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Sympathomimetic Actions of Methylenedioxymethamphetamine in Rat and Rabbit Isolated Cardiovascular Tissues

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Abstract—The aim of this study was to investigate the actions of methylenedioxymethamphetamine (MDMA) in several isolated cardiovascular tissues. In spontaneously beating rat atria, concentration-dependent positive chronotropic responses to MDMA and amphetamine were blocked by the neuronal-uptake inhibitor desipramine (1 μM) and the β-adrenoceptor antagonist propranolol (1 μM). In atria incubated with [^{3}H]noradrenaline to label transmitter stores, 10 μM MDMA and 1 μM amphetamine increased the resting outflow of radioactivity, while 1 μM desipramine had no effect on resting outflow. The MDMA- and amphetamine-induced release of radioactivity were blocked by 1 μM desipramine. MDMA, amphetamine and desipramine each enhanced the electrical stimulation-induced (2 Hz, 30-s train) release of radioactivity; the enhancing effects of MDMA and amphetamine were blocked by 1 μM desipramine. In rat isolated perfused hearts, MDMA (1 and 10 μM) increased heart rate by a similar amount to the increase caused by noradrenaline (10 and 50 nM). MDMA also induced dysrhythmias in 7 out of 11 rat isolated perfused heart preparations. In rabbit isolated perfused and superfused ear arteries preloaded with [^{3}H]noradrenaline, MDMA increased the resting release of radioactivity by 230 ± 18% (n = 6) of control resting release; the increase was accompanied by a rise in perfusion pressure of 17 ± 7 mmHg (n = 6). MDMA also facilitated the vasoconstrictor responses to noradrenaline (3–9 ng) and perivascular nerve stimulation (1–5 Hz, 10-s train). MDMA-induced vasoconstriction and the facilitation of vasoconstrictor responses to noradrenaline and electrical stimulation were blocked by 1 μM desipramine. These results suggest that MDMA has similar sympathomimetic activity to amphetamine on cardiovascular tissues. The sympathomimetic actions of MDMA could account for the cardiovascular side-effects associated with its use.

3,4-Methylenedioxymethamphetamine (MDMA) is a psychoactive amphetamine derivative (Fig. 1) that is used in the community as the recreational drug Ecstasy. MDMA is known to release monoamine transmitters in the central nervous system (Johnson et al 1986; Schmidt et al 1987; Fitzgerald & Reid 1990, 1993); however, there have been few reports on its effects in the peripheral nervous system. Side-effects common to users of both amphetamine and MDMA include tachycardia and hypertension (Hayner & McKinney 1986), and several deaths associated with the use of MDMA have been thought to be due to the exacerbation of predisposing cardiovascular conditions (Dowling et al 1987).

There is some evidence that MDMA has appreciable effects on the cardiovascular system. Thus in rats, MDMA (20 mg kg^{-1}) produces a large increase in heart rate (Gordon et al 1991) and in the mouse heart, MDMA transiently decreases noradrenaline content (Steele et al 1989). The major metabolite of MDMA, methylenedioxyamphetamine (MDA) (Fitzgerald et al 1989) has sympathomimetic effects which have been reported by a number of investigators. MDA increases heart rate in the cat isolated perfused heart (Gunn et al 1939), increases blood pressure and heart rate in the anaesthetized cat (Nichols et al 1975) and anaesthetized dog (Bell et al 1974), and causes the release of [^{3}H]noradrenaline from rabbit isolated atria (Paton 1975). The sympathomimetic effects of MDA resemble those of amphetamine, which is known to increase atrial rate (Pesce & Adler-Graschinsky 1983) through the release of transmitter noradrenaline from intraneuronal stores (Paton 1975). The present study was designed to characterize the sympathomimetic actions of MDMA on noradrenergic transmission in several isolated cardiovascular tissues.

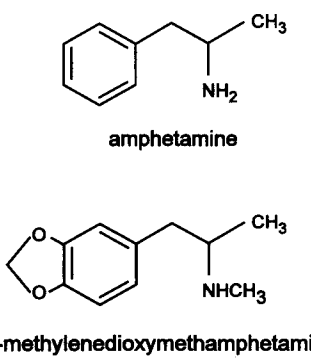

FIG. 1. The structural formulae of amphetamine and 3,4-methylenedioxymethamphetamine.

Materials and Methods

Chronotropic responses in rat isolated atria

Female Sprague-Dawley rats, 250–300 g, were decapitated and the right and left atria were rapidly removed. The

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combined right and left atrial preparations were mounted under a resting tension of 1 g in physiological salt solution (PSS) of the following composition (mM): NaCl 118·0, KCl 4·7, $CaCl_2$ 2·5, $MgSO_4$ 0·45, $NaHCO_3$ 25·0, KH_2PO_4 1·03, D-glucose 11·1, Na_2EDTA 0·067, ascorbic acid 0·14. The PSS was continuously gassed with 95% O_2–5% CO_2 and maintained at 37°C. The rate and force of contraction were measured with a strain-gauge transducer and recorded on a Grass polygraph recorder. Intramural nerves were electrically stimulated at various frequencies with square wave pulses of 1 ms duration at a voltage gradient of 12·5 V cm^{-1}, delivered through two platinum wire electrodes, one on either side of the atrial preparation. Atropine (1 μM) was present in the PSS at all times to block cholinergic responses to nerve stimulation. Atria were equilibrated in PSS for 30 min before any experimental observations were made.

Chronotropic responses to cumulative concentrations of MDMA (0·01–60 μM) and amphetamine (0·1–60 μM) were obtained before and 30 min after the addition of desipramine (1 μM) or propranolol (1 μM). Chronotropic responses to electrical stimulation (4 Hz, 5-s train) and tyramine (3 μM) were also obtained in the presence and absence of desipramine (1 μM) or propranolol (1 μM).

Release of radioactivity from rat atria prelabelled with [^{3}H]noradrenaline

Changes in noradrenaline release were investigated according to the method described by Loiacono et al (1985). Atria were incubated with 0·4 μM [^{3}H]noradrenaline for 20 min to radioactively label transmitter stores. Following incubation, the bathing solution was changed initially every 1 min for 10 min, and then every 3 min over a 50-min period to remove any extracellular or loosely bound radioactivity. Thirty minutes after the commencement of this wash-out period, atria were given a priming stimulation (2 Hz, 30 s). Following the wash-out period, atria were given two periods ($Stim_1$ and $Stim_2$) of electrical stimulation (2 Hz, 30 s), 33 min apart. Unless otherwise indicated, drugs were added to the bathing solution 21 min before $Stim_2$ and were present for the remainder of the experiment.

The bathing solution was collected every 3 min beginning 9 min before $Stim_1$, until 9 min after $Stim_2$. At the completion of the experiment, atria were blotted dry and solubilized in Soluene (Packard Instruments). The radioactive contents of solubilized atria and 3-min samples of the bathing solution were determined by liquid scintillation counting after the addition of 6 mL Pico-fluor 40 (Packard Instruments). Corrections for counting efficiency were made by automatic external standardization.

The outflow of radioactivity from the atria was expressed as a percentage of the total tissue radioactivity at the time of sample collection. The resting outflow of radioactivity was calculated as the average radioactive outflow in the two samples immediately before stimulation. The resting outflow before $Stim_2$ was expressed as a ratio of that before $Stim_1$ (R_2/R_1).

The stimulation-induced (S-I) outflow of radioactivity was used as an index of noradrenaline release. It was calculated as the difference between the outflow of radioactivity in the two samples following electrical stimulation and the two samples before stimulation. The S-I outflow evoked by $Stim_2$ has been expressed as a ratio of that evoked by $Stim_1$ (S_2/S_1).

Rat isolated perfused heart

Female Sprague-Dawley rats, 250–300 g, pretreated with heparin (1000 units kg^{-1}, i.p.) 30 min before the experiment, were decapitated. Hearts were rapidly removed and retrogradely perfused through the aorta by the Langendorff method, with PSS bubbled with 95% O_2–5% CO_2 at 37°C at a rate of 7 mL min^{-1}. A tension of 2 g was applied to the apex of the heart, and the force and rate of beating were measured with a strain-gauge transducer. Perfusion pressure in the aortic cannula was measured with a pressure transducer. Responses were recorded on a Grass polygraph. Drugs were given in the perfusion fluid over a 7-min period when specified.

Vasoconstrictor responses in rabbit isolated perfused ear artery

The effects of MDMA in the rabbit isolated ear artery were investigated according to the method of Wong-Dusting & Rand (1988). Rabbits, 1·5–3 kg, of either sex were killed by a blow to the head and 4-cm proximal segments of central ear artery were placed vertically under 0·5 g tension and perfused and superfused with PSS at a rate of 2 mL min^{-1}. Perivascular nerves were electrically stimulated with square-wave pulses of 1 ms duration at 50 V, by a bipolar platinum electrode placed around the artery. Perfusion pressure was measured by a pressure transducer and recorded on either a Rikadenki or Grass recorder and an increase in perfusion pressure was taken as an index of vasoconstriction. Responses to bolus injections of noradrenaline (3, 6 and 9 ng), and to perivascular nerve stimulation (1, 2 and 5 Hz for 10 s) were obtained before and 30 min after exposure to 10 μM MDMA. In some experiments desipramine (1 μM) was present throughout perfusion from 15 min before the addition of MDMA to the PSS.

Release of radioactivity from rabbit ear arteries preloaded with [^{3}H]noradrenaline

Artery segments were incubated with [^{3}H]noradrenaline (4 μCi mL^{-1}, 1 μM) for 60 min to radioactively label transmitter stores. Following incubation, segments were perfused and superfused with PSS for at least 90 min to remove loosely bound radioactivity. Perivascular nerves were stimulated with square-wave pulses of 1 ms duration at 50 V, by a bipolar platinum electrode placed around the artery. The superfusate was collected in 2-min fractions and the amount of radioactivity in each sample measured by liquid scintillation spectroscopy. The resting outflow of radioactivity was taken as the mean amount of radioactivity present in the two samples before each stimulation period. The S-I outflow of radioactivity was calculated as the difference between the radioactive outflow in the two samples following electrical stimulation and the two samples immediately before stimulation.

Statistical analyses

Values are expressed as means ± s.e.m., or means with 95% confidence limits, and n represents the number of animals tested. The differences between means were assessed by either a one-way multivariate analysis of variance or a two-way analysis of variance followed by a Student's

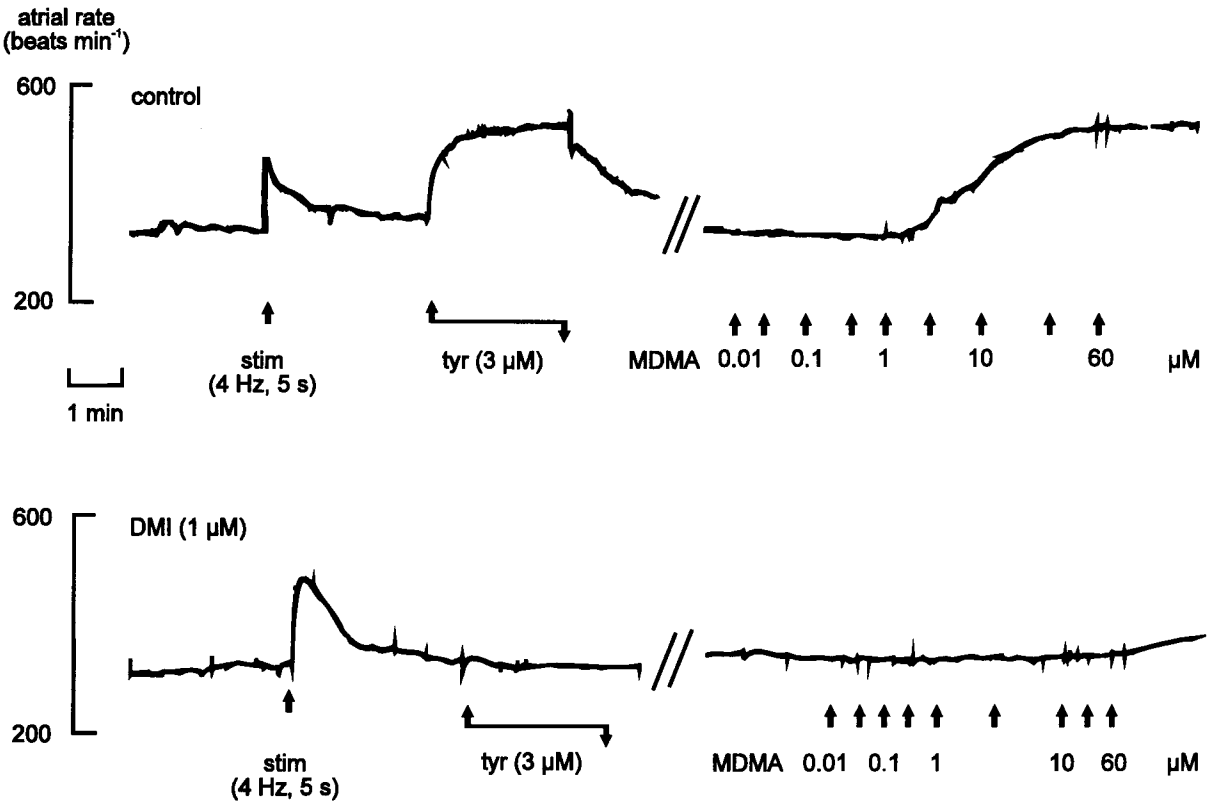

FIG. 2. Typical trace from an experiment showing the chronotropic responses to electrical stimulation (stim), tyramine (tyr) and MDMA in rat isolated atria before (control) and after a 30-min exposure to 1 μM desipramine (DMI).

t-test. Probability values of less than 0·05 were taken to indicate statistical significance. Regression lines were fitted to the linear portion of the log concentration-response curves for MDMA and amphetamine by the method of least squares. EC50 values were interpolated from the regression lines, and correspond to a concentration producing 50% of the maximum response.

Drugs

The following drugs were used: (±)-amphetamine sulphate (Sigma, USA), atropine sulphate (Sigma, USA), desipramine hydrochloride (Sigma, USA), (±)-methylenedioxymethamphetamine hydrochloride (Makor, Israel), noradrenaline bitartrate (Sigma, USA), (−)-[7,8-^{3}H]-noradrenaline (sp. act. 10·8 Ci mmol^{-1}, New England Nuclear, USA), propranolol hydrochloride (Sigma, USA) and tyramine hydrochloride (Sigma, USA).

All drugs were dissolved in distilled water to give a concentration of 10 mM, and then made up to appropriate concentrations with PSS.

Results

Chronotropic responses in isolated atria

The basal rate of spontaneously beating atria was 325 ± 11 beats min^{-1} (n = 8). Electrical stimulation (4 Hz, 5-s train) and tyramine (3 μM) caused increases in rate of 107 ± 10 (n = 8) and 115 ± 8 beats min^{-1} (n = 8), respectively (Fig. 2).

MDMA and amphetamine increased atrial rate in a concentration-dependent manner (Fig. 3). Amphetamine was approximately 3-fold more potent than MDMA; the EC50 values were 0·94 μM (95% confidence limits: 0·66–1·35 μM, n = 10) and 2·92 μM (2·58–3·30 μM, n = 10), respectively. There was no significant difference between the maximal response to MDMA and amphetamine (Fig. 3). Positive chronotropic responses to MDMA were abolished in the presence of either 1 μM desipramine or 1 μM propranolol (Figs 2, 3). Responses to amphetamine were markedly reduced in the presence of 1 μM desipramine (Fig. 3). Desipramine (1 μM) also prolonged the positive chronotropic response to nerve stimulation and completely inhibited the positive chronotropic response to 3 μM tyramine (Fig. 2). Time-control experiments performed in the absence of desipramine or propranolol showed that chronotropic responses to amphetamine (data not shown) and MDMA (Fig. 3B) were reproducible.

Release of radioactivity from isolated atria preloaded with [^{3}H]noradrenaline

MDMA (10 μM) and amphetamine (1 μM) increased the resting outflow of radioactivity (R_2/R_1), but desipramine had no significant effect on resting outflow (Table 1). In the presence of 1 μM desipramine, MDMA (10 μM) and amphetamine (1 μM) did not enhance the resting outflow (Table 1). Electrical stimulation (2 Hz, 30-s train) evoked an outflow of radioactivity from atria incubated with [^{3}H]noradrenaline. The S-I outflow of radioactivity (S_2/S_1) was significantly enhanced ($P < 0·05$, n = 5) by 10 μM MDMA, 1 μM amphet-

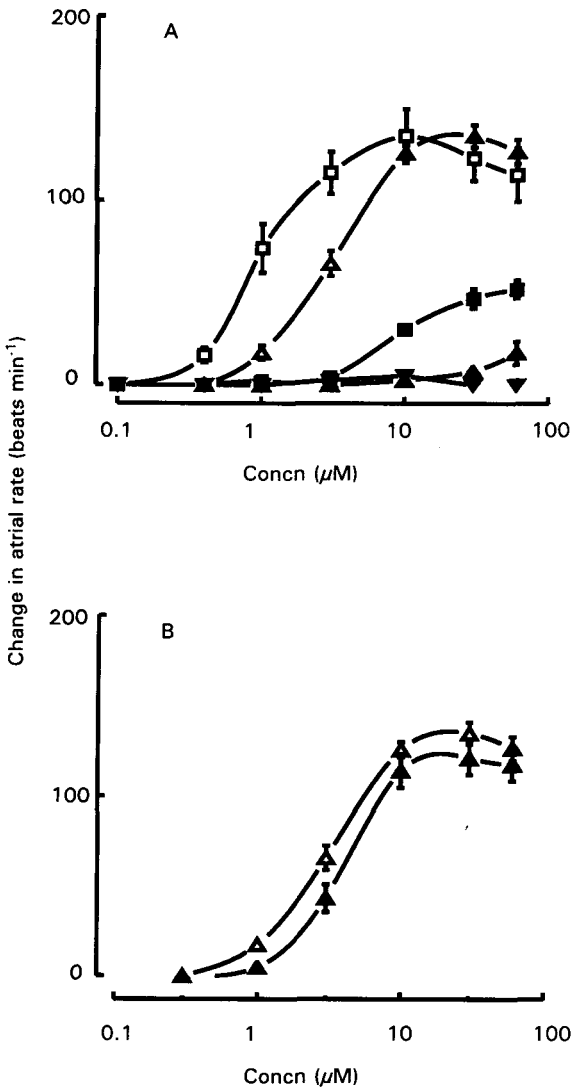

FIG. 3. A. Increases in atrial rate produced by MDMA and amphetamine before (△ and □, respectively) and after 30 min exposure to 1 μM desipramine (▲ and ■, respectively) or 1 μM propranolol (▼). Each point is the mean and vertical bar the s.e.m. of values from 10 animals. B. Time-control concentration-response curves for the positive chronotropic effect of MDMA in the absence of desipramine or propranolol. A 30-min equilibration was allowed between curves 1 (△) and 2 (▲). Each point is the mean and vertical bar the s.e.m. of values from 4–10 animals.

Table 1. The effects of MDMA (10 μM), amphetamine (1 μM), and desipramine (1 μM) on the resting outflow of radioactivity (R_2/R_1) and the stimulation-induced (S-I) outflow of radioactivity (S_2/S_1) from atria previously incubated with [^{3}H]noradrenaline.

	Resting outflow (R_2/R_1)	S-I outflow (S_2/S_1)	With desipramine present throughout	
			Resting outflow (R_2/R_1)	S-I outflow (S_2/S_1)
Control	0·75 ± 0·05	1·28 ± 0·06	0·83 ± 0·02	1·21 ± 0·06
MDMA	1·81 ± 0·21*	1·75 ± 0·10*	0·77 ± 0·06	1·21 ± 0·07
Amphetamine	1·50 ± 0·03*	1·65 ± 0·22*	0·74 ± 0·04	1·23 ± 0·09
Desipramine	0·91 ± 0·03	1·73 ± 0·07*	—	—

Mean ± s.e.m. from 3–5 experiments. *$P < 0·05$ by one-way, multiple analysis of variance, compared with the control value.

Table 2. Effect of 10 μM MDMA on vasoconstrictor responses (change in perfusion pressure as % control responses) to electrical stimulation in the rabbit isolated ear artery.

	Frequency of stimulation		
	1 Hz	2 Hz	5 Hz
MDMA (10 μM)	172 ± 34	155 ± 15	133 ± 7
MDMA (10 μM) + desipramine (1 μM)	66 ± 18	77 ± 8	78 ± 14

Mean ± s.e.m. from 3–6 experiments.

amine and 1 μM desipramine (Table 1). In the presence of 1 μM desipramine (Table 1), MDMA (10 μM) and amphetamine (1 μM) had no effect on S-I outflow (Table 1).

Rat isolated perfused heart

The basal rate of rat isolated perfused hearts was 295 ± 8 beats min^{-1} (n = 14) and the basal perfusion pressure was 41 ± 2 mmHg (n = 14). Noradrenaline (10 and 50 nM) increased the heart rate by 10 ± 2 (n = 8) and 25 ± 4 beats min^{-1} (n = 5), respectively. MDMA (1 and 10 μM) increased the heart rate by 16 ± 3 (n = 6) and 45 ± 7 beats min^{-1} (n = 5), respectively. There were no consistent effects of MDMA on either force of contraction or perfusion pressure (Fig. 4B). Dysrhythmias were observed in 6 out of 20 hearts during a 7-min perfusion with 50 nM noradrenaline, and in 7 out of 11 hearts during perfusion with 10 μM MDMA (Fig. 4).

Rabbit isolated perfused and superfused ear artery

A 14-min exposure to MDMA (10 μM) caused a sustained increase in the basal perfusion pressure (30 ± 2 mmHg, n = 6) of 17 ± 7 mmHg (n = 6) and caused a 231 ± 18% (n = 6) increase in the resting outflow of radioactivity (Fig. 5). The vasoconstrictor response to 10 μM MDMA was abolished in the presence of 1 μM desipramine (data not shown).

Perivascular nerve stimulation (1, 2 and 5 Hz, 10-s train) caused an increase in perfusion pressure of 57 ± 18 (n = 6), 97 ± 31 (n = 6), and 140 ± 38 mmHg (n = 6), respectively. MDMA (10 μM) enhanced the vasoconstrictor responses to nerve stimulation and the enhancement was abolished in the presence of 1 μM desipramine (Table 2). Electrical stimulation (1–5 Hz, 10-s train) caused a S-I outflow of radioactivity which was significantly enhanced ($P < 0·05$, two-way analysis of variance, n = 5) by 10 μM MDMA (Table 3).

Vasoconstrictor responses to bolus injections of noradrenaline (3, 6 and 9 ng) were significantly enhanced ($P < 0·05$, n = 6) in the presence of 10 μM MDMA (Fig. 6).

Table 3. Effect of 10 μM MDMA on the stimulation-induced outflow of radioactivity (d min^{-1}) from arteries previously incubated with [^{3}H]noradrenaline.

	Frequency of stimulation		
	1 Hz	2 Hz	5 Hz
Before exposure to MDMA	451 ± 110	893 ± 184	2422 ± 306
After exposure to MDMA	1389 ± 400	3252 ± 533	6870 ± 411

Mean ± s.e.m. from 3–5 animals.

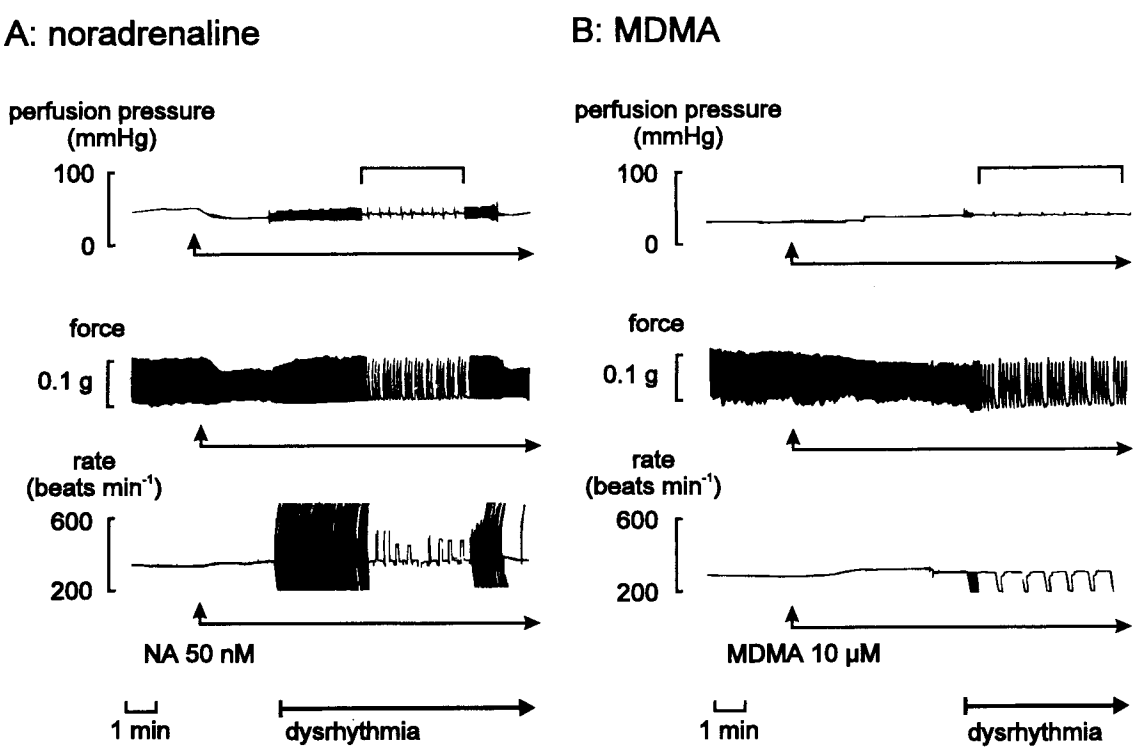

FIG. 4. Representative traces showing changes in perfusion pressure, force of contraction and heart rate in response to A. 50 nM noradrenaline (NA) or B. 10 μM MDMA in the rat isolated perfused heart. Note that in both instances, the heart became dysrhythmic after perfusion with noradrenaline or MDMA; the chart speed was increased in the periods indicated under the brackets, to allow a more detailed examination of changes occurring during the dysrhythmias.

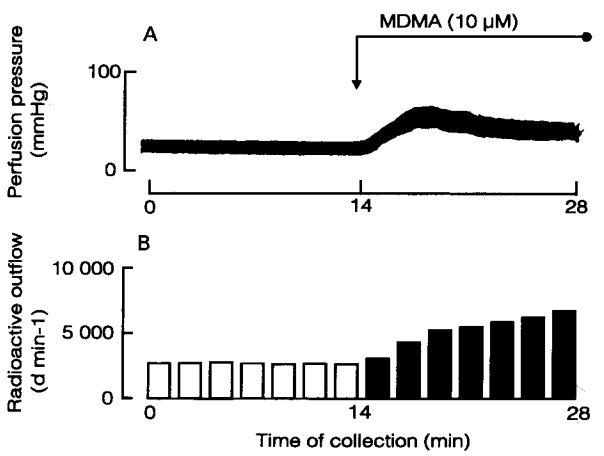

FIG. 5. A. Representative recording showing the effect of MDMA (10 μM) on perfusion pressure in rabbit isolated ear artery. B. Effect of MDMA (10 μM) in the same experiment on radioactive outflow from rabbit ear artery previously incubated with [^{3}H]noradrenaline to preload transmitter stores. Each column represents the radioactive outflow measured in 2-min samples of the perfusate. MDMA (10 μM) was added to the perfusate where indicated, 14 min after the commencement of sample collection.

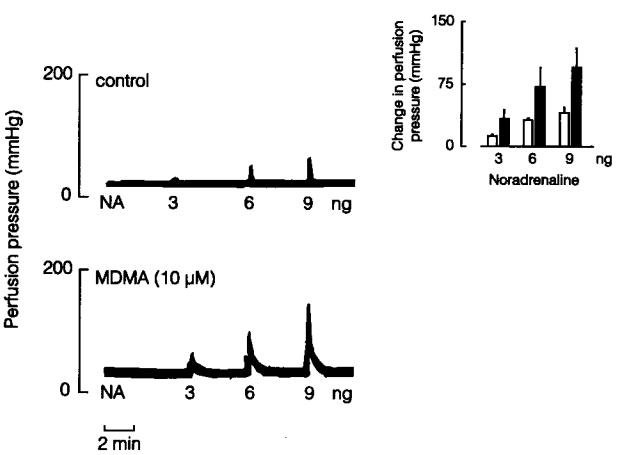

FIG. 6. Representative trace from an experiment showing vasoconstrictor responses to bolus injections of noradrenaline (NA) before (control) and after 30 min exposure to 10 μM MDMA. Note that the direct vasoconstrictor action of 10 μM MDMA was prominent immediately on addition of MDMA to the perfusion fluid, but had waned considerably after 30 min. Inset. Mean results from six experiments. Columns represent the mean and vertical bars the s.e.m. of values obtained in the absence (□) and the presence (■) of 10 μM MDMA.

Discussion

In the peripheral autonomic nervous system, indirectly-acting sympathomimetic amines such as amphetamine, cause the release of noradrenaline (Burn & Rand 1958), inhibit the neuronal uptake carrier (Burgen & Iversen 1965), and facilitate responses to neuronally released and exogenous noradrenaline (Furchgott et al 1963). As the cardiovascular effects of indirectly acting amines are mediated through carrier-mediated release of neurotransmitter noradrenaline, the effects can be attenuated by adrenoceptor antagonists (Nichols et al 1975), inhibitors of the neuronal uptake carrier (Ross & Kelder 1979), and agents such as reserpine that deplete the neuronal stores of noradrenaline (Burn & Rand 1958; Trendelenberg et al 1963).

The present study provides the first evidence that MDMA, like amphetamine, has sympathomimetic actions in isolated cardiovascular tissues. In rat atria, MDMA and amphetamine had concentration-dependent positive chronotropic actions; maximal effects were approximately the same, but amphetamine was slightly (3-fold) more potent than MDMA. The chronotropic effects of MDMA and amphetamine were blocked by the neuronal uptake blocker desipramine and those of MDMA by the β-adrenoceptor antagonist propranolol, suggesting that the responses to MDMA and amphetamine were mediated indirectly by noradrenaline release. This was confirmed by the finding that MDMA and amphetamine increased the outflow of radioactivity from atria previously incubated with [^{3}H]noradrenaline; this effect was also abolished by neuronal uptake blockade with desipramine.

Desipramine enhanced the S-I outflow of radioactivity from rat atria incubated with [^{3}H]noradrenaline, in accordance with Story et al (1974), who demonstrated in guinea-pig atria labelled with [^{3}H]noradrenaline, that desipramine (1 μM) enhanced the S-I outflow of radioactivity without affecting the resting outflow of radioactivity. MDMA and amphetamine also enhanced the S-I outflow of radioactivity in the present study, but this action cannot be explained by blockade of neuronal reuptake, since MDMA and amphetamine also increased the resting outflow of radioactivity, whereas neuronal uptake inhibition with desipramine did not affect the resting outflow of radioactivity. It is likely, therefore, that the effects of MDMA on both functional responses and release of transmitter are mediated by noradrenaline released through reversal of the neuronal uptake carrier, as suggested by several investigators for the brain (Johnson et al 1986; Schmidt et al 1987; Fitzgerald & Reid 1990, 1993). In a previous study using rabbit atrial strips (Paton 1975), a similar mechanism was suggested for the action of MDA in inhibiting [^{3}H]metaraminol accumulation and in releasing [^{3}H]noradrenaline.

In the rat isolated perfused heart MDMA not only increased heart rate, but frequently produced dysrhythmias similar to those produced by noradrenaline. This supports the suggestion that MDMA may act as an indirectly-acting sympathomimetic in the heart to release noradrenaline.

In the rabbit isolated ear artery preloaded with [^{3}H]noradrenaline, MDMA-induced vasoconstriction was accompanied by an increase in the radioactive outflow, and was abolished by the addition of desipramine. These results suggest that, in agreement with results in the atria, MDMA exerts its sympathomimetic effects in the ear artery by releasing noradrenaline from perivascular nerves, via an amphetamine-like mechanism. In addition, vasoconstrictor responses to nerve stimulation and exogenous noradrenaline were enhanced by MDMA in the rabbit ear artery. The facilitatory action of MDMA on responses to vasoconstrictor stimuli was blocked when desipramine was present in the superfusion fluid, and is likely to be due to inhibition of the neuronal uptake of noradrenaline resulting in an enhancement of the response to noradrenaline.

The concentrations of MDMA which exert sympathomimetic effects in isolated cardiac and vascular preparations from experimental animals, are similar to the concentrations of MDMA found in human autopsy blood samples from deaths associated with MDMA use (Dowling 1990). Tolerance develops to the cardiovascular sympathomimetic effects of amphetamine when it is used repeatedly (Rosenberg et al 1963). However, the infrequent or occasional use patterns characteristic of some MDMA users (Rosenbaum et al 1990), may place high-dose users at risk of cardiovascular complications, as previously reported for acute MDA poisoning (Simpson & Rumack 1981).

MDMA use is often accompanied by cardiovascular effects such as increased heart rate and high blood pressure (Hayner & McKinney 1986). The results from this study, which demonstrate the actions of MDMA on the cardiovascular system, give a basis for understanding some of the cardiovascular complications associated with the use of MDMA.

Acknowledgement

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