding room kept at 20±2°C, at –10 min and immediately prior to commencement of the challenge. The animals were then placed in a room maintained at a high ambient temperature (30±0.5°C) for 60 min, during which rectal temperature was recorded at 20-min intervals. The animals were subsequently returned to the 20°C environment and rectal temperature was monitored for a further 2.5 h.

Long-term effects of acute MDMA administration: 5-HT receptor function

Three to 4 weeks following MDMA administration, a group of both MDMA-pretreated and control groups ($n$=12, in each case) were injected with the 5-$HT_{1A}$ receptor agonist 8-OH-DPAT (0.11 mg/kg SC). Rectal temperature was recorded at –10 min and immediately prior to 8-OH-DPAT administration, then at 25 and 45 min post-injection. This experiment was repeated at two further doses of 8-OH-DPAT (0.057 and 0.09 mg/kg SC), where $n$=6 for both treated and control groups.

Studies on the temperature effect of *m*-CPP and DOI

The 5-$HT_{2C}$ agonist *m*-chlorophenylpiperazine (*m*-CPP) and the 5-$HT_{2A}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) were injected (IP) to groups of rats ($n$=4) over a range of concentrations (DOI: 1–2 mg/kg; *m*-CPP: 1.5–20 mg/kg). Rectal temperature was measured at –10 min and immediately prior to drug administration, then at regular intervals for a further 90 min.

Measurement of 5-HT and 5-HIAA

For measurement of brain 5-HT and 5-HIAA concentrations, a different group of rats was used to those studied in the thermoregulatory challenge or 8-OH-DPAT experiments to avoid any influence of experimental manipulation on the monoamine concentration, other than the effect of the MDMA administration. Since there is good evidence that brain 5-HT content is maximally decreased by 7 days and then remains lowered for several months (see Green et al. 1995), these studies were conducted 18 days after MDMA administration. Rats were killed by cervical dislocation and decapitation, the brains were rapidly removed and the hypothalamus and hippocampus dissected out on ice. Tissue was homogenised and 5-HT and 5-HIAA measured by high performance liquid chromatography (HPLC) with electrochemical detection, as described in detail by Colado et al. (1997).

Statistics

Statistical analysis was performed using GraphPad Prism (San Diego, Calif., USA). All data is presented as mean±SE. Temperature data were analysed by two-way analysis of variance (ANOVA), with treatment as the between subject factor and time as the repeated measure. Bonferroni post-hoc tests were performed where appropriate. The interaction and main effects of treatment and time are quoted. Indole levels were analysed by Student's unpaired *t*-test.

## Results

Acute effect of MDMA administration

Following administration of MDMA (12.5 mg/kg IP), rectal temperature increased by over 1.5°C (Fig. 1). The peak effect occurred around 60 min after injection and hyperthermia was sustained for over 3.5 h. Saline injection also produced a modest increase in temperature. There were significant main effects of both treatment [$F(1,77)=161.2$, $P<0.0001$] and time [$F(7,88)=24.69$, $P<0.0001$], where the temperature of the MDMA-treated group was significantly higher than that of the control group post-treatment. There was also a significant interaction between treatment and time [$F(7,88)=4.404$, $P=0.0003$] and the post-hoc test showed significant differences at each time point within the range $t_{20–210}$ ($P<0.001$).

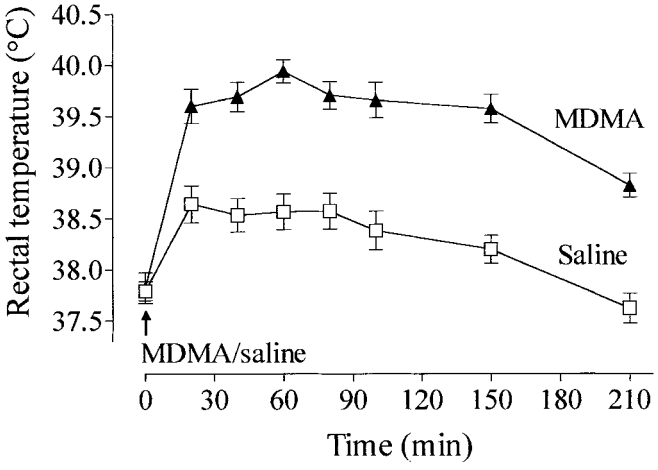


**Fig. 1** Acute effect of MDMA (12.5 mg/kg IP) on rectal temperature. Pretreatment values were: control group, 37.8±0.1°C ($n$=12), MDMA-treated group, 37.8±0.1°C ($n$=12). MDMA-treated group different from control group: $F(1,88)=187.0$, $P<0.0001$

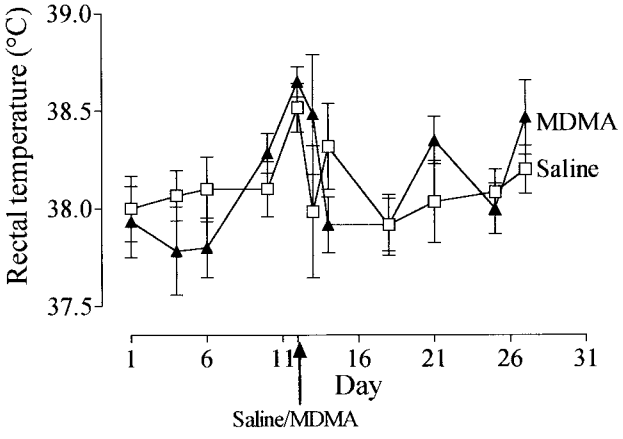


**Fig. 2** The rectal temperature of a group of saline-injected ($n$=6) and MDMA (12.5 mg/kg IP) injected rats ($n$=6) prior to and subsequent to treatment. MDMA treated group did not differ from control group prior to or subsequent to MDMA administration

Rectal temperature during 2 weeks following MDMA administration and cerebral 5-HT content

In another group of animals injected with MDMA (12.5 mg/kg IP) it was observed that the baseline temperature values were restored within 24 h of drug treatment and the temperature of both MDMA-treated and control groups remained similar over the subsequent 2 weeks (Fig. 2) [$F(1,55)=0.14$, $P=0.71$]. There was no significant interaction between treatment and time [$F(10,55)=0.98$, $P=0.47$]; the post-hoc test showed no significant differences on any of the days tested ($P>0.05$).

**Table 1** The concentration of 5-HT and 5-HIAA in the hypothalamus and hippocampus of rats administered MDMA (12.5 mg/kg) 18 days previously. Indole concentrations expressed in ng/g tissue. Results shown as mean±SE with number of observations in brackets

| | Saline | MDMA | % Loss |
|---|---|---|---|
| Hypothalamus | | | |
| 5-HT | 589±58 (6) | 367±41 (6)** | 37 |
| 5-H1AA | 339±29 (6) | 262±34 (5)* | 23 |
| Hippocampus | | | |
| 5-HT | 303±15 (6) | 186±30 (6)** | 39 |
| 5-H1AA | 431±25 (6) | 324±41 (6) | 25 |

Different from saline: *$P$=0.05, **$P$<0.01

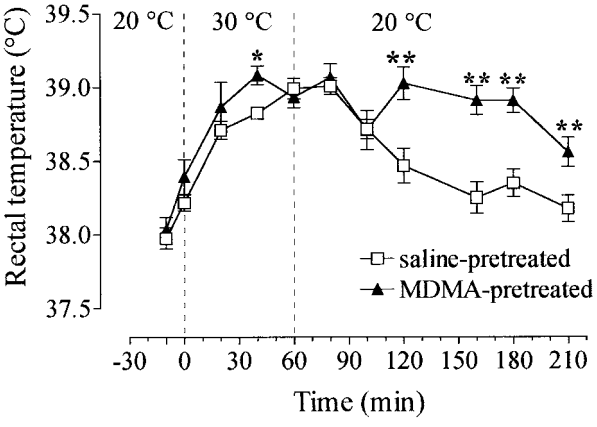


**Fig. 3** Effect of MDMA-pretreatment on rectal temperature, both during and following exposure to a high ambient temperature (30.0±0.5°C) for 60 min. Pretreatment values were: control group, 38.0±0.1°C ($n$=12) and MDMA-pretreated group, 38.0±0.1°C ($n$=12). MDMA-treated group different from control group at $t_{0–60}$ [$F$(1,44)=8.78, $P$=0.005] and at $t_{60–210}$ [$F$(1,77)=72.2, $P$<0.0001]. Pairwise comparisons *$P$<0.05; **$P$<0.001 versus control group

A separate group were injected with MDMA (12.5 mg/kg IP) and the 5-HT content of the hypothalamus and hippocampus measured 18 days later, at a time when 5-HT loss would have been maximal and constant. MDMA administration resulted in a significant loss of 5-HT in both hippocampus and hypothalamus (Table 1).

### Thermoregulatory challenge

Approximately 5 weeks (33 days) after MDMA administration, there was no difference between the rectal temperature of the control and MDMA-pretreated groups. When both groups were subjected to a high ambient temperature challenge, the MDMA-pretreated animals responded in a different manner to the control group (Fig. 3). During the hyperthermic challenge (30±0.5°C; $t_{0–60}$), the temperature of rats pretreated with MDMA was different from the control group [$F$(1,44)=8.78, $P$=0.0049]. However, there was no significant interaction between treatment and time [$F$(3,44)=0.82, $P$=0.49],

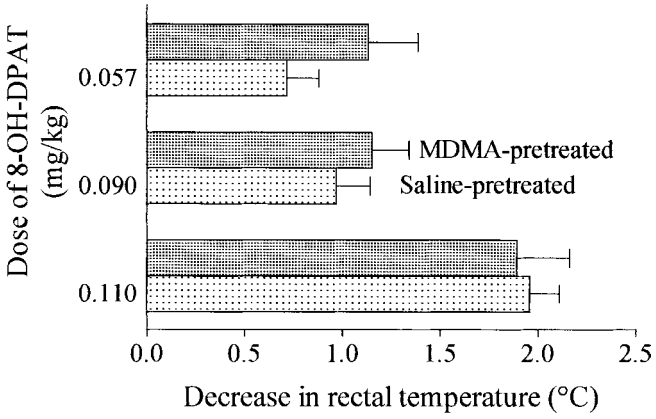


**Fig. 4** Acute effect of 8-OH-DPAT (0.057, 0.09, 0.11 mg kg$^{-1}$ SC) on rectal temperature in MDMA-pretreated and control animals ($n$=6, for both treated and control groups at the 0.057 and 0.09 mg/kg dose and $n$=12 at 0.11 mg/kg dose. dose, respectively). Results show ΔT at 25 min post-injection. A post-hoc test showed no significant differences at any of the doses administered ($P$>0.05)

which was further confirmed by the post-hoc test, only demonstrating a significant difference at $t_{40}$ ($P$<0.05). Upon return to a normal environment (20±2°C; $t_{60–210}$), significant effects of both treatment [$F$(1,77)=72.2, $P$<0.0001] and time [$F$(6,77)=7.83, $P$<0.0001] were again observed. A sustained hyperthermia was seen in the MDMA-pretreated animals, as demonstrated by a significant interaction between treatment and time effects [$F$(6,77)=3.31, $P$=0.006], and by the post-hoc tests which indicated significant differences ($P$<0.001) at all time points between 120 and 210 min.

### Long-term effects of acute MDMA administration on 5-HT receptor function

Administration of 8-OH-DPAT (0.11 mg/kg SC) produced acute hypothermia, with a nadir at 25 min post-injection (data not shown). MDMA-pretreatment did not alter the size or time-course of the 8-OH-DPAT-induced temperature response, where there was no significant effect of treatment [$F$(1,44)=3.92, $P$=0.05] or interaction between treatment and time effects [$F$(3,44)=1.04, $P$=0.38]. A similar response was seen in both control and MDMA-pretreated rats at all doses of 8-OH-DPAT investigated (Fig. 4).

Both the 5-$HT_{2C}$ agonist $m$-CPP and the 5-$HT_{2A}$ agonist DOI failed to induce hyperthermia in Dark Agouti rats, so we were unable to examine the effect of MDMA pretreatment on this response.

## Discussion

The MDMA-induced acute hyperthermic response previously observed (Nash et al. 1988; Colado et al. 1993; Dafters 1994) was again seen in this study, the animals

displaying a rise in rectal temperature of greater than 1.5°C, which was sustained for over 3.5 h. Following this dose of MDMA and the appearance of an acute hyperthermic response, the rectal temperature had returned to normal 24 h later and over the next 2 weeks the daily rectal temperature of the MDMA-treated rats did not differ from that seen in a parallel saline-treated control group. Since this dose of MDMA was shown in another group of rats to produce a hypothalamic loss in 5-HT content of around 35%, this result suggests that a neurotoxic dose of MDMA resulting in this degree of 5-HT loss does not affect the body temperature of rats kept at normal ambient room temperature. When the group of MDMA-pretreated and control animals were subjected to a high ambient temperature challenge (30°C) 5–6 weeks later, the MDMA-pretreated group demonstrated a sustained hyperthermia when the animals were returned to normal (20°C) conditions. This response indicated that there was a long-term defect in thermoregulation in MDMA-pretreated rats that only became apparent when the animals were exposed to high ambient temperature. The data obtained both confirm and extend the report of Dafters and Lynch (1998) who, using different methods of both temperature measurement and data analysis, observed that rats treated with MDMA 4 and 14 weeks earlier showed an extended period of hyperthermia on exposure to a high ambient temperature when compared with their pretreatment response.

It is probable that the altered thermoregulatory response is related to damage to central serotonergic pathways, since 5-HT is associated with thermoregulatory mechanisms (Jacob and Girault 1980; Salmi and Ahlenius 1998). Therefore, we next examined the effect of several 5-HT agonists that have been reported to produce changes in body temperature to see whether the response of MDMA-treated animals to these drugs was altered.

5-$HT_{1A}$ receptor function was investigated by administering the 5-$HT_{1A}$ receptor agonist, 8-OH-DPAT. This compound produces an acute hypothermia in Sprague-Dawley rats (Goodwin et al. 1987) and the current study demonstrated the same response in DA rats, although the drug showed greater potency in this strain. Current data regarding change in 5-$HT_{1A}$ receptor function following MDMA pretreatment are conflicting. McNamara et al. (1995) reported that the hypothermic response to 8-OH-DPAT in animals pretreated 8 days earlier with MDMA was unchanged. In contrast, Aguirre et al. (1998) observed enhanced 8-OH-DPAT-induced hypothermia in rats pretreated with MDMA 1 week earlier. However, these authors also observed a similarly altered response to 8-OH-DPAT after acute treatment with MDMA which suggests that the change they observed was not associated with any neurodegenerative effect of MDMA. Our data are consistent with McNamara et al. (1995) since we observed no alteration in the 8-OH-DAT hyperthermic response following a neurotoxic dose of MDMA.

It has been reported that both the 5-$HT_{2C}$ agonist *m*-CPP (Mazzola-Pomietto et al. 1997) and the 5-$HT_2$ agonist DOI (Mazzola-Pomietto et al. 1997; Salmi and Ahlenius 1998) produce acute hyperthermia. However, in our study, administration of either compound to DA rats failed to alter rectal temperature. It may be that the temperature changes following either drug are not very robust and require particular conditions for their expression rather than reflecting some specific feature of DA rats. Other investigators have also failed to see consistent temperature changes in both Sprague-Dawley and Wistar rats following administration of either compound (Kennett, personal communication).

It nevertheless seems reasonable to assume that defective 5-HT function may be involved in the altered thermoregulatory response to high ambient temperature, even though this defect does not impair the ability of the animal to regulate body temperature at normal ambient temperature. It appears that this defect only becomes apparent during "challenging" situations. A marked rise in body temperature is arguably the major adverse event that can follow recreational use of MDMA (Henry et al. 1992; Green et al. 1995). Several of the other major clinical problems which also occur, including rhabdomyolysis, disseminated intravenous coagulation and renal failure (Brown and Osterloh 1987; Chadwick et al. 1991; Henry et al. 1992), are probably associated with the hyperthermia (Green et al. 1995). The hyperthermic response following ingestion of MDMA can prove fatal (Henry et al. 1992; Randall 1992), therefore a long-term defect in thermoregulation following prolonged or high dose use of MDMA could have serious clinical consequences. Recreationally, MDMA is often taken in nightclubs and during crowded dances and, therefore, in conditions of high ambient temperature. If heavy users of MDMA have impaired thermoregulation then these current data suggest that they may be more susceptible to hyperthermia and its associated adverse events. A further concern is that there is considerable evidence in rodents that MDMA-induced neurodegeneration is exacerbated by hyperthermia (Broening et al. 1995; Farfel and Seiden 1995a, 1995b; Malberg et al. 1996; Colado et al. 1998). Regular MDMA users may therefore be at greater risk from both the acute and long-term toxicity following ingestion of the drug under conditions of high ambient temperature.

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