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Effects of methylenedioxymethamphetamine on noradrenaline-evoked contractions of rat right ventricle and small mesenteric artery

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Abstract

We have compared the effects of methylenedioxymethamphetamine (MDMA) and cocaine on contractions to noradrenaline in 1 Hz paced rat right ventricular strips, and in rat small mesenteric artery and aorta. Noradrenaline increased the force of contraction of 1 Hz paced ventricular strips with a pD_2 ($-\log EC_{50}$) of 5.64 ± 0.07. Both cocaine (10 μM) and MDMA (10 μM) significantly increased the potency of noradrenaline to 6.31 ± 0.11 and 6.42 ± 0.13, respectively. However, in the presence of cocaine (10 μM) which increased the potency of noradrenaline to 6.78 ± 0.15, MDMA (10 μM) no longer increased the potency of noradrenaline (pD_2 of 6.78 ± 0.32). Likewise, following chemical sympathectomy, MDMA failed to increase the potency of noradrenaline. The potency of the agonist isoprenaline, which is not a substrate for the noradrenaline transporter, was not increased by either cocaine or MDMA. In rat small mesenteric artery, but not aorta, MDMA and cocaine significantly increased the potency of noradrenaline, but in the presence of cocaine, MDMA had no further effect. Hence, MDMA shares with cocaine an ability to potentiate the actions of noradrenaline, an action in the case of MDMA which may involve competitive blockade of the noradrenaline transporter, rather than simply displacement of noradrenaline. Since cocaine is linked to an increased incidence of myocardial infarction, these results may have implications in terms of cardiac morbidity of MDMA.

Keywords: MDMA (methylenedioxymethamphetamine); Cocaine; Ventricle; Mesenteric artery, small; Noradrenaline

1. Introduction

Cocaine abuse is widespread, and as a result, cocaine related cardiovascular and autonomic complications have multiplied (Rubin and Neugarten, 1992; Das, 1993). Cocaine use has been shown to trigger myocardial infarction: the risk of myocardial infarction was more than 20-fold increased in the hour after taking cocaine (Mittleman et al., 1999). This action of cocaine presumably involves the well known effect to block re-uptake of noradrenaline into nerve terminals and so increase postjunctional effects of released noradrenaline. This action may result in coronary vasoconstriction (Lange et al., 1989) and cardiac stimulation (Boehrer et al., 1992). The resultant increased cardiac work and/or decreased coronary blood flow may trigger a myocardial infarction.

Ecstasy (3,4-methylenedioxymethamphetamine; MDMA) is now widely abused resulting in fatalities, but has been much less studied than cocaine and classical amphetamines. It is reported to have cardiac stimulant actions in rats resulting in tachycardia (Gordon et al., 1991) and arrhythmias and is also reported to facilitate vasoconstriction in the rat (Fitzgerald and Reid, 1994). Tachycardia and hypertension (Hayner and McKinney, 1986) and cardiovascular mortality (Dowling et al., 1987) have been reported in man. In addition, MDMA has been linked to intracerebral haemorrhage (Harries and De Silva, 1992), and cerebral hyperperfusion can be demonstrated in rats (Kelly et al., 1994). Certainly, chronic use of methamphetamine may also result in serious cardiovascular changes including tachycardia and palpitations (Chan et al., 1994), and another amphetamine derivative, fenfluramine has been linked to valvular heart disease (Connolly et al., 1997).

MDMA acts to displace noradrenaline from adrenergic nerve terminals (FitzGerald and Reid, 1993; Lavelle et al., 1999) so that it may act like cocaine to increase levels of

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noradrenaline but perhaps via a different mode of action: displacement of noradrenaline rather than block of re-uptake. In addition, MDMA may have direct α-adrenoceptor mediated actions (Lavelle et al., 1999). The purpose of this study was to compare the abilities of cocaine and MDMA to potentiate the actions of noradrenaline in rat right ventricular strips and in rat small resistance arteries (mesenteric arteries), as models of possible cardiac morbidity.

2. Methods

Male Wistar rats (250–350 g) were obtained from Trinity College Dublin. The studies conform to the Declaration of Helsinki and have been approved by the Department of Health and by the RCSI Research Ethics Committee.

2.1. Rat right ventricle

Following overdose of CO_2 and exsanguination, rat heart was removed, and strips of right ventricle (one or sometimes two strips per heart) were placed in Krebs–Henseleit solution of the following composition (mM): NaCl 119; $NaHCO_3$ 25; D-glucose 11.1; KCl 4.7; $CaCl_2$ 2.5; KH_2PO_4 1.2; $MgSO_4$ 1.0; EDTA 0.28. The total number of animals employed was 70. Strips of right ventricle were set up between platinum electrodes under 2 g tension and paced at a frequency of 1 Hz (supramaximal voltage, 0.5 ms pulses). Vessels were allowed to equilibrate at 37 °C and were gassed with 5% CO_2 in O_2.

Following 30 min equilibration, responsiveness was tested with noradrenaline or isoprenaline (10 μM). One hour later, a concentration–response curve to noradrenaline or isoprenaline was carried out in 0.5 log units increments, beginning with 10 nM, until a maximum response was reached. Bathing fluid was then changed every 15 min for the next hour. Tissues were then exposed to MDMA (10 μM), cocaine (10 μM) or vehicle for 30 min; a concentration response curve to noradrenaline or isoprenaline was then repeated in the continuing presence of MDMA, cocaine or vehicle. In some experiments, the effects of MDMA or vehicle were investigated in the presence of cocaine (10 μM). Two concentration–response curves were obtained per tissue.

2.2. Sympathectomy

Rats were injected with 6-hydroxydopamine (50 mg/kg) i.p. on day 1, followed by 6-hydroxydopamine (100 mg/kg) i.p. on day 4. Experiments were carried out on day 5 or day 6. Effects of MDMA or vehicle were investigated against the effects of noradrenaline in paced right ventricular strips.

2.3. Rat mesenteric artery

Following stunning and exsanguination, rat intestine and mesentery was removed and placed in Krebs–Henseleit solution of the same composition as listed above. In addition, propranolol (3 μM) and indomethacin (10 μM) were present to block beta-adrenoceptors and inhibit prostaglandin synthesis, respectively. In some experiments, as stated in Section 3, cocaine (30 μM) was present to block neuronal uptake of noradrenaline. Using a dissecting microscope, a segment of rat small mesenteric artery, approximately 1.5 mm in length, corresponding to a second or third order branch of the superior mesenteric artery, was carefully dissected free from its vein. The artery was mounted in a small vessel myograph using 40 μm tungsten wires. Up to four vessels were obtained from each animal. Data was recorded on a dual channel electronic display recorder (Dual Myograph MK-4) and pen recorder. Vessels were allowed to equilibrate at 37 °C and gassed with 5% CO_2 in O_2. The vessel was set to a tension equivalent to that generated at 0.9 times the diameter of the vessel at 100 mm Hg transmural pressure (Mulvany and Warshaw, 1977).

Interactions with MDMA (1 or 10 μM) or vehicle were investigated, with and without cocaine. After equilibration under resting tension for 30–60 min, tissues were contracted with KCl (40 mM) and exposed to acetylcholine (10 μM) to test for endothelium-dependent relaxations. Tissues, which failed to relax to ACh, were discarded due to the absence of a functional endothelium. Bathing fluid was changed every 15 min for the next hour. A concentration–response curve to noradrenaline was then carried out in 0.5 log units increments, beginning with 10 nM, until a maximum response was reached. Bathing fluid was then changed every 15 min for the next hour. Tissues were then exposed to MDMA (10 μM) for 1 h; a concentration response curve to noradrenaline was then repeated in the continuing presence of MDMA.

2.4. Rat aorta

Following stunning and exsanguination, thoracic aortic rings of 3–5 mm in length were attached to myograph transducers under 1 g tension in organ baths at 37 °C in Krebs–Henseleit solution of the same composition as listed above. In some experiments, cocaine (10 μM) was present. Cumulative concentration–response curves were carried out to noradrenaline in 0.5 log unit increments, beginning with 1 nM. Interaction experiments with MDMA (10 μM) or vehicle were carried out as described for small mesenteric artery.

2.5. Statistics

Values are expressed as mean and standard error (S.E.) of the mean. Noradrenaline pD_2 ($-\log EC_{50}$) values were

calculated using the GraphPad Prism programme for PC. Maximum contraction was measured in gram weight. Effects of test agents or vehicle on contractions were expressed as a percentage of initial contraction. Differences between groups and vehicle were compared, using the Instat programme for Macintosh, by Student's *t*-test for paired or unpaired data, where appropriate, and by Analysis of Variance with Dunnett's or Tukey's test. Means were considered significantly different when P values were < 0.05.

2.6. Drugs

Cocaine hydrochloride (Sigma); 6-hydroxydopamine hydrobromide (Sigma); indomethacin (Sigma); (−)-isoprenaline hydrochloride (Sigma); (±)-methylenedioxymethamphetamine (MDMA: Research Biochemicals); (−)-noradrenaline hydrochloride (Sigma).

All drugs were dissolved in distilled water with the exception of 6-hydroxydopamine (ascorbic acid, 1 mg/ml) and indomethacin (100% ethanol).

3. Results

3.1. Rat right ventricle

In rat right ventricular strips, 1 Hz stimulation produced a contraction of 0.38 ± 0.04 g ($n = 18$). Noradrenaline produced dose-dependent contractions with a maximum increase in the stimulation-evoked contraction to $158.6 \pm 6.4\%$ of baseline and a pD_2 of 5.64 ± 0.07 (−log M) ($n = 18$) in the first concentration response curve. Incubation with cocaine (10 μM) or incubation with MDMA (10 μM) significantly increased the potency of noradrenaline as compared with the effects of vehicle (to 6.31 ± 0.11 and 6.42 ± 0.13, respectively, as compared to vehicle of 5.78 ± 0.18) (see Figs. 1 and 2). However, the maximum effect of noradrenaline was not significantly affected by cocaine or MDMA (vehicle: $241.7 \pm 51.6\%$; cocaine: $306.3 \pm 40.8\%$; MDMA: $213.4 \pm 39.8\%$; $n = 6$ each), but there was a great variability between experiments in the magnitude of the potentiation (Fig. 1). Potency differences are more easily seen in the format of Fig. 2.

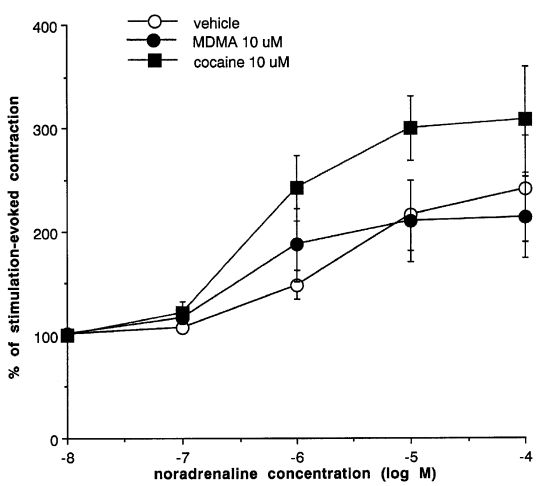

Fig. 1. Effects of vehicle, cocaine (10 μM) or MDMA (10 μM) on contractions to noradrenaline in 1 Hz paced rat right ventricle. Responses to noradrenaline shown are from the second (test) concentration–response curve and are expressed as a percentage of the baseline 1 Hz stimulation-evoked contraction. Vertical bars represent S.E. of mean from six experiments.

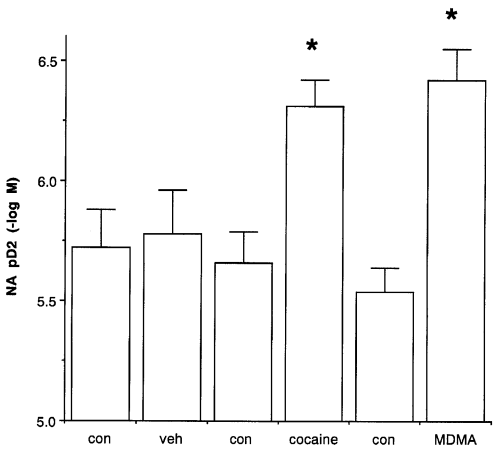

Fig. 2. Effects of vehicle, cocaine (10 μM) or MDMA (10 μM) on the contractile potency (pD_2, $-\log EC_{50}$) of noradrenaline in 1 Hz paced rat right ventricle. Responses shown are the control (con) response to noradrenaline obtained in the first concentration–response curve and test response to noradrenaline in the second concentration–response curve following vehicle (veh), cocaine or MDMA. Vertical bars represent S.E. of mean from six experiments. Asterisks denote significance of difference from corresponding control value (analysis of variance and Tukey's test) and between test drug and vehicle (analysis of variance and Dunnett's test).

In experiments carried out in the presence of cocaine (10 μM), noradrenaline produced a maximum increase in the stimulation-evoked contraction to $173.9 \pm 10.2\%$ of baseline with a pD_2 of 6.78 ± 0.15 (−log M) ($n = 8$). In the presence of cocaine, MDMA (10 μM) did not significantly affect potency of noradrenaline (Fig. 3). The maximum effect of noradrenaline was not significantly affected by MDMA (vehicle: $214.3 \pm 32.4\%$ of control; MDMA: 254.0 ± 43.3 % of control; $n = 4$ each).

In experiments carried out in right ventricle taken from sympathectomised animals, noradrenaline produced a maximum increase in the stimulation-evoked contraction to $225.6 \pm 19.6\%$ of baseline with a pD_2 of 6.57 ± 0.14 (−log M) ($n = 9$). MDMA (10 μM) did not significantly affect potency of noradrenaline (Fig. 4). The maximum effect of noradrenaline was not significantly affected by MDMA (vehicle: $199.2 \pm 17.3\%$ of control; MDMA: $213.1 \pm 24.8\%$ of control; $n = 5$ each).

In experiments carried out in right ventricle taken from control animals, isoprenaline produced a maximum increase in the stimulation-evoked contraction to $217.7 \pm$

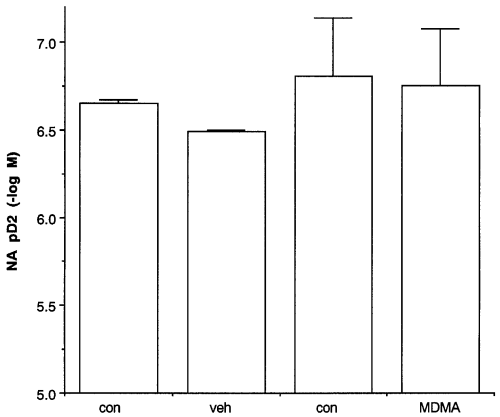

Fig. 3. Effects of vehicle or MDMA (10 μM) on the contractile potency (pD_2, $-\log EC_{50}$) of noradrenaline in 1 Hz paced rat right ventricle in the presence of cocaine (10 μM). Responses shown are the control (con) response to noradrenaline obtained in the first concentration–response curve and test response to noradrenaline in the second concentration–response curve following vehicle (veh) or MDMA. Vertical bars represent S.E. of mean from four experiments. There were no significance differences from corresponding control values or between test drug and vehicle (analysis of variance and Tukey's or Dunnett's test).

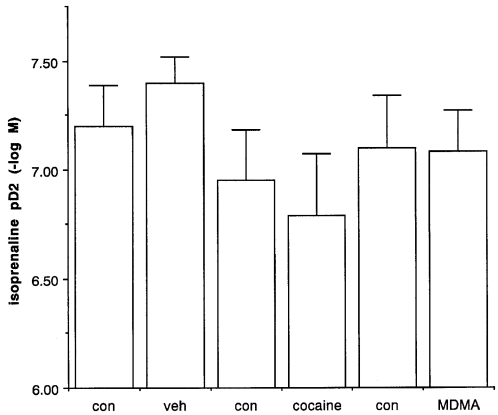

Fig. 5. Effects of vehicle, cocaine (10 μM) or MDMA (10 μM) on the contractile potency (pD_2, $-\log EC_{50}$) of isoprenaline in 1 Hz paced rat right ventricle. Responses shown are the control (con) response to isoprenaline obtained in the first concentration–response curve and test response to isoprenaline in the second concentration–response curve following vehicle (veh), cocaine or MDMA. Vertical bars represent S.E. of mean from six experiments. There were no significance differences from corresponding control values or between test drug and vehicle (analysis of variance and Tukey's or Dunnett's test).

13.9% of baseline with a pD_2 of 7.12 ± 0.12 ($-\log$ M) ($n = 18$). Cocaine (10 μM) or MDMA (10 μM) did not significantly affect potency of isoprenaline (Fig. 5). The maximum effect of isoprenaline was not significantly affected by cocaine or MDMA (vehicle: 276.5 ± 45.1% of control; cocaine: 302.4 ± 33.1% of control; MDMA: 252.4 ± 22.3 % of control; $n = 6$ each).

3.2. Rat small mesenteric artery

Noradrenaline produced dose-dependent contractions with a maximum contraction of 0.99 ± 0.05 g and a pD_2 of 5.76 ± 0.07 ($-\log$ M) ($n = 16$) in the first concentration response curve (pre-vehicle) or 1.04 ± 0.10 g and a pD_2 of 5.69 ± 0.08 ($n = 15$) (pre-MDMA). Incubation with MDMA (10 μM) significantly increased the potency of noradrenaline as compared with the effects of vehicle (see Fig. 6). However, the maximum contraction to noradrenaline was not significantly affected by MDMA (vehicle: 109.8 ± 4.3% of control; MDMA: 102.9 ± 3.4% of control).

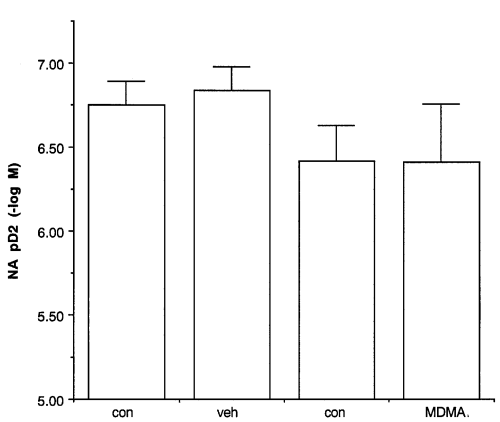

Fig. 4. Effects of vehicle or MDMA (10 μM) on the contractile potency (pD_2, $-\log EC_{50}$) of noradrenaline in 1 Hz paced rat right ventricle from sympathectomised rats. Responses shown are the control (con) response to noradrenaline obtained in the first concentration–response curve and test response to noradrenaline in the second concentration–response curve following vehicle (veh) or MDMA. Vertical bars represent S.E. of mean from five experiments. There were no significance differences from corresponding control values or between test drug and vehicle (analysis of variance and Tukey's or Dunnett's test).

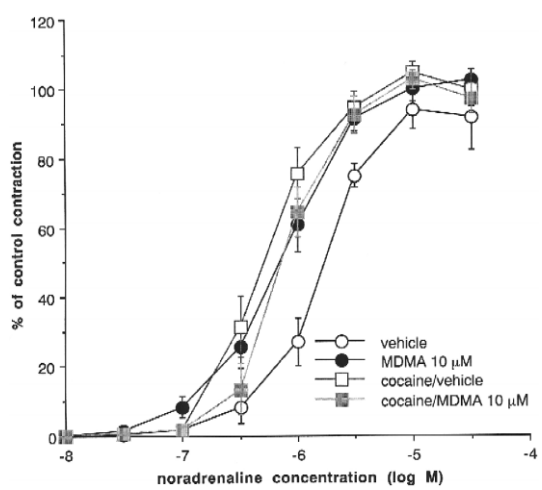

Fig. 6. Effects of vehicle or MDMA (10 μM) on contractions to noradrenaline in rat small mesenteric artery in the absence or presence of cocaine (10 μM). Responses to noradrenaline shown are from the second (test) concentration–response curve and are expressed as a percentage of the maximum response to noradrenaline obtained in the first (control) concentration–response curve. Vertical bars represent S.E. of mean from 5–16 experiments. The potency of noradrenaline was increased in the presence of cocaine or MDMA as compared with vehicle (analysis of variance and Dunnett's test).

In experiments carried out in the presence of cocaine (30μM), noradrenaline produced contractions with a maximum contraction of 0.88 ± 0.07 g and a pD_2 of 6.26 ± 0.07 (−log M) ($n = 5$) in the first concentration response curve (pre-vehicle) or 0.91 ± 0.05 g and a pD_2 of 6.21 ± 0.10 ($n = 5$) (pre-MDMA). Cocaine significantly increased the potency of noradrenaline ($P < 0.05$). However, in the presence of cocaine, MDMA (10 μM) did not significanty affect potency of noradrenaline (Fig. 6). The maximum contraction to noradrenaline was not significantly affected by MDMA (vehicle: 103.4 ± 2.9% of control; MDMA: 105.7 ± 3.5% of control).

3.3. Rat aorta

Noradrenaline produced dose-dependent contractions with a maximum contraction of 1.00 ± 0.10 g and a pD_2 of 7.83 ± 0.06 (−log M) ($n = 6$) in the first concentration response curve (pre-vehicle) or 1.01 ± 0.09 g and a pD_2 of 7.78 ± 0.08 ($n = 6$) (pre-MDMA). Incubation with MDMA (10 μM) did not significantly affect the potency of noradrenaline as compared with the effects of vehicle (data not shown). The maximum contraction to noradrenaline was not significantly affected by MDMA (10 μM) (vehicle: 99.8 ± 8.6% of control; MDMA: 108.4 ± 8.9% of control). In experiments carried out in the presence of cocaine (10 μM), noradrenaline produced a maximum contraction of 1.23 ± 0.18 g with a pD_2 of 7.69 ± 0.33 (−log M) ($n = 6$) (not significantly different from responses in absence of cocaine).

4. Discussion

In this study, we have investigated the effects of MDMA and cocaine on contractile responses to noradrenaline in paced rat right ventricle, as an index of cardiac morbidity. Although the left ventricle is much more susceptible to events such as infarction, the present study employed right rather than left ventricle only because the former is thin walled and so much more viable in vitro. Effects on the right ventricle are likely to be similar to effects on the left ventricle. Likewise, we have employed rat small mesenteric artery as a model of resistance arteries to assess the vasoconstrictor actions of MDMA, which are likely to lead to cardiac morbidity if similar effects occur in coronary arteries.

Cocaine and MDMA at the concentration of 10 μM had similar actions at potentiating the effects of noradrenaline in rat right ventricular strips. The effects of cocaine presumably involve its well-known action to block the noradrenaline re-uptake transporter and the effects of MDMA could be presumed to involve its well-known action of entering nerves via the noradrenaline transporter and displacing noradrenaline. Hence, cocaine and MDMA were not additive in their actions: cocaine prevents the actions of MDMA. Similar interactions between MDMA and re-uptake blockers have been demonstrated in radioactive overflow studies: in rat atrium, MDMA significantly increased basal release of tritium in the absence of uptake blockers (Lavelle et al., 1999). This effect of MDMA was reduced by cocaine (3–30 μM) and abolished by desipramine (1 μM), and was due to entry of MDMA into nerve terminals via the noradrenaline transporter to displace noradrenaline (see Chan et al., 1994): desipramine is reported to have greater potency as a noradrenaline uptake blocker than cocaine (Docherty and McGrath, 1978). Depletion of noradrenaline can be shown in mouse heart in response to MDMA (Steele et al., 1989). In spontaneous beating rat atria, MDMA is reported to produce a tachycardia which is blocked by desipramine (FitzGerald and Reid, 1994).

However, the results obtained with isoprenaline in rat right ventricle conflict with the mode of action of MDMA suggested above. Isoprenaline is a beta-adrenoceptor agonist which is not a substrate for the noradrenaline uptake transporter (Hertting, 1964), and hence is often used in comparison with noradrenaline. In our studies, isoprenaline was more potent than noradrenaline, as expected. Not surprisingly, cocaine did not affect the potency of isoprenaline in rat right ventricle, since isoprenaline is not a substrate for the transporter. The interesting result was obtained with MDMA: MDMA also failed to increase the potency of isoprenaline. Now, if the action of MDMA was simply to displace noradrenaline from nerve terminals, one might expect MDMA also to potentiate the effects of isoprenaline. The most likely interpretation is that although MDMA is indeed taken up by the transporter and displaces noradrenaline, the more important mode of action is a competitive blockade of the transporter by the law of mass action. Indeed, MDMA is reported to inhibit synaptosomal uptake of noradrenaline (Steele et al., 1987). Hence, the actions of MDMA are more cocaine-like than we previously believed. It is uptake blockade by MDMA which potentiates the actions of noradrenaline but not isoprenaline.

In rat small mesenteric artery, but not aorta, cocaine or MDMA potentiated contractions to noradrenaline, and cocaine prevented the potentiation by MDMA . Rat aorta has few nerves so that a failure of MDMA or cocaine to potentiate contractions to noradrenaline can be explained. If the MDMA induced potentiation of contractions to noradrenaline in small mesenteric artery is paralleled by similar effects in coronary artery, such an action could contribute to cardiac morbidity.

In addition to indirect actions to bind to the transporter and to displace noradrenaline from nerve terminals, MDMA also has direct actions at α-adrenoceptors, particularly α_2-adrenoceptors (see Lavelle et al., 1999). However, given the ability of cocaine to prevent actions of MDMA in ventricle and mesenteric artery, direct actions of MDMA appear less important in this study.

How do the present results relate to the ability of cocaine to increase the incidence of myocardial infarction in man? Cocaine, by blocking the noradrenaline transporter, and MDMA by blocking the transporter and by displacing noradrenaline, were able to produce similar potentiations of the contractile actions of noradrenaline in rat ventricle. An increased force of cardiac contraction results in an increase in cardiac work, which increases the oxygen demand. The left ventricle has areas of zero blood flow during systole: the increased oxygen demand could provoke further hypoxia. In addition, coronary vasoconstrictor actions would further compromise ventricular blood flow (Lange et al., 1989).

Cocaine and MDMA were chosen at the concentration of 10 μM. This compares with typical human dose of MDMA of 1–2 mg/kg (illegal tablets can contain 57–136 mg; see O'Loinsigh and O'Boyle, 1998) which can be calculated as approximately 4–8 μmol/kg. Pharmacokinetic studies in man have employed 50–150 mg of MDMA (Mas et al., 1999; De La Torre et al., 2000), resulting in cardiovascular changes including increased blood pressure and tachycardia (Mas et al., 1999). Likewise, cocaine at a dose of 1 mg/kg (2.9 μmol/kg) is reported to cause cerebrovascular abnormalities in a subject (Johnson et al., 1997). Hence, the effects seen in our study of rat ventricle occur in the range of doses taken by abusers. Since cocaine is known to increase acutely the risk of myocardial infarction (Mittleman et al., 1999), it might be expected that MDMA has similar actions both in terms of ventricular and vasoconstrictor actions.

In conclusion, cocaine and MDMA potentiate the actions of noradrenaline in rat right ventricular strips, and in rat small mesenteric artery. The action of MDMA may involve competitive blockade of the noradrenaline transporter, rather than simply displacement of noradrenaline. This action of MDMA may result in cardiac morbidity as previously shown for cocaine.

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