

Cutaneous Vasoconstriction Contributes to Hyperthermia Induced by 3,4-Methylenedioxymethamphetamine (Ecstasy) in Conscious Rabbits

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3,4-Methylenedioxymethamphetamine (MDMA; “Ecstasy”) increases body temperature. This process could be associated with increased cutaneous blood flow, as normally occurs with exercise-induced hyperthermia. Alternatively, an MDMA-induced fall in cutaneous blood flow could contribute to the hyperthermia by diminishing normal heat transfer from the body to the environment. We investigated these possibilities by administering MDMA (1.5–6 mg/kg, i.v.) to conscious freely moving rabbits, determining effects on body temperature, cutaneous blood flow (measured by a Doppler ultrasonic probe that was chronically implanted around the ear pinna artery), and other cardiovascular parameters. MDMA caused a dose-dependent increase in body temperature (from 38.3 ± 0.3 to $41.2 \pm 0.4^\circ\text{C}$ after 6 mg/kg; $p < 0.01$; $n = 5$), preceded and accompanied by a dose-dependent cutaneous vasoconstriction

(from 29 ± 6 to 5 ± 1 cm/sec after 6 mg/kg; $p < 0.01$; $n = 5$). MDMA (3 mg/kg) did not change blood flow to the mesenteric vascular bed. Prior unilateral cervical sympathectomy reduced the increase in body temperature elicited by MDMA (6 mg/kg) from 2.0 ± 0.2 to $1.3 \pm 0.2^\circ\text{C}$ ($p < 0.01$; $n = 5$). On the denervated side, ear pinna blood flow after MDMA injection was 13 ± 3 cm/sec, compared with 3 ± 1 cm/sec on the sympathetically intact side ($p < 0.05$; $n = 5$). Thus, sympathetically mediated cutaneous vasoconstriction is one mechanism whereby MDMA causes hyperthermia. Reversal of cutaneous vasoconstriction by appropriate pharmacological means could be of therapeutic benefit in humans suffering from life-threatening hyperthermia induced by MDMA.

Key words: MDMA; ecstasy; temperature regulation; skin blood flow; heat loss; serotonin; 5-HT; hyperthermia

3,4-Methylenedioxymethamphetamine (MDMA; “Ecstasy”), a common recreational drug, increases body temperature in humans, occasionally fatally (Chadwick et al., 1991; Scream et al., 1992; Callaway and Clark, 1994; Steele et al., 1994; Vollenweider et al., 1998; Milroy, 1999). When body temperature increases with physical exercise, or in a warm environment, cutaneous blood flow normally increases so that the body is cooled as heat is transferred via the skin to the external environment. MDMA increases metabolic rate (Gordon et al., 1991), but at present we do not know what happens to cutaneous blood flow during MDMA-induced hyperthermia, either in humans or in experimental animals. Experimental models have been established in rats (Schmidt et al., 1990; Gordon et al., 1991; Dafters, 1995; De Souza et al., 1997; Malberg and Seiden, 1998), and clearly it is important to learn as much as possible concerning the physiological mechanisms underlying the hyperthermia.

The ear pinna of rabbits is a predominantly cutaneous bed (Grant et al., 1932; Grant, 1935), one in which blood flow can readily be measured using chronically implanted Doppler ultrasonic probes (Yu and Blessing, 1997). We have administered MDMA to conscious freely moving rabbits to determine whether the drug increases body temperature in this species and whether

any resulting hyperthermia is associated with increases or decreases in cutaneous blood flow. Ear pinna blood flow was compared with superior mesenteric blood flow. To determine whether sympathetic denervation affects MDMA-induced changes in blood flow and whether these changes in blood flow contribute to MDMA-induced hyperthermia, we performed experiments combining transection of one cervical sympathetic trunk with simultaneous measurement of blood flow to both ears. Finally, we determined whether MDMA-induced changes in body temperature and cutaneous blood flow depend on ambient temperature.

MATERIALS AND METHODS

All experiments were performed in accordance with the guidelines of the Flinders University Animal Welfare Committee.

Instrumentation of animals. New Zealand White rabbits (3–4 kg) were anesthetized with Hypnorm (0.3 ml/kg, i.m.) (0.315 mg/ml fentanyl citrate and 10 mg/ml fluanisone; Janssen, Beerse, Belgium), followed 10 min later by Hypnovel 0.4 ml/kg, i.m. (midazolam 5 mg/ml; Roche Diagnostics, Castle Hill, NSW, Australia) and supplemented when necessary with 1–2% halothane in oxygen, delivered via a facial mask. Doppler ultrasonic probes were implanted around the central artery of one or both ear pinnae in all animals and around the superior mesenteric artery in some animals (Yu and Blessing, 1997). Probe wires were passed subcutaneously and soldered to a socket that was then fixed to the skull with screws and dental cement. A radiotelemetric temperature-measuring implant (TA10TA-D70; Data Science International, St. Paul, MN) was placed into the peritoneal cavity. In some animals, the probe of an arterial pressure telemetric implant (TA11PA-C40; Data Science International) (diameter, 15 mm; length, 20 mm) was inserted into the terminal abdominal aorta. A small cellulose patch was fixed over the insertion site using cyanoacrylate glue. The implant was then sutured to the abdominal wall, and the laparotomy was closed. In some animals, the left cervical sympathetic trunk was identified and cut just proximal to the

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superior cervical ganglion. Rabbits recovered in the animal house for at least 1 week before experiments were performed.

On the day of the experiment, the rabbit was placed in a cage with a swivel device (Stoelting, Wood Dale, IL) in the roof. A flexible cable connected the skull socket to the swivel device. A fluid line, passing through the swivel device and the flexible cable, was attached to a catheter in the marginal ear vein. Experiments were conducted with the rabbit's cage placed in a controlled temperature (13–40°C) environmental chamber.

A Data Sciences International receiver (model RPC-1) was placed under the cage. A multiplexer (model RMX-10) transmitted the signal to a Data Sciences International transducer device (temperature, catalog #273-0016; arterial pressure, catalog #R11CPA). Wires from the Doppler blood flow probes were connected via the swivel device to a Triton System 6 flowmeter (model 200; Triton Technology, San Diego, CA). Doppler probes were calibrated in centimeters per second using the internal calibration of the flowmeter. Arterial pressure probes were precalibrated with a mercury manometer.

Data acquisition and statistical analysis. Rabbits were placed in the controlled temperature chamber for at least 1 hr before the experiment commenced. Then, data signals were continuously acquired during a 30 min control period. An appropriate dose of MDMA in 2 ml saline was administered then via the line connected through the swivel to the marginal ear vein. Continuous data acquisition continued for either 2 or 3 hr depending on the experiment.

Analog blood flow, pressure, and temperature signals were digitized with MacLab and Chart software (ADInstruments, Castle Hill, Australia) and stored on a Macintosh Centris 660AV computer. Sampling rate was 40 Hz for arterial pressure and blood flow signals and 2 Hz for the temperature signal. Data were analyzed off-line using Chart and IgorPro (Wavemetrics Inc., Lake Oswego, OR) software. Heart rate was calculated from phasic blood flow or arterial pressure signals. Traces from individual rabbits were processed using the “decimation” function in IgorPro software (the function replaces data points by the mean value for the points) to reduce the number of points in traces from individual rabbits to one per minute.

For individual rabbits, we calculated the mean temperature and ear pinna blood flow for the 30 min control period, and the maximum (temperature) and minimum (flow) values reached during the 3 hr postinjection period. To provide a duration-related measure of the effect of MDMA in individual rabbits, we used IgorPro software to calculate the mean value for the temperature signal for the period from 15 to 75 min after injection of MDMA, and the mean value for the blood flow signal for the period from 5 to 90 min after injection of MDMA. From these values, we subtracted the mean of the appropriate 30 min preinjection control period, yielding a measure of MDMA-induced change in temperature and blood flow. Control and postinjection values were compared using repeated measures ANOVA. We also used linear regression to examine the relationship between log dose of MDMA and postinjection changes in temperature and ear pinna blood flow.

We assessed the functional blood flow effects of unilateral cervical sympathectomy by comparing ear pinna signals recorded simultaneously from intact and denervated ear pinnae at rest and during alerting responses elicited by administration of salient stimuli (tapping the cage, touching the fur, moving the cage) as described in our previous papers (Yu and Blessing, 1997, 1999).

The effects of unilateral cervical sympathectomy and the effects of ambient environmental temperature on the temperature response to administration of MDMA (3 and 6 mg/kg) were assessed using ANOVA to compare appropriate postinjection changes (mean of the 15–75 min period minus mean of the control period). For the unilateral cervical sympathectomy experiments, MDMA-elicited changes in ear pinna blood flow were assessed by comparing blood flow in the sympathectomized (left) ear with the intact (right) ear of the same rabbit using repeated measures ANOVA. We also used repeat measures ANOVA to compare minimum postinjection ear pinna blood flow values in intact and sympathectomized ear pinnae for 3 and 6 mg/kg doses of MDMA. The effect of ambient environmental temperature on MDMA-elicited changes in ear pinna blood flow was determined using appropriate ANOVAs.

For the data presented in Figures 4 and 5, we first reduced the number of data points in traces from individual rabbits to one per 7 min. Mean values of these traces, across rabbits, are presented for the different time points in Figures 4 and 5. Overall SEs for pre- and post-MDMA injection

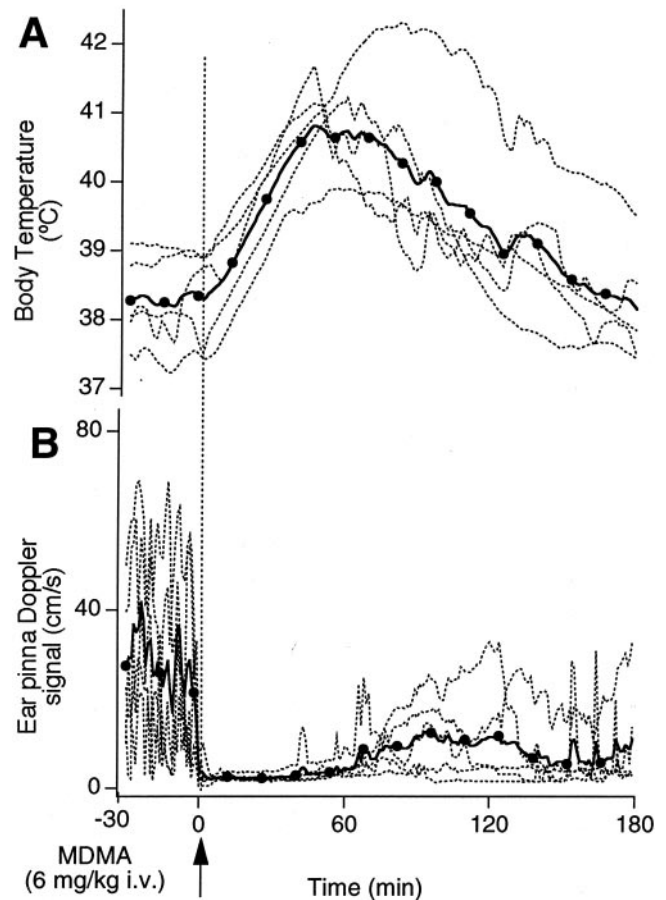


Figure 1. Body temperature (*A*) and ear pinna blood flow (*B*) in individual rabbits (1 min bins; *dashed lines*) and the mean of the individual traces (*solid line with filled circles*; $n = 5$ rabbits) before and after injection of MDMA (6 mg/kg; *arrow*). The maximum of the mean postinjection temperature trace (40.8°C) is slightly less than the mean of the five individual postinjection maxima (41.2 ± 0.4°C) because of differences in the time of each postinjection maximum.

periods were calculated from the residual mean square error obtained from repeated measure ANOVAs.

Drugs. Racemic *N*-methyl-3,4-methylenedioxyamphetamine hydrochloride (MDMA) was obtained from the National Analytical Research Laboratory of the Australian Government Analytical Laboratories (Pymble, New South Wales, Australia). The required quantity of MDMA was weighed out 30 min before use and dissolved in 0.9% NaCl solution.

RESULTS

Effect of MDMA on body temperature, ear pinna blood flow, and other cardiovascular variables

Baseline body temperature was $38.4 \pm 0.5^\circ\text{C}$ (mean ± SD) over a 30 min period on 24 occasions in 11 rabbits. At a dose of 6 mg/kg, MDMA sometimes caused excessive hyperthermia, so that the rabbit lost motor coordination and required killing to prevent distress. Results from these animals ($n = 4$; temperature at the point of killing, $43 \pm 0.6^\circ\text{C}$, mean ± SD) were not included in subsequent analyses. The animals included in Figures 1*A* and 2*A* recovered from their period of hyperthermia, appearing in good health. With MDMA doses of 3 mg/kg or less, all animals appeared in good health.

MDMA caused hyperthermia in a dose-dependent manner (Figs. 1*A*, 2*A*). With the highest dose (6 mg/kg), body temperature commenced to rise a few minutes after the injection, reached

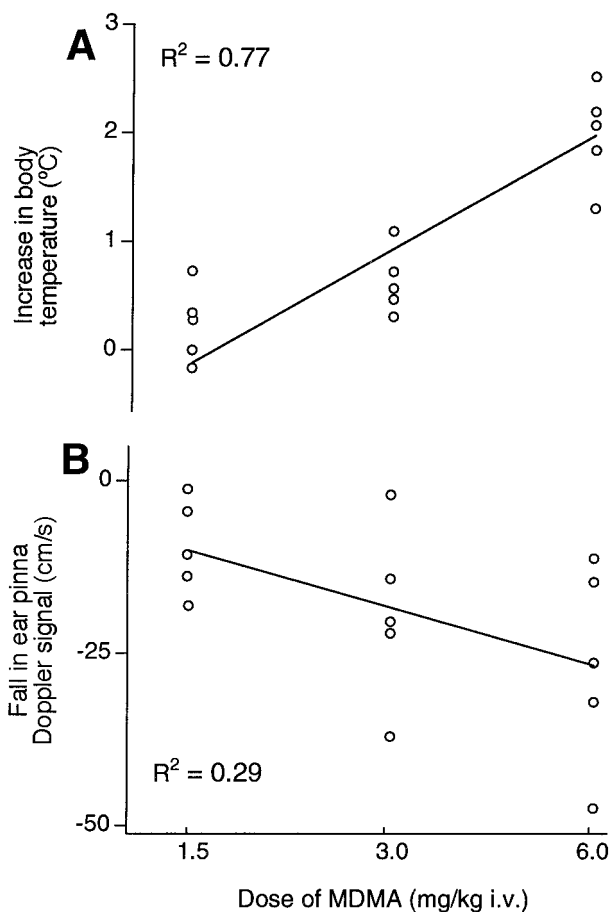


Figure 2. Linear regression relationship between log dose of MDMA and mean change in body temperature during the period from 15 to 75 min after injection of MDMA compared with preinjection baseline (*A*) ($p < 0.01$; $n = 5$ rabbits at each dose), and log dose of MDMA and change in ear pinna blood flow during the period from 5 to 90 min after injection of MDMA, compared with preinjection baseline (*B*) ($p < 0.05$; $n = 5$ rabbits at each dose).

a maximum ~ 1 hr after injection, and returned to, or near to, the preinjection baseline value within ~ 3 hr of injection. The mean value of the individual post-MDMA maxima was $41.2 \pm 0.4^\circ\text{C}$, compared with a preinjection mean of $38.3 \pm 0.3^\circ\text{C}$ ($p < 0.01$; $n = 5$). The mean trace of the five individual rabbits is shown as the *unbroken line with filled circles* in Figure 1*A*. MDMA-induced increase in body temperature (15–75 min postinjection period minus the preinjection control period) was significantly related to the dose of MDMA, as shown in Figure 2*A*.

MDMA caused a fall in ear pinna blood flow for the 5–90 min postinjection period as compared with the 30 min preinjection period ($p < 0.01$) (Figs. 1*B*, 2*B*). At each of the three doses, ear pinna blood flow fell within 1–2 min of drug injection. At the highest dose, blood flow velocity fell from 29 ± 6 to 5 ± 1 cm/sec ($p < 0.01$; $n = 5$), and remained low. Mean blood flow was still well below the preinjection value after 180 min, although body temperature had returned to preinjection baseline levels by this time (Fig. 1). The fall in ear pinna blood flow was significantly related to the dose of MDMA, as shown in Figure 2*B*.

MDMA (3 mg/kg, i.v.) did not change superior mesenteric blood flow in the 5–90 min postinjection period as compared with the preinjection period ($+1 \pm 3$ cm/sec; $p > 0.05$; $n = 5$) (Fig. 3*A*). In the same animals, at the same time as mesenteric flow was

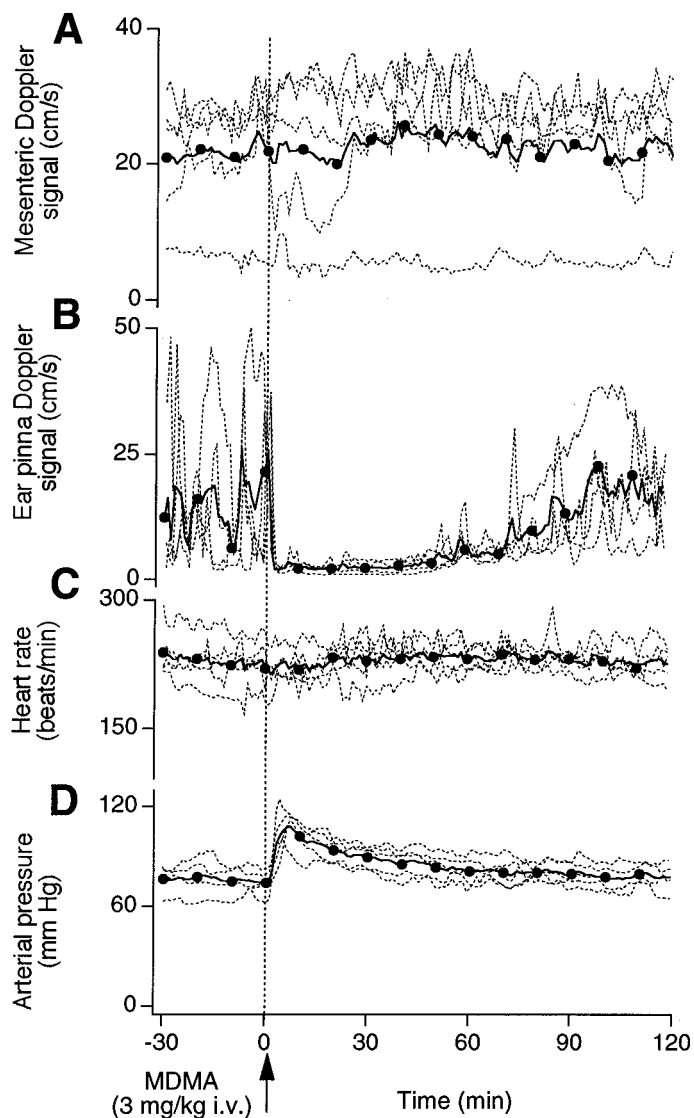


Figure 3. Superior mesenteric Doppler blood flow signal (*A*), ear pinna Doppler blood flow signal (*B*), heart rate (*C*), and mean arterial pressure (*D*) in individual rabbits (1 min bins; *dashed lines*), and the mean value (*solid line with filled circles*; $n = 5$ rabbits for each panel) before and after injection of MDMA (3 mg/kg; *arrow*). The ear pinna blood flow signals in *B* were recorded from the same rabbits at the same time as the superior mesenteric blood flow signals in *A*.

measured, MDMA caused an acute fall in ear pinna blood flow (-14 ± 3 cm/sec; $p < 0.01$; $n = 5$) (Fig. 3*B*). There was no change in heart rate after injection of MDMA (Fig. 3*C*). Arterial pressure increased by ~ 30 mmHg within a few minutes of MDMA injection and then gradually decreased toward the preinjection level, but was still slightly elevated 120 min after MDMA injection (Fig. 3*D*).

Effects of unilateral cervical sympathectomy

After unilateral cervical sympathectomy, at ambient temperature basal body temperature was unchanged compared with intact rabbits (38.3 ± 0.2 vs $38.2 \pm 0.2^\circ\text{C}$; $p > 0.05$; $n = 7$ rabbits in each condition). Left cervical sympathectomy did not change ($p > 0.05$) the temperature response to the 3 mg/kg dose of MDMA (Fig. 4*A*). However, after 6 mg/kg of MDMA, unilateral cervical sympathectomy reduced the maximal increase in temperature

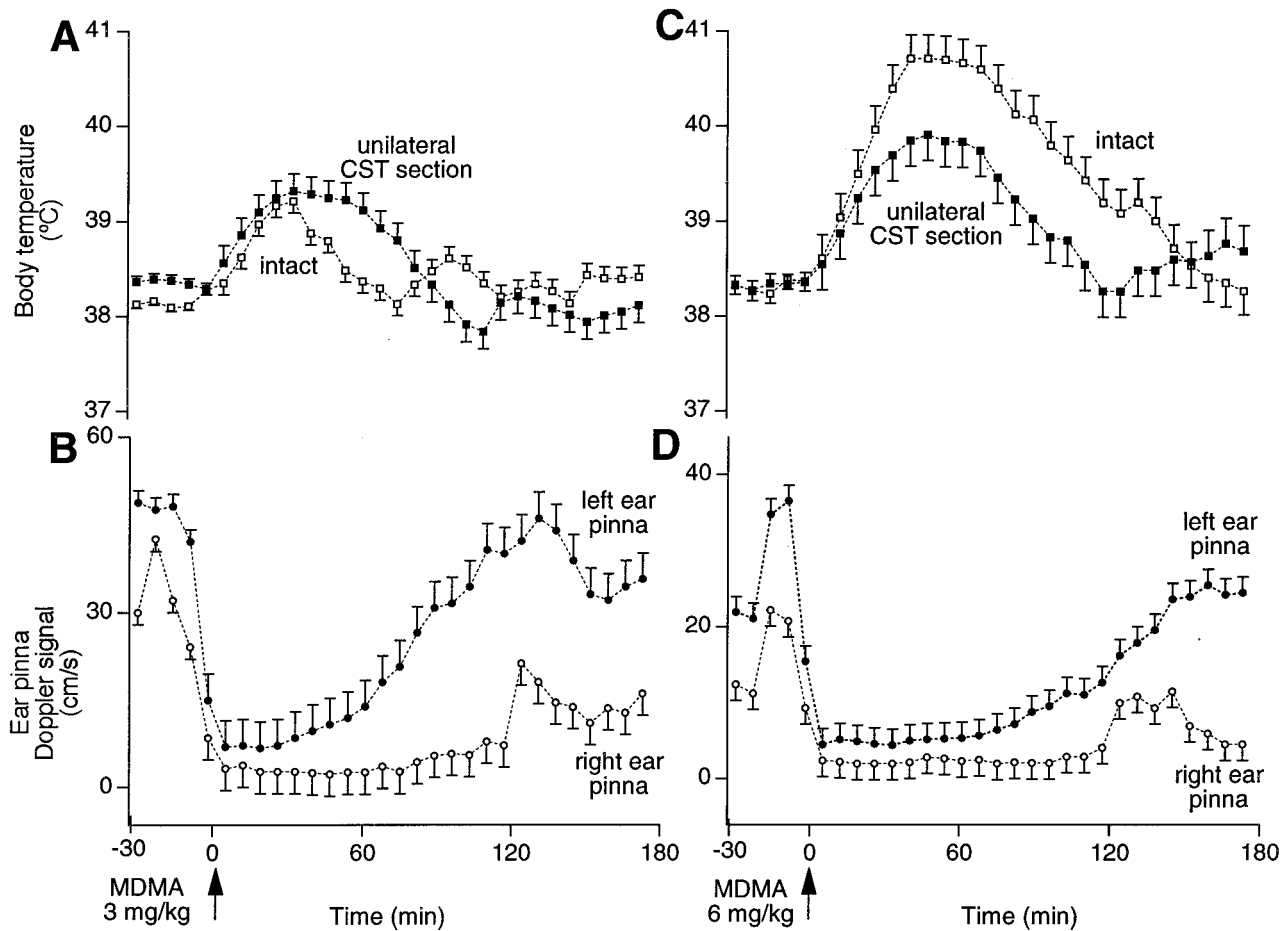


Figure 4. *A*, Means (averaged across rabbits, 1 point per 7 min) and SEs for body temperature before and after injection of MDMA (3 mg/kg) in intact animals (*open squares*) and in animals subjected to unilateral sympathetic denervation of the ear pinna (*filled squares*) by section of the left cervical sympathetic trunk (*CST*). *B*, Means (averaged across rabbits, 1 point per 7 min) and SEs for ear pinna blood flow in the left (sympathetically denervated) ear pinna (*filled circles*) and corresponding values in the right (sympathetically intact) ear pinna (*open circles*), before and after injection of MDMA (3 mg/kg; *arrow*). *C*, *D*, Similar traces after injection of 6 mg/kg MDMA.

from 2.9 ± 0.28 to $2.0 \pm 0.28^\circ\text{C}$ ($p < 0.05$; $n = 5$). The 15–75 min increase in body temperature elicited by the 6 mg/kg dose was also significantly reduced by unilateral cervical sympathectomy ($p < 0.05$; $n = 5$) (Fig. 4C). The mean trace for intact rabbits shown in Figure 4C is the same mean data as is shown in Figure 1A.

Unilateral cervical sympathectomy increased basal ear pinna blood flow on the ipsilateral (left) side in comparison to the intact (right) side (37 ± 4 vs 24 ± 4 cm/sec; $p < 0.01$; $n = 10$ rabbits) measured over a 30 min period in a room temperature environment. In response to perception of a salient alerting stimulus, ear pinna blood flow fell to $35 \pm 4\%$ of the prestimulus blood flow level in the denervated ear pinna, compared with a greater fall to $10 \pm 1\%$ of the prestimulus blood flow level in the intact ear pinna ($p < 0.01$; $n = 12$ episodes in six rabbits).

Mean left and right ear flow values for grouped rabbits before and after injection of MDMA are shown in Figure 4, *B* and *D*, where it is clear that ear pinna blood flow was significantly reduced by MDMA in both denervated and intact ears for both doses of MDMA, but the duration of the fall was less in denervated ears, especially after the 3 mg/kg dose. ANOVA indicated that the 5–90 min postinjection blood flow values for the intact (right) ear pinna were significantly less than values for the denervated (left) ear pinna for both doses of MDMA ($p < 0.01$; $n =$

5). Individual postinjection minimal blood flow values for the denervated ear pinnae were also significantly greater ($p < 0.05$; $n = 5$) than corresponding means for intact ear pinnae (2.7 ± 0.4 vs 1.6 ± 0.3 cm/sec for the 3 mg/kg dose and 5 ± 1.7 vs 1 ± 0.3 cm/sec for the 6 mg/kg dose).

Effect of ambient temperature on response to MDMA

Rabbits maintained in cool ($13\text{--}16^\circ\text{C}$) or warm ($29\text{--}31^\circ\text{C}$) environments had similar baseline body temperatures ($38.7 \pm 0.2^\circ\text{C}$, $n = 5$, vs $38.5 \pm 0.3^\circ\text{C}$, $n = 6$, respectively; $p > 0.05$) (Fig. 5A). In rabbits maintained in the cool environment, basal preinjection ear pinna blood flow was low (7 ± 3 cm/sec; $n = 5$), significantly less ($p < 0.01$) than in rabbits maintained in the warm environment (48 ± 8 cm/sec; $n = 5$), as shown in Figure 5B.

Administration of MDMA (3 mg/kg) to rabbits in the warm environment caused body temperature to increase by $1.5 \pm 0.2^\circ\text{C}$ ($n = 6$ rabbits) during the 15–75 min period after injection, significantly greater ($p < 0.05$) than the corresponding increase ($0.7 \pm 0.3^\circ\text{C}$) observed in rabbits maintained in the cool environment. Administration of MDMA (3 mg/kg) in the cool environment did not reduce further the ear pinna blood flow. Administration of MDMA in the warm environment promptly reduced blood flow, but this change was not maintained for a prolonged period (compare Figs. 1B, 5B). After ~ 1 hr, blood flow com-

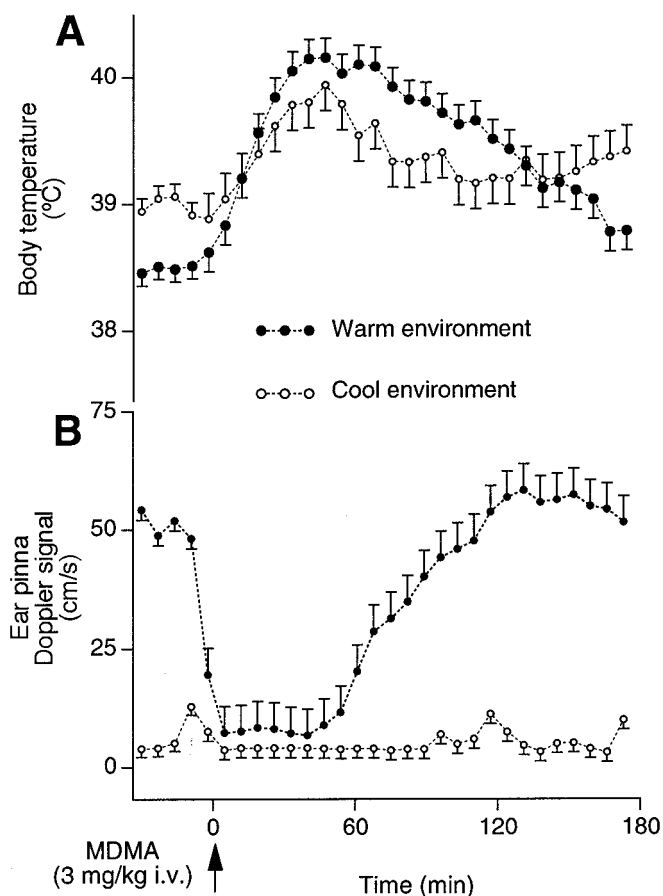


Figure 5. Means (averaged across rabbits, 7 min time points) and SEs for body temperature (*A*) and ear pinna blood flow (*B*), before and after injection of MDMA (3 mg/kg; *arrow*) for animals in a warm environment (29–31°C; *filled circles*) and for animals in a cool environment (13–16°C; *open circles*).

menced to increase from the near zero postinjection level, so that within 90 min of MDMA injection in the warm environment, ear pinna blood flow had returned to the preinjection level (Fig. 5*B*). Mean ear pinna blood flow for the period 60–90 min after the injection of MDMA in the warm environment was 46 ± 9 cm/sec, significantly greater ($p < 0.01$) than the value (5 ± 3 cm/sec) for the corresponding time period in rabbits maintained at room temperature.

Repeatability of MDMA effects in the same animal

Rabbits appeared normal the day after MDMA treatment, with temperatures and ear pinna blood flows restored to pretreatment values. Three rabbits each received the 6 mg/kg dose of MDMA on three consecutive occasions, with repeated doses at least 1 week apart. For each rabbit on each occasion, we calculated the MDMA-elicited change in temperature and blood flow (see Materials and Methods). The 15–75 min post-MDMA increases in body temperature for the three occasions were 1.91 ± 0.17 , 1.98 ± 0.35 , and $1.87 \pm 0.19^\circ\text{C}$, respectively ($n = 3$ rabbits). The 5–90 min post-MDMA decreases in ear pinna blood flow were -18 ± 3 , -26 ± 6 , and -23 ± 2 cm/sec, respectively.

DISCUSSION

Selective action of MDMA on cutaneous blood flow

Our study is the first in any species to demonstrate that vigorous cutaneous vasoconstriction precedes and accompanies the

MDMA-induced rise in body temperature. In contrast, blood flow to the mesenteric bed was unchanged by MDMA, and arterial pressure was only mildly increased. MDMA thus induces an integrated thermogenic response, with an appropriately patterned sympathetic outflow to the different arterial beds.

Gordon et al. (1991) noted that MDMA did not increase tail temperature in rats as much as it increased the animal's core body temperature, suggesting constriction of the tail (cutaneous) vascular bed. This hypothesis has not yet been tested by direct measurement of tail blood flow in rats, a measurement that can be made in the conscious unrestrained rat using chronically implanted Doppler ultrasonic blood flow probes (Garcia et al., 2000).

The initial marked change in pressure was not associated with a marked constriction in the mesenteric bed, indicating that a generalized sympathetic vasomotor discharge did not occur. MDMA causes secretion of hormones such as vasopressin (Henry et al., 1998), and possibly ACTH and adrenal catecholamines, actions that could contribute to its cardiovascular effects. There was no MDMA-induced increase in heart rate, possibly because any centrally elicited increase in neurohumoral drive to the heart was overridden by arterial baroreceptor reflex mechanisms. In humans, "recreational" doses of MDMA (0.25–1.7 mg/kg, by mouth) cause a moderate rise in arterial pressure and a tachycardia (Grob et al., 1996; Vollenweider et al., 1998). In rats, variable effects of MDMA on heart rate have been observed, with a consistent rise in arterial pressure (O'Caïn et al., 2000). The peripheral mechanisms mediating MDMA-elicited rise in arterial pressure are not yet understood.

Cutaneous blood flow and the degree of hyperthermia after unilateral section of the cervical sympathetic trunk; mode and site of action of MDMA

Unilateral sympathectomy did not entirely abolish alerting-related falls in ear pinna blood flow, although these changes are presumably sympathetically mediated. Grant et al. (1932) and Grant (1935) noted the complexity of the pathways whereby sympathetic fibers reach the ear pinna. Not all preganglionic ear pinna cutaneous vasomotor fibers travel in the cervical sympathetic trunk. Results from the alerting-related ear pinna vasoconstriction experiment confirm the occurrence of partial functional sympathetic denervation on the operated side, in agreement with the observation that resting ear pinna blood flow was greater in the denervated ear.

After administration of MDMA, blood flow to the normally innervated ear pinna fell to a lower level, and remained at a lower level for a longer period, than did blood flow to the denervated ear pinna. This provides evidence that cutaneous vasoconstriction elicited by MDMA is at least partially sympathetically mediated, indicating a primary action of the drug in the CNS. MDMA still caused substantial ear pinna vasoconstriction on the side ipsilateral to the sectioned cervical sympathetic trunk. This may reflect an action via sympathetic nerves reaching the ear by alternative pathways or it may reflect an additional peripheral action of MDMA (Pawlak et al., 1998). The increase in body temperature after administration of MDMA (6 mg/kg) in intact animals was greater than the increase occurring after unilateral section of the cervical sympathetic trunk. Together with the observation of greater cutaneous vasoconstriction in the sympathetically intact ear pinna, this finding suggests that the increase in temperature after administration of MDMA at least partially reflects a reduction in the normal loss of body heat via the cutaneous circulation.

MDMA increases metabolic rate and bodily movement (Gordon et al., 1991), actions presumably mediated via CNS pathways. MDMA has a complex pharmacology, but a major effect is its ability to release 5-HT after the drug is taken up into the neuron via the 5-HT transporter (Battaglia et al., 1988; Rattray, 1991; Green et al., 1995; Barnes and Sharp, 1999). Released 5-HT results in increased heat production via activation of 5-HT_{2A} receptors (Gudelsky et al., 1986; Barnes and Sharp, 1999). 5-HT_{2A} receptors are widely distributed in the CNS (Cornea-Hebert et al., 1999; Fay and Kubin, 2000), but the sites relevant to hyperthermia have not yet been localized.

The central component of the cutaneous vasoconstricting action of MDMA could also be mediated via release of 5-HT acting at 5-HT_{2A} receptors. One hypothesis, consistent with evidence implicating raphe magnus–pallidus neurons in control of cutaneous blood flow in rabbits (Blessing and Nalivaiko, 2000; Nalivaiko and Blessing, 2001), is that the vasoconstricting sites of action of MDMA include the spinal cord. 5-HT_{2A} receptors are present in the intermediolateral column (Cornea-Hebert et al., 1999) and MDMA could release 5-HT from the terminals of raphe-spinal neurons, with consequent activation of 5-HT_{2A} receptors on perikarya and dendrites of preganglionic sympathetic cutaneous vasomotor neurons.

Different ambient environmental temperatures

At cool ambient temperatures, ear pinna blood flow was already at near zero levels before injection of MDMA, remaining at this low level although body temperature rose substantially after MDMA administration. At warm ambient temperatures, ear pinna blood flow was high before injection of MDMA. In this environment, the drug still substantially decreased ear pinna blood flow, but the duration of the fall was reduced. Thus CNS temperature-regulating pathways modified the cutaneous vasoconstricting effects of MDMA. One previous study in rats found that MDMA actually lowered body temperature when the animal was maintained in a cool environment (Gordon et al., 1991), but this observation was not made by Dafters (1995). In our rabbits, MDMA increased body temperature in animals maintained in a cool environment.

Effects of MDMA in humans

The limited physiological information that is available from MDMA-treated humans confirms that the drug causes a rise in body temperature, an increase in arterial pressure and possibly heart rate, and an increase in motor activities such as jaw clenching (Downing, 1986; Chadwick et al., 1991; Sreaton et al., 1992; Callaway and Clark, 1994; Steele et al., 1994; Vollenweider et al., 1998; Milroy, 1999). The hyperthermic effect of MDMA in humans is prevented by pretreatment with citalopram (5-HT uptake inhibitor) or by ketanserin (5-HT_{2A} receptor antagonist), but not by dopamine receptor blockade with haloperidol (Liechti and Vollenweider, 2000; Liechti et al., 2000a,b).

To our knowledge, cutaneous blood flow has never been measured in humans after ingestion of MDMA, although such measurements could be done simply and noninvasively with laser flowmetry or infrared procedures. Our results in rabbits suggest that cutaneous vasoconstriction could contribute to MDMA-induced hyperthermia in humans. Our demonstration that the atypical antipsychotic agent clozapine substantially reverses MDMA-induced cutaneous vasoconstriction in rabbits (Blessing et al., 2001) suggests that this drug, or other clozapine-like atypical antipsychotic agents acting as antagonists at 5-HT_{2A} recep-

tors (Barnes and Sharp, 1999; Meltzer, 1999), might be therapeutically important in treating the severe, occasionally fatal, hyperthermia that sometimes occurs in humans who take MDMA.

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