

Cardiovascular and sympathetic responses and reflex changes elicited by MDMA

Peggy A. O'Cain¹, Sarah B. Hletko², Brian A. Ogden, Kurt J. Varner^{1,*}

*Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center,
1901 Perdido St., New Orleans, LA 70112, USA*

Received 20 October 1999; received in revised form 10 February 2000; accepted 11 February 2000

Abstract

The recreational use of 3,4-methylenedioxymethamphetamine (MDMA) has increased as have the number of clinical reports linking MDMA use with cardiovascular toxicity. Nonetheless, the cardiovascular and sympathetic nerve responses elicited by MDMA have not been well characterized. The purpose of this study was to characterize the mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve responses elicited by the acute administration of MDMA and to determine whether neurotoxic doses of MDMA change cardiovascular and/or cardiovascular reflex function. In conscious rats, MDMA or *d*-amphetamine elicited similar dose-dependent increases in MAP. MDMA elicited significant bradycardia at doses above 1.0 mg/kg. Pretreatment with phentolamine significantly reduced the duration but not the magnitude of the pressor response elicited by MDMA. In pentobarbital-anesthetized rats, MDMA (0.1 mg/kg) increased renal sympathetic nerve activity (RSNA; $33 \pm 10\%$), while larger doses significantly decreased RSNA ($-91 \pm 3\%$, max). Neurotoxic doses of MDMA (20 mg/kg, s.c., b.i.d. for 4 days) significantly enhanced the bradycardic component of the Bezold–Jarisch reflex elicited by i.v. serotonin when tested either 2 days or 2 weeks after the last neurotoxic treatment. However, neurotoxic treatment did not significantly affect baroreceptor reflex function. These results indicate that the acute administration of MDMA and *d*-amphetamine produce similar cardiovascular and sympathetic responses. Neurotoxic doses of MDMA can also significantly alter cardiovascular reflex function. These findings raise the possibility that MDMA may have the potential to produce cardiovascular and/or cardiac toxicity similar to that elicited by other amphetamine analogs. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Arterial pressure; Sympathetic nerve activity; Heart rate; 3,4-Methylenedioxymethamphetamine; Rat; Bezold–Jarisch reflex; Baroreceptor reflex

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is an amphetamine derivative, possessing both stimulant and hallucinogenic properties [16,34]. The recreational use of MDMA has increased dramatically in recent years along with the popular perception that this is a relatively safe drug [8]. However, increasing clinical reports indicate that MDMA use is associated with significant cardiovascular toxicity including tachycardia, cardiac ischemia, arrhythmia, and death [15,19,27]. Despite the potential to produce cardiovascular toxicity, the cardiovascular actions of MDMA have not been well characterized. MDMA produces tachycardia and hypertension in humans [11,36] and tachycardia

in rats [14]. Most likely, the sympathomimetic actions of MDMA result from its ability to stimulate the release of monoamines [12,13,21]. In view of the limited data regarding the cardiovascular affects of MDMA, one of the main goals of this study was to characterize the acute cardiovascular and sympathetic nerve responses elicited by the administration of MDMA.

MDMA is also a selective serotonergic neurotoxin producing prolonged (lasting months) decreases in the levels of serotonin (5-HT), its primary metabolite, 5-hydroxyindoleacetic acid, and the number of 5-HT uptake sites on serotonergic nerve terminals in many brain regions [4, 10,29,31]. Immunohistochemical studies have also verified extensive decreases in the number of 5-HT reactive nerve fibers in many brain regions after MDMA treatment [7,29].

The majority of studies examining MDMA-mediated neurotoxicity have focused on the affected forebrain serotonergic systems and the potential behavioral and/or psy-

* Corresponding author. Fax: 504-568-2361

E-mail address: KVARNE@LSUMC.EDU

¹ Current address: School of Medicine, Louisiana State University Health Sciences Center, New Orleans, LA.

² Current address: Kalamazoo College, Kalamazoo, MI

chological consequences resulting from this damage (see [16,34]). To our knowledge, no studies have examined the neurotoxic effects of MDMA on descending central or peripheral serotonergic systems that play a significant role in the basal and reflex control of cardiovascular function [17]. Alteration of these monoaminergic systems via the neurotoxic actions of MDMA has the potential to cause either acute and/or chronic cardiovascular changes leading to hypertension, arrhythmia, syncope, and/or other clinically relevant problems. Therefore, the second major goal of this study was to determine whether the administration of neurotoxic doses of MDMA could alter cardiovascular or cardiovascular reflex function by damaging descending central and/or peripheral monoaminergic neural systems.

2. Materials and methods

2.1. Animals

Experiments were performed on male Sprague–Dawley rats (275–350 g; Harlan, Indianapolis, IN). All procedures were in accordance with National Institutes of Health guidelines for the care and use of laboratory animals, and were approved by the Institutional Animal Care and Use Committee at Louisiana State University Health Sciences Center. During the experiments the rats were housed individually in a room with a 12-h light/dark cycle. The rats had unlimited access to food and water. All testing was conducted on animals in their home cages.

2.2. Acute and chronic implantation of cannulae

For the implantation of chronic cannulae, rats were anesthetized using an i.p. injection of a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg). Anesthesia was supplemented (20 and 2 mg/kg, i.v. or i.p.) in response to spontaneous movements or movements in response to tail or foot pinch. Body temperature was maintained at $37 \pm 1^\circ\text{C}$ using a water-filled heating pad and/or a heat lamp. Catheters (PE-50 fused to PE-10) were placed in the femoral artery and vein for the recording of arterial pressure and administration of drugs, respectively. The free ends of the cannulae were tunneled subcutaneously and exteriorized between the scapulae. Catheters were filled with heparinized saline (200 U/mL) to prevent clotting. In acute studies, arterial and venous cannulae were implanted in pentobarbital-anesthetized (40–50 mg/kg, i.p.) rats as described above. Supplemental doses of pentobarbital (25 mg/kg, i.v. or i.p.) were administered as required. In acute and chronic studies, pulsatile arterial pressure and mean arterial pressure (MAP) were recorded using standard techniques [1]. Heart rate (HR) was derived from the arterial pressure pulse using a Grass (Quincy, MA) 7P tachygraph. HR, MAP, and pulsatile arterial pressure were displayed on a Grass (Quincy, MA) polygraph.

2.3. Sympathetic nerve recording

Renal sympathetic nerve activity (RSNA) was recorded in pentobarbital-anesthetized rats (45–50 mg/kg, i.p.) using bipolar platinum electrodes as described previously [1]. RSNA was recorded using a Grass (Quincy, MA) P511 preamplifier (band pass 30–3000 Hz) and converted to slow-wave activity using a moving averager (CWE, Ardmore, PA, Model M821, 100 ms time constant). The moving average of RSNA was integrated using a Grass (Quincy, MA) 7P10 cumulative integrator and displayed on a Grass (Quincy, MA) chart recorder along with the moving average [1].

2.4. Experimental protocols

2.4.1. Cardiovascular responses to MDMA and amphetamine in conscious rats

Rats were instrumented with chronic arterial and venous cannulae. Two days later the venous and arterial lines were connected to the recording equipment and the animals allowed 30 min to acclimate to the testing conditions. After achieving stable baseline recordings, bolus doses of MDMA (0.01–3.0 mg/kg, i.v.) or amphetamine (0.01–3.0 mg/kg, i.v.) were administered over 10–20 s, followed by a 10-s saline flush (0.1 mL), and the changes in MAP and HR recorded. The doses were administered in ascending order, with the interval between doses being sufficient to allow for the return of cardiovascular parameters to predrug levels. Interdose intervals ranged from 15–25 min for doses less than 1.0 mg/kg, and up to 2–3 h for larger doses. Preliminary studies showed that very little tachyphylaxis develops to the repeated administration of MDMA (1 mg/kg, i.v.) when the doses are separated by 2 h (unpublished data).

A separate group of rats ($n = 5$) were prepared with chronic arterial and venous cannulae. Two days later, the conscious rats were given MDMA (2 mg/kg, i.v.) and the changes in MAP and HR recorded. Approximately 5 to 6 h later the rats were treated with phentolamine (3 mg/kg, i.v.) 10 min prior to readministering MDMA. In preliminary studies, we found that this dose of phentolamine completely blocked the MAP and HR responses elicited by the i.v. administration of norepinephrine (0.33 $\mu\text{g/kg}$) (unpublished data).

2.4.2. Sympathetic nerve responses to MDMA in anesthetized rats

Pentobarbital-anesthetized rats were instrumented with arterial and venous cannulae. The trachea was cannulated and the rats ventilated mechanically using a rate (60–70 breaths/min) and tidal volume (2–2.5 mL), which mimicked normal respiration. A recording electrode was then placed on a renal sympathetic nerve. After the neural and cardiovascular parameters had stabilized, doses of MDMA (0.01–3.0 mg/kg) were administered, and the MAP, HR, and renal sympathetic nerve responses recorded. The doses of MDMA were administered in ascending order with interdose intervals sufficient to allow HR, MAP, and RSNA to return to predrug levels between doses.

2.4.3. Cardiovascular reflex responses after neurotoxic doses of MDMA

Rats were treated with MDMA (20 mg/kg, s.c.) twice per day for 4 days. This treatment regime has been shown to significantly reduce 5-HT content in the brains of rats and other animals [4,7]. Control rats received injections of saline according to the same schedule. One or 13 days after administering the last dose of MDMA or saline, chronic cannulae were placed in the femoral artery and vein under ketamine/xylazine anesthesia. The next day baroreceptor and Bezold–Jarisch reflex function were assessed in the conscious unrestrained rats. Baroreceptor reflex activity was assessed by measuring the magnitude of the reflex-mediated changes in HR produced in response to graded changes in AP elicited by bolus i.v. doses of phenylephrine (0.15–6 μ g/kg) or sodium nitroprusside (3–60 μ g/kg). Doses of phenylephrine and nitroprusside were administered in random order and interdose intervals were sufficient to allow cardiovascular parameters to return to baseline. Bezold–Jarisch reflex function was assessed by measuring the magnitude of the peak changes in HR elicited by the i.v. injection of graded doses of 5-HT (3.0–15.0 μ g/kg) in random order.

2.5. Data analysis

The peak changes in HR and MAP elicited by drug administration were calculated directly from the polygraph records. Changes in integrated RSNA were quantified by comparing mean epoch length (integrated records) before and after drug administration [1]. The level of background noise in the neural recordings was determined after euthanizing the animal and subtracted from total nerve activity.

Baroreceptor reflex function was quantified using the exponential curve fitting analysis program developed by Head and McCarty [18]. The five parameters derived from this analysis were: G, the sensitivity or gain of the reflex; P_2 , the upper plateau that signifies the maximal increase in HR in response to decreases in AP; P_1 , the lower plateau, which signifies the maximal decrease in HR in response to increases in AP; R, the reflex range ($P_2 - P_1$), and BP_{50} , which corresponds to the MAP at the midpoint of the HR range. The analysis program also calculated resting HR and MAP.

Bezold–Jarisch reflex function was calculated by measuring the magnitude of the peak bradycardic response elicited by graded i.v. doses of 5-HT.

2.6. Statistics

The dose–effect relationships of amphetamine and MDMA for HR and MAP were compared using one-way analysis of variance (ANOVA). Differences between means were compared using the Tukey–Kramer multiple comparison test. Comparison of peak bradycardic responses elicited by 5-HT in MDMA-treated and control animals were compared using two-way ANOVA. Comparisons between indi-

vidual means were made using the Tukey–Kramer multiple comparison test. The effects of phentolamine on baseline MAP and HR were made using paired Student's *t*-tests. Comparison of the baroreceptor reflex parameters in control and MDMA-treated rats were made using Student's *t*-tests. Significance was defined at $p < 0.05$.

2.7. Drugs used

Drugs used were *d*-amphetamine HCl and 3,4-methylenedioxymethamphetamine HCl (National Institute on Drug Abuse), pentobarbital sodium and xylazine (Butler Co., Columbus, OH), heparin (Lymphomed, Deerfield, IL), phenylephrine, norepinephrine, sodium nitroprusside, phentolamine, and serotonin (Sigma, St. Louis, MO), and ketamine HCl (Mallinkrodt Veterinary, Mundelein, IL).

3. Results

3.1. Acute cardiovascular responses to MDMA and amphetamine in conscious rats

The baseline levels of HR and MAP in the conscious rats treated with MDMA (402 ± 10 bpm and 100 ± 3 mmHg, respectively, $n = 5$) or amphetamine (392 ± 14 bpm and 100 ± 4 mmHg, respectively, $n = 6$) were not significantly different. Figure 1 compares the dose–effect relationships of MDMA and *d*-amphetamine for HR and MAP in conscious rats. MDMA (0.01–3.0 mg/kg, i.v.) elicited significant, $F(4, 20) = 10.7$, $p < 0.001$, dose-dependent increases in MAP (Fig. 1A). Amphetamine elicited similar dose-dependent, $F(4, 23) = 17.8$, $p < 0.001$, increases in MAP (Fig. 1A). The duration of the pressor responses elicited by 1.0 mg/kg of MDMA was 4.02 ± 1.3 min, while the duration of the pressor responses elicited by amphetamine was 2.8 ± 5 min. MDMA significantly changed HR, $F(4, 20) = 7.3$, $p < 0.001$, producing a significant bradycardia ($p < 0.05$) at the highest dose (Fig. 1B). Amphetamine produced a similar pattern of HR responses (Fig. 1B); however, due to large variability, these responses were not significantly different than baseline, $F(4, 21) = 2.7$, $p = 0.062$. The duration of the HR responses elicited by 1.0 mg/kg of MDMA and amphetamine were 29 ± 3 and 92 ± 37 s, respectively.

In a separate group of conscious rats ($n = 5$), pretreatment with the nonselective α -adrenergic receptor antagonist phentolamine (3 mg/kg, i.v.) failed to attenuate the magnitude of the peak pressor response elicited by MDMA (2 mg/kg, i.v.) (Fig. 2A). However, phentolamine significantly decreased the duration of the pressor responses elicited by MDMA (5.2 ± 2 min versus 20 ± 2 s). In phentolamine-treated rats the pressor response elicited by MDMA was followed by hypotension (-22 ± 5 mmHg). The hypotensive response was reversed by the administration of propranolol (1 mg/kg, i.v.) (data not shown). In these rats the administration of phentolamine significantly reduced resting MAP (113 ± 4 to 93 ± 6 mmHg) and increased resting HR (371 ± 19 to 462 ± 15 bpm).

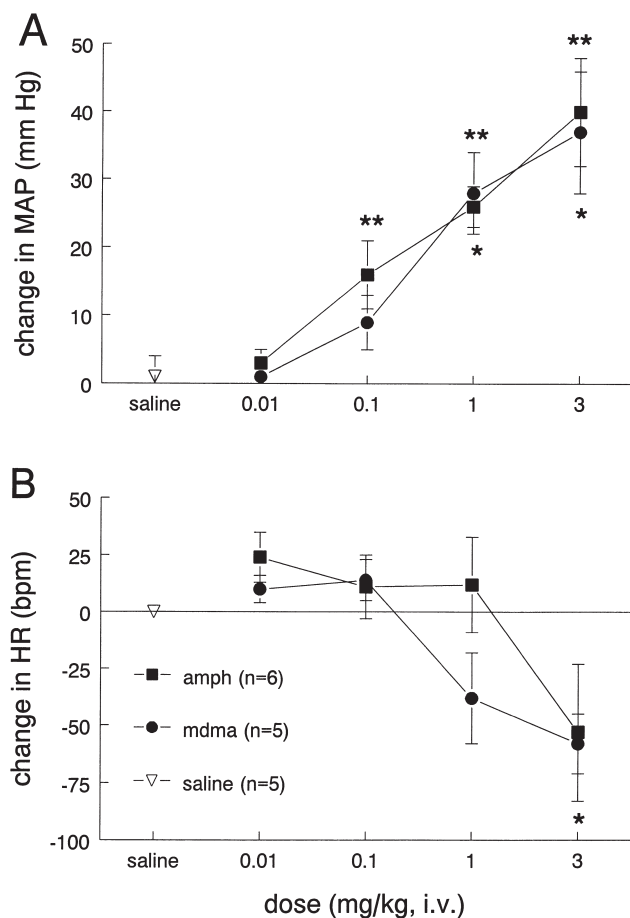


Fig. 1. Comparison of the dose–effect relations for MDMA and *d*-amphetamine (amph) and mean arterial pressure (MAP) and heart rate (HR) in conscious rats. In A and B, respectively, peak changes in MAP and HR are plotted versus dose. * $p < 0.05$, response to MDMA different from baseline. ** $p < 0.05$, response to amph different from baseline.

Administration of phentolamine significantly increased the magnitude of the bradycardic response elicited by MDMA (Fig. 2 B). In the phentolamine-treated rats, the bradycardic response was followed by an increase in HR of 52 ± 16 bpm above baseline. The rebound tachycardia was reversed by the administration of propranolol (data not shown).

Sympathetic nerve responses to MDMA in anesthetized rats. MDMA (0.01–3.0 mg/kg, i.v.) was administered to five pentobarbital-anesthetized rats. Figure 3 summarizes the peak HR, MAP and renal sympathetic nerve responses elicited by the i.v. injection of MDMA (0.01–3 mg/kg) in these rats. MDMA produced dose-related, $F(4, 20) = 2.6$, $p < 0.001$, increases in MAP (Fig. 3B). MDMA produced significant changes in HR, $F(4, 20) = 2.2$, $p < 0.001$, although only the increase in HR produced by the 1.0 mg/kg dose was significantly different from baseline (Fig. 3A). MDMA significantly, $F(4, 20) = 40.0$, $p < 0.001$, altered RSNA (Fig. 3A). The 0.01 mg/kg dose of MDMA elicited a small, but significant increase in RSNA (Fig. 3C). How-

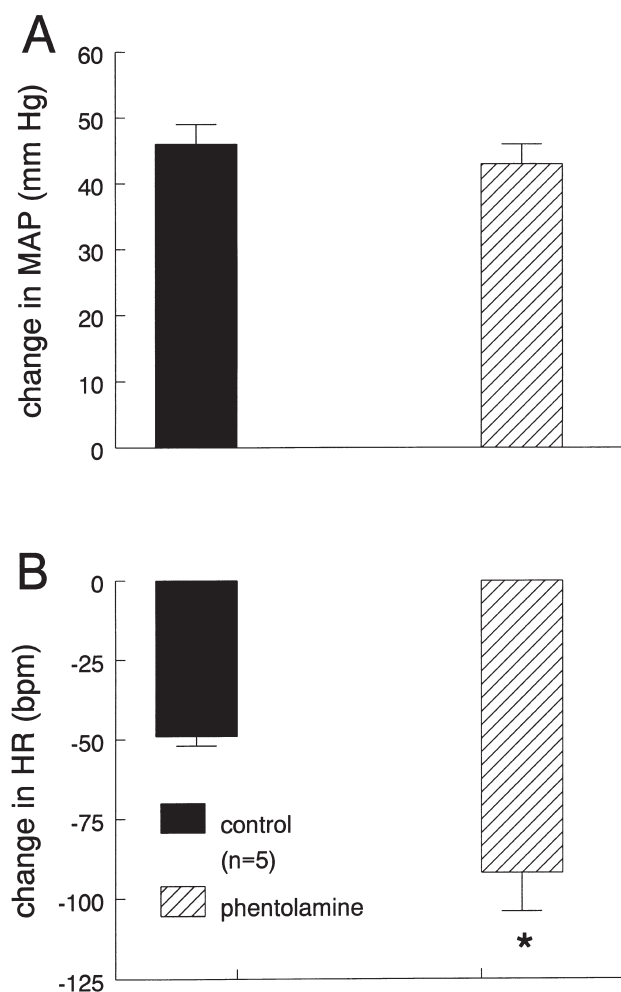


Fig. 2. Comparison of the changes in mean arterial pressure (MAP) and heart rate (HR) elicited by MDMA (2 mg/kg, i.v.) before and after α -adrenergic blockade using phentolamine (3 mg/kg, i.v.). (A) and (B), respectively, magnitude of the peak changes in MAP and HR elicited by MDMA. * $p < 0.05$, different from control.

ever, at doses above 0.1 mg/kg, RSNA was significantly decreased (Fig. 3A). The duration of the decrease in RSNA produced by MDMA at doses of greater than 0.1 mg/kg ranged from 3.7 ± 0.9 to 8.3 ± 2.3 min.

Cardiovascular reflex responses in rats after neurotoxic doses of MDMA. After 4 days of treatment with neurotoxic doses of MDMA or saline, baroreceptor and Bezold–Jarisch reflex function were assessed in conscious rats. Two days after the last neurotoxic dose of MDMA ($n = 7$) or saline ($n = 7$), resting HR and MAP in the two groups were not significantly different (355 ± 8 bpm and 115 ± 2 mmHg versus 397 ± 11 bpm and 115 ± 2 mmHg, respectively). Similarly in the groups tested 2 weeks after administering the last neurotoxic dose of MDMA ($n = 8$) or saline ($n = 8$), resting HR and MAP were also not significantly different (368 ± 4 bpm and 118 ± 2 mmHg versus 393 ± 12 bpm and 114 ± 2 mmHg, respectively). Treatment with MDMA

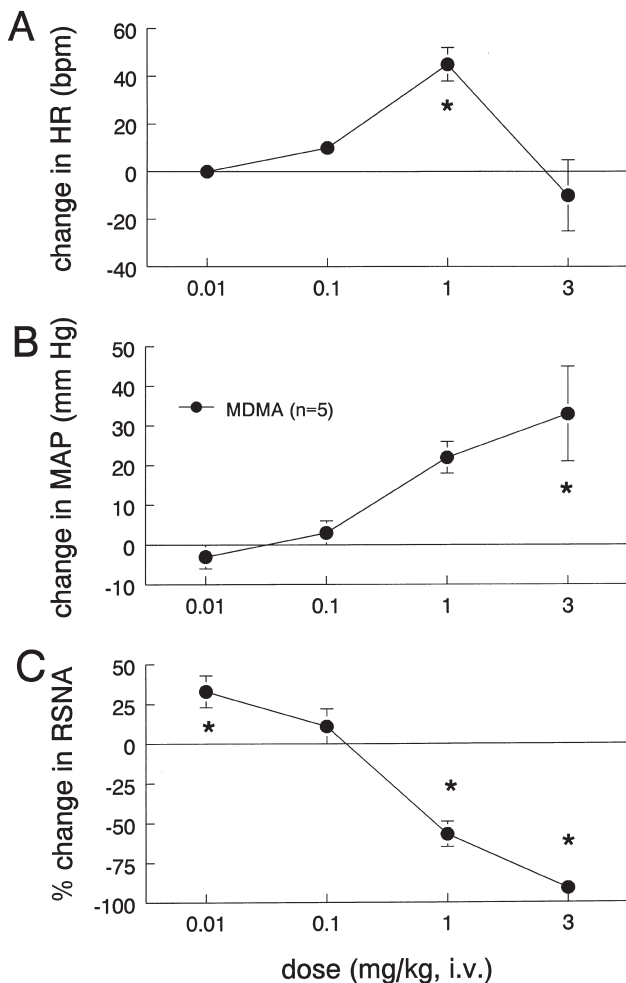


Fig. 3. Dose–effect relations for MDMA and heart rate (HR), mean arterial pressure (MAP) and renal sympathetic nerve activity (RSNA) in rats anesthetized with pentobarbital. In A and B, respectively, peak changes in HR and MAP are plotted versus dose. (C) Magnitude of the peak changes in RSNA (percentage of control) quantified by comparing 1-min intervals of integrated RSNA (epochs/min) before and after drug administration. * $p < 0.05$, different from baseline.

significantly shifted the dose–effect curves for 5-HT and HR to the left, both 2 days, $F(1, 36) = 6.35$, $p < 0.05$, and 2 weeks, $F(1, 41) = 7.96$, $p < 0.05$, after administering the last dose of MDMA (Fig. 4A and B, respectively).

Treatment with neurotoxic doses of MDMA did not alter any of the baroreceptor reflex parameters when reflex function was tested either 2 days or 2 weeks after administering the last neurotoxic dose of MDMA (Table 1).

4. Discussion

In conscious and anesthetized rats, MDMA elicited dose-dependent increases in MAP that were nearly identical to those produced by *d*-amphetamine. These results are consistent with reports that MDMA increases AP in humans [11,36]. MDMA stimulates the release of catecholamines

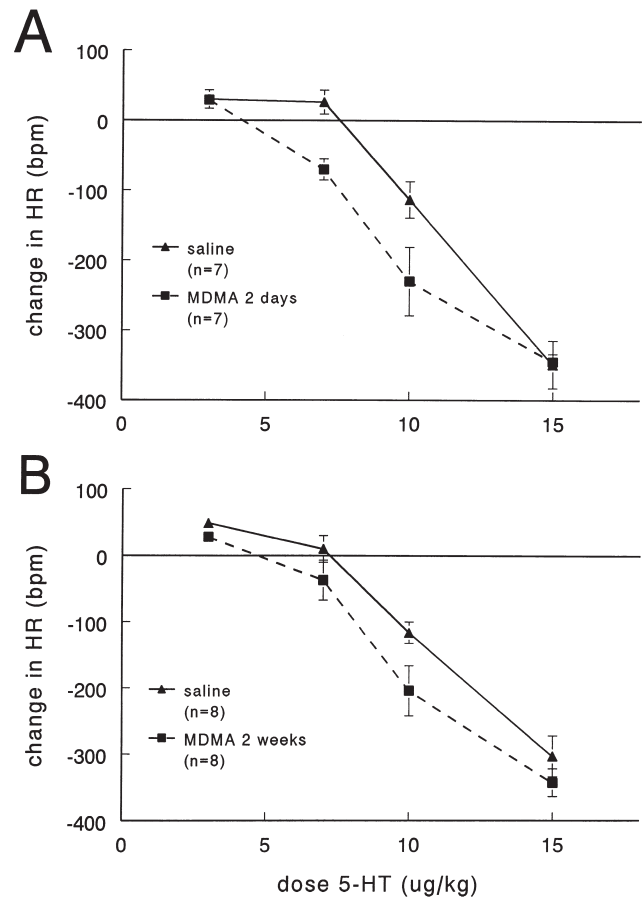


Fig. 4. Comparison of the dose–effect relations for HR and i.v. serotonin (5-HT) in conscious rats pretreated with neurotoxic doses of MDMA (20 mg/kg, s.c., b.i.d. for 4 days) or saline. (A) Magnitude of the peak decrease in heart rate (HR) plotted versus dose of 5-HT in rats tested 2 days after the last MDMA or saline treatment. (B) Magnitude of the peak decrease in HR plotted versus dose of 5-HT in a separate group of rats tested 2 weeks after the last MDMA or saline treatment.

from cardiovascular tissue in vitro [13]. Thus, it would seem logical to conclude that the pressor responses result from the MDMA-mediated release of norepinephrine from peripheral sympathetic nerves. Alpha-adrenergic receptor blockade completely blocks the pressor response elicited by other amphetamines such as methamphetamine [30]. However, in the present study, complete α -adrenergic receptor blockade using phentolamine failed to decrease the magnitude of the pressor response elicited by MDMA, suggesting that the release of norepinephrine from peripheral sympathetic terminals does not produce this initial pressor response. Whether the initial pressor response involved a direct action of MDMA on the vascular smooth muscle, an increase in cardiac output, the release of an endothelial factor, or the release of a cotransmitter from sympathetic terminals remains to be determined. Although phentolamine pretreatment did not affect the magnitude of the pressor response to MDMA, α -adrenergic receptor blockade significantly shortened the duration of the pressor response, sug-

Table 1

Baroreceptor reflex function in rats 2 days or 2 weeks after administering neurotoxic doses of MDMA or control injections of saline

	<i>n</i>	MAP ^a mmHg	HR bpm	P ₁ bpm	P ₂ bpm	R bpm	BP ₅₀ mmHg	G
2 days								
Saline	7	115 ± 2	379 ± 11	312 ± 16	472 ± 12	160 ± 14	111 ± 2	−2.83 ± 0.3
MDMA	7	115 ± 2	355 ± 8	269 ± 13	469 ± 9	200 ± 15	112 ± 8	−3.50 ± 0.5
2 weeks								
Saline	8	114 ± 2	393 ± 12	323 ± 18	488 ± 8	156 ± 17	111 ± 3	−3.00 ± 0.2
MDMA	8	118 ± 2	368 ± 4	303 ± 4	473 ± 9	171 ± 9	113 ± 1	−3.68 ± 0.5

Data are mean ± SEM of number (*n*) of experiments in conscious unrestrained rats. Baroreceptor reflex function was assessed as described in the method section. Neurotoxic doses of MDMA (20 mg/kg, s.c.) were administered twice per day for 4 days.

^a MAP, baseline mean arterial pressure; HR, heart rate, P₁, lower plateau showing the maximal decrease in HR elicited by increases in arterial pressure; P₂, upper plateau showing maximal increase in HR elicited by decreases in arterial pressure; R, range of the reflex (P₂–P₁); BP₅₀, MAP at the midpoint of R; and G, reflex sensitivity or gain.

gesting that catecholamine release, possibly from the adrenal gland played a role in maintaining the pressor response. In the α -adrenergic receptor blocked rats the initial, brief pressor response was followed by hypotension and tachycardia, both of which could be reversed by propranolol. These results further indicate that MDMA releases catecholamines *in vivo*.

The HR responses elicited by MDMA were dependent on the dose administered. Low doses of MDMA produced small but not statistically significant increases in HR, while higher doses elicited bradycardia. In conscious rats, amphetamine also elicited a similar pattern of responses, but due to the variability of the responses, these failed to achieve statistical significance. In a previous study [26] we reported that amphetamine (0.01 to 1 mg/kg, i.v.) elicited small increases in HR (36 ± 17 bpm, max) in conscious rats. Whether doses greater than 1.0 mg/kg would have decreased HR in our original study is unknown. Cocaine, another sympathomimetic stimulant, also elicits a pattern of bradycardic responses in conscious and anesthetized rats that is similar to that elicited by MDMA [1,2,23]. Although the mechanism(s) mediating the changes in HR are unknown, the bradycardic responses elicited by higher doses of MDMA may result from pressor-mediated baroreceptor reflex activation. However, in sinoaortically denervated rats (SAD; lacking a baroreceptor reflex) only a small portion of the bradycardic response elicited by large doses of amphetamine can be attributed to baroreceptor reflex activation [26]. Presumably, the bradycardic response observed in SAD rats reflects the drug's ability to activate vagal input to the heart. Whether the acute administration of MDMA also increases vagal input to the heart remains to be tested.

This study provides the first demonstration that the i.v. administration of MDMA in anesthetized rats produces primarily sympathoinhibition. We have previously shown that amphetamine dose dependently decreases sympathetic nerve activity in pentobarbital-anesthetized rats, and that these responses are mediated, in large part, by the activation of α_2 -adrenergic receptors in the rostral ventrolateral medulla [26]. Pressor-mediated baroreceptor reflex activation

provided only a small component of the sympathoinhibitory response to amphetamine. Although not yet tested, it is reasonable to predict that MDMA also inhibits sympathetic nerve activity by an action on medullary α_2 -adrenergic receptors.

A surprising finding in this study was the observation that i.v. administration of 0.01 mg/kg of MDMA elicited a small, but significant increase in RSNA in anesthetized rats. The increase in RSNA was not accompanied by significant changes in AP or HR. In our previous study, amphetamine did not increase SND in pentobarbital-anesthetized rats at any of the doses tested [26]. However, in some chloralose-anesthetized and conscious rats cocaine produces a brief (lasting less than 5 s) increase in sympathetic nerve activity that precedes a large, prolonged sympathoinhibitory response [1,23]. Although the mechanism responsible for the brief increase in SND elicited by cocaine is unknown, the sympathoinhibitory response that follows results from the activation of medullary α_2 -receptors [2]. In the present study, the sympathoexcitatory responses elicited by small doses of MDMA were not followed by decreases in RSNA. Whether this sympathoexcitatory response reflects an action of MDMA in the central nervous system, sympathetic ganglia or spinal cord is not known.

The repeated administration of MDMA, at doses known to produce serotonergic neurotoxicity, significantly enhanced the sensitivity of the bradycardic portion of the Bezold–Jarisch reflex for at least 2 weeks after giving the last dose of MDMA. The vasovagal, Bezold–Jarisch reflex, is the primary mechanism responsible for vasodepressor or neurocardiogenic syncope [33]. The clinical literature contains reports of syncope and respiratory depression occurring in individuals using MDMA [25,32]. An increase in the sensitivity or effectiveness of the Bezold–Jarisch reflex may also increase the risk of cardiac arrhythmia, especially in the presence of elevated catecholamine levels [22,37].

In contrast to its effects on the Bezold–Jarisch reflex, the administration of neurotoxic doses of MDMA failed to significantly affect baroreceptor reflex control. To our knowledge, no studies have looked at the effect of the repeated ad-

ministration of amphetamine-like drugs on baroreceptor reflex control. However, several investigators have suggested that the acute administration of cocaine attenuates baroreceptor reflex control of HR [3,24]. The fact that neurotoxic doses of MDMA altered Bezold–Jarisch, but not baroreceptor reflex-mediated vagal control of HR, suggests that separate pathways and/or mechanism(s) may be mediating the vagal components of each reflex.

In our study, neurotoxic doses of MDMA enhanced the vagal portion of the Bezold–Jarisch reflex without altering baroreceptor reflex function. However, in human subjects with a long history of MDMA use (1.5 to 7 years), examination of the cardiac responses to the Valsalva maneuver and heart rate variability showed evidence of decreased vagal tone and autonomic dysfunction [5]. Although these data are tempered by the fact that all of the subjects in this study were polydrug users, they do suggest that, in addition to neurotoxic doses, long-term use of MDMA may also produce significant cardiovascular and cardiovascular reflex changes. Supporting this possibility are our preliminary findings that daily administration of MDMA to rats for a total of 28 days produces significant myocardial pathology including contraction band necrosis, inflammation, leucocytic infiltration, fibrosis, and ultrastructural changes [9,35]. In addition, at autopsy the hearts of five of seven individuals who died after using MDMA showed evidence of necrosis and inflammatory responses similar to those seen in our rat study [27]. The amount or duration of MDMA use by these individuals was not reported. Amphetamine and methamphetamine also produce similar pathological alterations [6,20,28].

This study was the first to specifically evaluate the acute cardiovascular and sympathetic nerve responses elicited by MDMA in rats *in vivo*. We have demonstrated that the acute administration of MDMA elicits HR, MAP, and sympathetic nerve responses that are similar to those elicited by *d*-amphetamine, and that these responses appear to involve catecholaminergic and noncatecholaminergic-dependent mechanisms. The administration of MDMA, at doses known to produce serotonergic neurotoxicity, significantly enhanced the sensitivity of the bradycardic portion of the Bezold–Jarisch reflex for at least 2 weeks after administering the final dose of MDMA. As discussed above, such changes in cardiovascular reflex function may be clinically significant. Thus, it appears that MDMA has significant acute and chronic effects on cardiovascular and cardiovascular reflex function. MDMA may also produce cardiovascular toxicity similar to that produced by other amphetamine analogs. In view of the increasing recreational use of MDMA, further studies to evaluate the cardiovascular and cardiac toxicity of this agent are warranted.

Acknowledgment

This work was supported by a grant from the National Institute on Drug Abuse (DA 08255). The authors would

like to thank Dr. Daniel R. Kapusta for his editorial comments and suggestions.

References

- [1] Abrahams TP, Cuntapay MC, Varner KJ. Sympathetic nerve responses elicited by cocaine in anesthetized and conscious rats. *Physiol Behav* 1996;59:109–15.
- [2] Abrahams TP, Liu W, Varner KJ. Blockade of alpha-2 adrenergic receptors in the rostral ventrolateral medulla attenuates the sympathoinhibitory response to cocaine. *J Pharmacol Exp Ther* 1996;279:967–74.
- [3] Anderson MC, Yang M, Nelson SH, Steinslang OS. Cocaine inhibits baroreflex control of blood pressure by actions at arterial baroreceptors. *Am J Physiol* 1982;258:H1244–9.
- [4] Battaglia G, Yeh SY, O'Hern E, Molliver ME, Kuhar MJ, De Souza E. 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of (³H)paroxetine-labeled serotonin uptake sites. *J Pharmacol Exp Ther* 1987;242:911–6.
- [5] Brody S, Krause C, Veit R, Rau H. Cardiovascular autonomic dysregulation in users of MDMA ("ecstasy"). *Psychopharmacology (Berlin)* 1998;136:390–3.
- [6] Call TD, Hartneck J, Dickinson A, Hartman CW, Bartel AG. Acute cardiomyopathy secondary to intravenous amphetamine abuse. *Ann Intern Med* 1982;97:559–60.
- [7] Commins DL, Vosmer RM, Woolverton WL, Schuster CR, Seiden LS. Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 1987;241:338–45.
- [8] Cuomo M, Dymont P, Gammino V. Increasing use of ecstasy (MDMA) and other hallucinogens on a college campus. *J Am Coll Health* 1994;42:271–4.
- [9] Delcarpio JB, Moerschbaeher JM, Varner KJ. Electron microscopic evaluation of the cardiac toxicity elicited by 3,4 methylenedioxymethamphetamine (MDMA). *NIDA Res Monogr* 1998;179:111.
- [10] DeSouza EB, Battaglia G. Effects of MDMA and MDA on brain serotonin neurons: evidence from neurochemical and autoradiographic studies. *NIDA Res Monogr* 1989;94:196–222.
- [11] Downing J. The psychological and physiological effects of MDMA on normal volunteers. *J Psychoactive Drugs* 1986;18:335–40.
- [12] Fitzgerald JL, Reid JJ. Methylenedioxymethamphetamine (MDMA) has differential effects on monoamine release in rat brain slices. *Eur J Pharmacol* 1990;191:217–20.
- [13] Fitzgerald JL, Reid JJ. Sympathomimetic actions of methylenedioxymethamphetamine in rat and rabbit isolated cardiovascular tissues. *J Pharm Pharmacol* 1994;46:826–32.
- [14] Gordon CJ, Watkinson WP, O'Callaghan JP, Miller DB. Effects of 3,4-methylenedioxymethamphetamine on autonomic thermoregulatory responses of the rat. *Pharmacol Biochem Behav* 1991;38:339–44.
- [15] Graeme PD, McDonough ET, Bost RO. "Eve" and "Ecstasy" a report of five deaths associated with the use of MDEA and MDMA. *JAMA* 1987;257:1615–7.
- [16] Green AR, Cross AJ, Goodwin GM. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine. *Psychopharmacology (Berlin)* 1995;119:247–60.
- [17] Guyenet PG. Role of the ventral medulla oblongata in blood pressure regulation. In: Loewy AD, Spyer KM, editors. *Central Regulation of Autonomic Functions*. New York: Oxford University Press, 1988. pp. 45–167.
- [18] Head GA, McCarty R. Vagal and sympathetic components of the heart rate range and gain of the baroreceptor-heart rate reflex in conscious rats. *J Auton Nerv Syst* 1987;21:203–13.
- [19] Henry JA, Jefferys KJ, Dawling S. Toxicity deaths associated with

- 3,4-methylenedioxymethamphetamine "ecstasy." *Lancet* 1992;340:384–7.
- [20] Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. *JAMA* 1991;265:1152–4.
- [21] Johnson MP, Hoffman AJ, Nichols DE. Effects of the enantiomers of MDMA and related analogues on [^3H]serotonin and [^3H]dopamine release from superfused rat brain slices. *Eur J Pharmacol* 1986;132:269–76.
- [22] Josephson ME, Marchlinski FE, Buxton AE. The bradyarrhythmias and the tachyarrhythmias. In: Isselbacher KL, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, editors. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill Inc., 1994. pp. 1011–36.
- [23] Knuepfer MM, Branch CA. Cardiovascular responses to cocaine are initially mediated by the central nervous system in rats. *J Pharmacol Exp Ther* 1992;263:734–40.
- [24] Knuepfer MM, McCann RKL, Kamaly L. Effects of cocaine on baroreflex control of heart rate in conscious rats. *J Auton Nerv Syst* 1993;43:257–66.
- [25] Leister MB, Grob CS, Bravo GL, Wals RN. Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine use. *J Nerv Mental Dis* 1992;180:345–52.
- [26] Liu W, Varner KJ. Characterization of the sympathetic nerve responses to amphetamine: role of central α_2 -adrenergic receptors. *J Cardiovasc Pharmacol* 1996;28:1–11.
- [27] Milroy CM, Clarke JC, Forrest ARW. Pathology of deaths associated with "ecstasy" and "eve" misuse. *J Clin Pathol* 1996;49:149–53.
- [28] Ragland AS, Ismail Y, Arsura EL. Myocardial infarction after amphetamine use. *Am Heart J* 1993;125:247–9.
- [29] Ricaurte GA, Bryan G, Strauss L, Leiden L, Schuster C. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science* 1985;229:986–8.
- [30] Schindler CW, Zheng JW, Tella SR, Goldberg SR. Pharmacological mechanisms in the cardiovascular effects of methamphetamine in conscious squirrel monkeys. *Pharmacol Biochem Behav* 1992;42:791–6.
- [31] Seiden LS, Kleven MS. Methamphetamine and related drugs: toxicity and resulting behavioral changes in amphetamine and related designer drugs. *NIDA Res Monogr* 1989;94:146–60.
- [32] Solowij N, Hall W, Lee N. Recreational MDMA use in Sydney: a profile of "Ecstasy" and their experiences with the drug. *Br J Addict* 1992;87:1161–172.
- [33] Somers VK, Mark AL. The Bezold–Jarisch reflex. In: Robertson D, Low PA, Polinsky RJ, editors. *Primer on the Autonomic Nervous System*. San Diego: Academic Press, 1996. pp. 66–69.
- [34] Steele TD, McCann VD, Ricaurte GA. 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy"): pharmacology and toxicology in animals and humans. *Addiction* 1994;89:539–51.
- [35] Varner KJ, Delcarpio JB, Moerschbaecher JM. Cardiac toxicity elicited by repeated administration of 3,4 methylenedioxymethamphetamine (MDMA). *NIDA Res Monogr* 1998;179:214.
- [36] Vollenweider FX, Gamma A, Liechti M, Huber T. Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. *Neuropsychopharmacology* 1998;19:241–51.
- [37] Waldo AL, Witt AL. Mechanisms of cardiac arrhythmias and conduction disturbances. In: O'Rourke RA, Roberts R, Sonnenblick EH, editors. *The Heart*, 8th ed. New York: McGraw-Hill, 1994. pp. 659–704.