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ORIGINAL INVESTIGATION

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The role of 5-HT in the impairment of thermoregulation observed in rats administered MDMA ('ecstasy') when housed at high ambient temperature

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Abstract *Rationale:* Administration to rats of a neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) produces an impairment in thermoregulation which is reflected in a prolonged hyperthermic response to a subsequent dose of MDMA given to rats housed at high ambient temperature. *Objective:* We wished to examine whether the impaired thermoregulation was associated with decreased cerebral 5-HT content produced by the prior neurotoxic dose of MDMA. *Methods:* Rats were injected with drugs decreasing 5-HT function [the tryptophan hydroxlase inhibitor *p*-chlorophenylalanine (PCPA), and 5-HT receptor antagonists] and rectal temperature was measured after administering MDMA to rats housed at 30°C. *Results:* PCPA pretreatment decreased 5-HT and 5-HIAA concentrations in cortex, hippocampus and striatum by >80% and prolonged the hyperthermia induced in rats housed at 30°C by administering MDMA (5 mg/kg i.p.). A similar prolongation of the hyperthermic response to MDMA was seen when rats were pretreated with methysergide (10 mg/kg i.p.) or the 5-HT_{1A} antagonist WAY100635 (0.5 mg/kg s.c.). *Conclusions:* Decreasing 5-HT function in diverse ways enhanced the hyperthermic response to MDMA given to rats housed at high ambient temperature. This suggests that loss of 5-HT acting on 5-HT_{1A} receptors leads to impaired thermoregulation in rats and suggests that the impairment seen in MDMA pretreated rats housed at high ambient temperature is due to a loss in 5-HT function. These data could have implications for recreational users of MDMA, who may have damaged serotoninergic neurons because of prior heavy or frequent use of the drug, when taking further doses of MDMA in hot environments such as dance clubs.

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

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Introduction

Administration of the recreational drug 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') to rats induces both a rapid release of 5-HT and dopamine in the brain (see Green et al. 2003) and an acute hyperthermic response which lasts for several hours (Nash et al. 1988; O'Shea et al. 1998; Green et al. 2004a). However, the temperature response of rats following MDMA is complex in that a hypothermic has been seen when the animals are present in low ambient temperature conditions (Dafters 1994, 1995; Malberg and Seiden 1998; Green et al. 2004a). When MDMA is administered to rats housed at high ambient temperature (30°C) the hyperthermic response to the drug is enhanced compared to that seen in rats housed in normal room conditions (Dafters 1995; Malberg and Seiden 1998; Brown and Kiyatkin 2004; Green et al. 2004b). An acute hyperthermic response is also an established adverse event in human recreational users of MDMA (Brown and Osterloh 1987; Henry et al. 1992).

High or repeated doses of MDMA also produces a long-term neurotoxic degeneration of 5-HT terminals in the rat brain (see Green et al. 2003) but positive evidence for neurotoxic 5-HT loss in the human brain after repeated use of the drug remains controversial. Nevertheless, several studies do suggest that neurotoxic damage may be occurring in the brains of heavy users of MDMA (see Green et al. 2003).

Studies have shown that one of the consequences of MDMA-induced neurotoxic damage to the rat brain is an

impairment in the ability of the animals to thermoregulate. When prelesioned rats have been exposed to high ambient temperature conditions (30°C) and are then returned to normal room temperature (20°C), it takes longer for their body temperature to return to normal compared to control animals. This observation has been made using two rather different experimental approaches. Dafters and Lynch (1998) used telemetric techniques to examine the duration of the hyperthermic response in lesioned rats compared to the duration in the same animals prior to the neurotoxic dose of MDMA, while Mechan et al. (2001) measured the rectal temperature of parallel groups pretreated 4 weeks earlier with either saline or a lesioning dose of MDMA.

These data suggest that if human recreational users of MDMA do have damaged serotonergic function, they might also experience thermoregulatory problems if taking further doses of MDMA in a hot environment such as a crowded dance club. We therefore examined the effect on body temperature of giving a dose of MDMA to rats that had been administered a prior neurotoxic dose of MDMA, when they were subsequently housed at a high ambient temperature (30°C) during the challenge dose (Green et al. 2004b). The dose of MDMA used (5 mg/kg) produced a modest hyperthermic response in the control (saline-pretreated) group. However, the response in the MDMA-pretreated group was prolonged, indicating that the neurotoxic lesion had indeed impaired heat loss in those animals (Green et al. 2004b). Therefore, while there is good evidence to support the notion that MDMA disrupts thermoregulation acutely and also if its prior administration has produced neurotoxic damage, the neurochemical mechanisms involved have not been examined.

The current study was designed to examine whether the impaired thermoregulation seen in these animals was due to the loss in 5-HT function that had been produced by the neurotoxic dose of MDMA. This was done by pretreating rats with another 5-HT depleting drug, the tryptophan hydroxylase inhibitor *p*-chlorophenylalanine (PCPA), or with certain 5-HT receptor antagonists.

Materials and methods

Animals and drug administration

Male Dark Agouti rats, weighing 160–200 g, were used in all experiments (Harlan UK, Bicester, Oxon, UK). The animals were housed in groups of 5, at an ambient temperature of 20±2°C and a 12-h light/dark cycle (lights on: 07:30 h). Both food and water were freely provided. All procedures were carried out following approval by the De Montfort University Experimental Ethics Committee and in accordance with United Kingdom Home Office regulations which ensure humane and proper care of research animals.

(±)-MDMA was obtained from Ultrafine Chemicals (Manchester, UK) and dissolved in 0.9% w/v saline and injected i.p.

All studies were conducted with rats grouped in batches of five, both to simulate crowded dance club conditions and because amphetamines, including MDMA, produce more marked behavioural and toxic effects in grouped animals (Chance 1947; Fantegrossi et al. 2003). Animals were tested in a cohort group that had been both housed and pretreated 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 (T_a) during the experiment was maintained between 30 and 32°C (referred to as 30°C). Animals were housed in these conditions for 1 h before the start of the study. Rats were only ever used once in the investigations reported.

Effect of PCPA on MDMA-induced hyperthermia

Rats were pretreated with either PCPA (150 mg/kg i.p. daily for 2 days, n=10) or saline (1 ml/kg i.p., n=10). PCPA is a tryptophan hydroxylase inhibitor (Koe and Weissman 1966) and this dose regime is an established method for markedly decreasing the concentration of 5-HT in the brain (e.g. Nimgaonkar et al. 1985). On day 3, both groups were housed in a room at a T_a of 30°C. After 1 h acclimatisation, half of the rats in each group were injected with either saline (1 ml/kg i.p., n=5) or MDMA (5 mg/kg i.p., n=5) and their rectal temperature measured over the following 4 h. At this time the saline-injected group from the saline- and PCPA pretreatment groups were killed, and their brains dissected on ice into frontal cortex, hippocampus and striatum and frozen for subsequent measurement of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in all three regions and also dopamine in striatum.

Effect of methysergide on MDMA-induced hyperthermia

Rats were placed in a room at T_a=30°C. Sixty minutes later, they were injected with either saline (1 ml/kg i.p., n=10) or methysergide, the 5-$HT_{1/2}$ receptor antagonist (Barnes and Sharp 1999) at a dose of 10 mg/kg i.p. (n=10). The chosen dose of methysergide has previously been demonstrated to be effective for an antagonist action (Deakin and Green 1978). After a further 30 min, half of the rats in each group were injected with saline (n=5) or MDMA (5 mg/kg i.p., n=5) and their rectal temperature measured over the next 4 h.

Effect of WAY100635 on MDMA-induced hyperthermia

Rats were placed in a room at T_a=30°C and 60 min later they were injected with saline (1 ml/kg s.c., n=10) or WAY100635, the 5-HT_{1A} receptor antagonist (Forster et al.

1995) at a dose of 0.5 mg/kg s.c. (n=10). After a further 30 min half of the rats in each group were injected with saline (n=5) or MDMA (5 mg/kg i.p., n=5) and their rectal temperature was measured over the next 4 h. The dose of WAY100635 chosen has been shown to be an effective for 5-HT_{1A} receptor antagonist effects in other studies (Forster et al. 1995).

Effect of 8-OH-DPAT

A group of ten rats were injected with either saline (1 ml/kg i.p.) or a neurotoxic regime of MDMA (5 mg/kg i.p.×3 at 3-h intervals). These animals were killed 7 days later for analysis of the 5-HT and 5-HIAA concentrations in cortex, striatum and hippocampus. A further group of ten rats were identically pretreated, but were examined for their temperature response to 8-OH-DPAT, the 5-HT_{1A} receptor agonist (Middlemiss and Fozard 1983), 10 days later. These animals were placed in a room at T_a=30°C and 60 min later injected with 8-OH-DPAT (0.15 mg/kg s.c.); their rectal temperature was measured over the next 90 min. The dose of 8-OH-DPAT chosen induces clear hypothermia in rats housed in normal room temperature conditions (Goodwin and Green 1985).

Temperature measurement

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

Measurement of monoamines and their metabolites in cerebral tissue

At the end of the temperature study in the PCPA experiment, animals were killed by cervical dislocation and decapitation, the brains rapidly removed and cortex, hippocampus and striatum dissected out on ice. Tissue was homogenized and 5-HT, 5-HIAA and dopamine were measured by high performance liquid chromatography (HPLC) with electrochemical detection. Catechol concentration was only determined in the striatum since in this area the majority of monoaminergic terminals are dopaminergic. The method used was based on the procedure published in detail by Colado et al. (1997). Briefly, the mobile phase consisted of KH_2PO_4 (1.0 M), octanesulfonic acid (0.25 mM), EDTA (0.1 mM) and methanol (10%), and was adjusted to pH 3 with phosphoric acid, filtered and degassed. The flow rate was 1.2 ml/min and the working electrode potential was set at +0.8 V. The HPLC system consisted of a pump (Pharmacia LKB 2150) linked to a stainless steel reversed-phase column (C18 Phenomenex Lichrosher Select B, 5 μm, 150×4.6 mm) with a precolumn and a LC-4C amperometric detector (Bioanalytical Systems, Congleton, Cheshire). The current produced was monitored by using integration software (SP4400 Chromjet with Nelson Chromatography Software).

A study was also performed when MDMA (5 mg/kg i.p.×3, 3-h intervals) was given and 5-HT content of cortex, hippocampus and striatum measured 7 days later. Cerebral 5-HT content was measured exactly as described above.

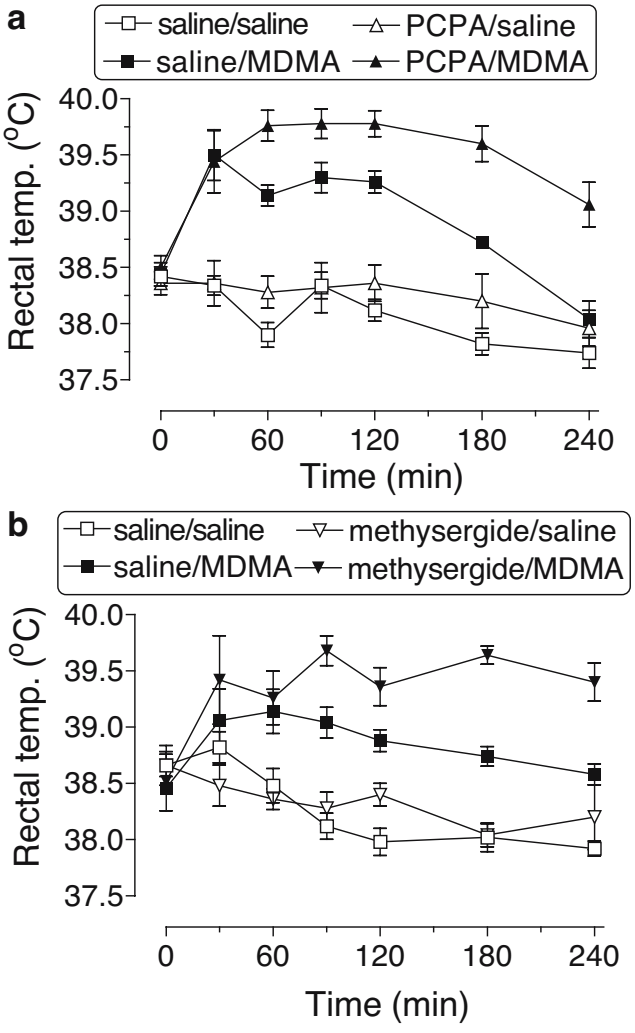

Fig. 1 The effect of pretreatment of rats with (**a**) PCPA or (**b**) methysergide on the hyperthermic response of rats to MDMA (5 mg/kg) when they were present at high ambient temperature (30°C). Experimental details of pretreatment schedules given in "Materials and methods". Results shown as mean±SEM. Data were analysed statistically from 30 to 240 min. **a** Saline/MDMA group different from saline/saline: $F(1,8)=59.16$, $p<0.001$; PCPA/MDMA group different from saline/MDMA: $F(1,8)=13.84$, $p<0.01$ and saline/saline group not different from PCPA/saline group: $F(1,8)=1.12$. **b** Saline/MDMA group different from saline/saline: $F(1,8)=21.03$, $p<0.01$; methysergide/MDMA group different from saline/MDMA: $F(1,8)=8.50$, $p<0.05$ and saline/saline group not different from methysergide/saline group: $F(1,8)=0.20$

Analysis of data

Statistical analyses of the temperature measurements were performed using the statistical computer package BMDP/386 Dynamic (BMDP Statistical Solutions, Cork, Eire). Data were analyzed by analysis of variance (ANOVA) with repeated measures (program 2V). Treatment was used as the between-subjects factor and time as the repeated measure. The ANOVA values represent a main effect of treatment. Biochemical data were analyzed by region using Student's *t*-test.

Results

Effect of PCPA on MDMA-induced hyperthermia

Pretreatment with PCPA did not alter the basal temperature response of rats exposed to high T_a. However, prior PCPA administration resulted in the rats having a more prolonged hyperthermic response after MDMA (5 mg/kg) was given at high T_a (Fig. 1a). The PCPA pretreatment had reduced the cerebral 5-HT and 5-HIAA content of the rats by >80% compared with control animals, but left the striatal dopamine content unaltered (Table 1).

Effect of methysergide on MDMA-induced hyperthermia

Pretreatment with methysergide (10 mg/kg) resulted in MDMA (5 mg/kg) producing a greater and more prolonged hyperthermic response in rats present at a T_a=30°C than in rats injected with saline (Fig. 1b). Methysergide pretreatment did not alter the basal temperature of rats exposed to high T_a (Fig. 1b).

Table 1 The effect of pretreatment with PCPA on the monoamine concentration in several regions of rat brain 1 day later

Brain region	Measurement	Pretreatment		
		Saline	PCPA	% Decrease
Cortex	5-HT	520±57	70±15*	86
	5-HIAA	621±44	65±17*	89
Hippocampus	5-HT	402±7	27±6*	93
	5-HIAA	882±100	45±9*	94
Striatum	5-HT	523±138	102±25*	81
	5-HIAA	734±126	18±9*	97
	Dopamine	9,805± 1,233	10,740± 1,110	–

Results shown as mean±SEM (n=5 each group) of monoamine or metabolite concentration in each region. Concentrations are expressed as ng/g tissue (wet weight). Different from saline-injected control group: *p<0.001. The measurements were made in the PCPA and saline-pretreated rats given a further saline injection during the experiment reported in Fig. 1

Effect of WAY100635 on MDMA-induced hyperthermia

Administration of WAY100635 produced a statistically significant increase in rectal temperature in rats housed at T_a=30°C, compared to their saline-injected cohort (Fig. 2, insert). After the administration of MDMA (5 mg/kg), the rectal temperature of both saline- and WAY100635-pretreated animals rose. The peak temperature rise was the same in both groups but hyperthermia was prolonged from 20 to 180 min in the WAY100635-treated group (Fig. 2). WAY100635 pretreatment also elevated the rectal temperature of saline-treated rats over the duration of the study compared to saline-pretreated rats (Fig. 2).

Effect of 8-OH-DPAT following pretreatment with a neurotoxic dose of MDMA

The neurotoxic dose regime of MDMA (5 mg/kg i.p.×3 at 3-h intervals) produced a significant decrease in 5-HT (reported as % of control concentration with statistical difference from control group) in the cortex (65±8%, p<0.02), striatum (68±9%, p<0.02) and hippocampus (28±4%, p<0.005) 1 week later. Administration of 8-OH-DPAT (0.15 mg/kg s.c.) failed to produce a clear hypother-

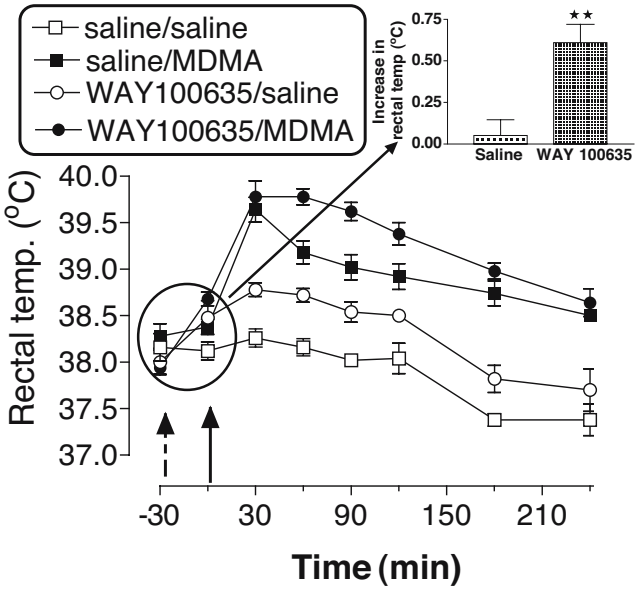

Fig. 2 The effect of pretreatment of rats with WAY100635 (0.5 mg/kg, s.c.) on the hyperthermic response of rats to MDMA (5 mg/kg) when they were present at high ambient temperature (30°C). Experimental details of pretreatment schedules given in "Materials and methods." *Dashed line arrow* indicates time when WAY100635 was injected and *solid line arrow* the time when MDMA was given. Results shown as mean±SEM. Data were analysed statistically from 30 to 240 min. saline/MDMA group different from saline/saline: $F(1,8)=84.69$, p<0.001; WAY100635/MDMA group different from saline/MDMA: $F(1,8)=6.05$, p<0.05 and saline/saline group different from WAY100635/saline group: $F(1,8)=30.10$, p<0.001. *Inset* shows the temperature change in rats injected with WAY100635 versus those injected with saline during the first 30 min, *filled stars* indicate WAY100635 group different from saline group p<0.01

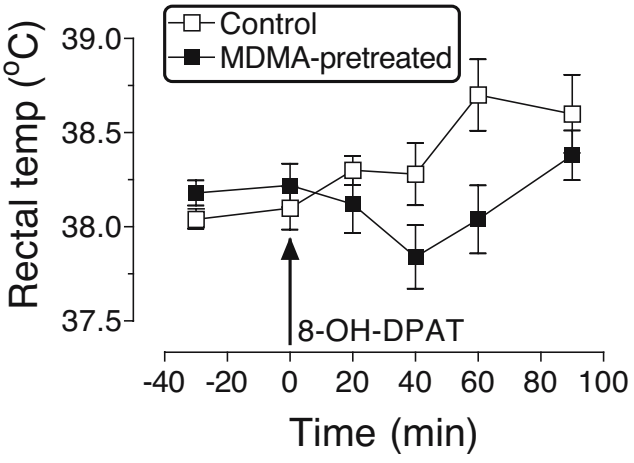

Fig. 3 The effect of pretreatment of rats with MDMA (5 mg/kg×3 at 3-h intervals) on the temperature response of rats 10 days later to 8-OH-DPAT (0.15 mg/kg, s.c.) when they were present at high ambient temperature (30°C). Experimental details of pretreatment schedules given in "Materials and methods". Results shown as mean± SEM. Data were analysed statistically from 30 to 90 min. No difference was detected in the response of the two groups: $F(1,8)=3.7$, $p=0.0908$

mic response in either a saline-treated or MDMA-lesioned group when housed at T_a=30°C (Fig. 3).

Discussion

Previous studies have demonstrated that a prior neurotoxic lesion induced by MDMA administration results in rats having an impaired thermoregulatory response when exposed to a high ambient temperature. This has been demonstrated using two different types of experimental condition. Firstly, when MDMA-lesioned rats are exposed to high temperature and then returned to normal room temperatures, they have a prolonged high body temperature (Dafters and Lynch 1998; Mechan et al. 2001). Secondly, MDMA-lesioned rats, when injected with a further low dose of MDMA while present in high T_a conditions, have a similar peak response but prolonged hyperthermia compared with control animals (Green et al. 2004b). This sustained response is not seen in MDMA-lesioned rats given either a high (Beveridge et al. 2004) or low (Green et al. 2004b) challenge dose of MDMA when they are present at a T_a of 20°C, which suggests that the problem is primarily one of heat loss occurring only under high T_a conditions. What may be a key point here is the thermoneutrality point in rats, since this has been recently demonstrated to be in the region of 29.5–30.5°C (Romanovsky et al. 2002). Heat loss in rats is primarily regulated by vasodilation of blood vessels in the tail, a major specialized heat-exchange organ in this species (Romanovsky et al. 2002). Presumably, this mechanism plays a major role in animals housed above thermoneutrality, and this is why no problems in heat dissipation are observed in MDMA-lesioned rats challenged with a further dose of MDMA when housed at normal room temperature.

The current study has examined the neurochemical basis of this MDMA-induced thermoregulatory impairment and data suggest that the heat-loss problem results from the decrease in 5-HT concentration that has been produced by the neurotoxic dose of MDMA. When a major decrease in cerebral 5-HT content was produced by pretreating rats with PCPA, it also resulted in a prolongation of the MDMA-induced hyperthermic response in rats kept at T_a=30°C. The results obtained following PCPA were strikingly similar to those seen following MDMA pretreatment (compare Fig. 1a in the current study with the Fig. 1 of Green et al. 2004b). These data thus provide strong support for the proposal that normal 5-HT release is required to assist temperature loss when rats are present at high ambient temperature. This mechanism was first proposed by Giacchino et al. (1983), who reported that heat-exposed rats pretreated with PCPA had a smaller rise in tail temperature than control rats. PCPA pretreatment also increases heat-induced mortality in rats housed at a high ambient temperature (Reid et al. 1968; Cronin 1976).

Further evidence for 5-HT involvement in heat-loss mechanisms in rats housed at high ambient temperature was provided by the experiment which demonstrated that the 5-$HT_{1/2}$ antagonist methysergide also prolonged MDMA-induced hyperthermia in rats present at high T_a. The fact that the selective 5-HT_{1A} antagonist WAY100635 had the same effect indicated strongly that released 5-HT has to act on 5-HT_{1A} receptors to initiate or enhance heat loss. While the prolongation of the hyperthermia was of a shorter duration than that seen after PCPA or methysergide, this was probably merely a consequence of the rather short (33 min) half-life of WAY100635 in rats (Zuideveld et al. 2002), resulting in the receptor blockade being of a shorter period than that of the study. What was striking about this experiment was the initial rise in rectal temperature in WAY100635-treated rats when housed at high T_a and the fact that WAY100635-treated rats had a higher rectal temperature than saline-injected animals when present at high ambient temperature. This suggests that heat-exposed rats normally promote heat loss under these environmental conditions by releasing 5-HT which, in turn, increases 5-HT_{1A} receptor function.

Since administration of the 5-HT_{1A} agonist 8-OH-DPAT produces a hypothermic response in rats housed under normothermic conditions (Goodwin and Green 1985; Hjorth 1985), we examined the effect of this drug in control (saline-pretreated) and MDMA-lesioned rats housed at high T_a to determine whether the receptor responded similarly in control and MDMA-lesioned animals. However, the results proved difficult to interpret since 8-OH-DPAT administration failed to produce a defined hypothermic response in rats housed at 30°C. Nicholas and Seiden (2003) also recently reported that the size of the hypothermic response of rats to 8-OH-DPAT administration diminished with increasing temperature. We did not study higher doses of 8-OH-DPAT as the drug can produce fatal hyperthermia in rats housed at high T_a (Nicholas and Seiden 2003). The reason why 8-OH-DPAT produces hypothermia in rats housed at

20°C, but severe hyperthermia when the animals are housed at 30°C is unknown.

The failure of 8-OH-DPAT to induce hypothermia, which it does by acting on 5-HT_{1A} postsynaptic receptors (Bill et al. 1991; O'Connell et al. 1992), contrasts with the ability of WAY100635 to enhance the hyperthermic response of rats given MDMA when housed at 30°C. However, the selectivity of the antagonist to block a selective heat loss mechanism may be in contrast to the promiscuous action of 8-OH-DPAT in stimulating 5-HT_{1A} receptors both pre- and postsynaptically (which might then affect other 5-HT-mediated temperature regulation mechanisms) and also 5-HT_7 receptors, which are also implicated in body temperature (Hedlund et al. 2004).

Given the substantial weight of evidence suggesting that 5-HT_{1A} receptor density is not altered by an MDMA-induced lesion (see Green et al. 2003; McGregor et al. 2003), it is reasonable to suggest that the altered hyperthermic response in MDMA-lesioned rats housed at 30°C results from impaired 5-HT release due to neurotoxic loss of 5-HT terminals rather than altered 5-HT_{1A} receptor density. This is supported by the experiment with PCPA.

The initial temperature rise following MDMA injection has been shown to be due to the drug enhancing the release of dopamine which acts at dopamine D_1 receptors (Mechan et al. 2002). Since a neurotoxic dose of MDMA does not damage dopaminergic neurons, one would not expect the peak temperature response to be altered when a further hyperthermic dose of MDMA is given and indeed this is what was seen. Thereafter, heat loss is presumably induced by 5-HT being released and acting on 5-HT_{1A} receptors. It is the impairment of this latter mechanism that becomes most apparent at T_a=30°C in MDMA-lesioned rats, because they have a decreased cerebral 5-HT concentration.

Since both the current and previous data (Green et al. 2004b) suggested that the impaired 5-HT-mediated thermoregulatory response is only apparent in high ambient temperature conditions, the current results may have implications for recreational users of MDMA. If heavy users of 'ecstasy' do have impaired 5-HT function, the consequences in relation to disruption of thermoregulation will only be problematical when the users are exposed to high ambient temperature room conditions. They are, therefore, more at risk of an acute adverse hyperthermic response following further MDMA ingestion in dance club conditions when the room is very hot. The corollary of this is that they may also risk further damaging their brain since the severity of hyperthermic response to MDMA is a major determinant in the degree of subsequent long-term neurotoxic damage to 5-HT nerve endings (Broening et al. 1995; O'Shea et al. 1998; Malberg and Seiden 1998; Sanchez et al. 2004).

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