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# Effects of amphetamine derivatives and cathinone on noradrenaline-evoked contractions of rat right ventricle

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**Abstract**

We have compared the effects of methylenedioxymethamphetamine (MDMA), methylenedioxyethylamphetamine (MDEA), methylenedioxyamphetamine (MDA) and cathinone on contractions to noradrenaline and isoprenaline in 1 Hz paced rat right ventricular strips. Noradrenaline increased the force of contraction of 1 Hz paced ventricular strips with a $pD_2$ ($-\log EC_{50}$) of 5.64 ± 0.07 ($n$ = 49). Cocaine (10 μM), MDMA (10 μM), MDA (10 μM) and cathinone (3 and 10 μM) significantly increased the potency of noradrenaline to 6.25 ± 0.11, 6.48 ± 0.13, 6.17 ± 0.05, 6.15 ± 0.07 and 6.27 ± 0.10, respectively ($n$ = 5–10 each) as compared with the effects of vehicle (5.42 ± 0.08, $n$ = 15). However, MDEA (10 μM) failed to affect the potency of noradrenaline, although MDEA (100 μM) significantly increased noradrenaline potency (5.98 ± 0.12). The potency of the agonist isoprenaline, which is not a substrate for the noradrenaline transporter, was not increased by cocaine, MDMA, cathinone, MDA or MDEA. Hence, MDMA, cathinone, MDA and MDEA share with cocaine an ability to potentiate the actions of noradrenaline, an action 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 amphetamine derivatives and cathinone.


*Keywords:* MDMA (3,4-methylenedioxymethamphetamine); MDEA (3,4-methylenedioxyethylamphetamine); MDA (3,4-methylenedioxyamphetamine); Cathinone; Cocaine; Ventricular strip, rat; Contraction

## 1. Introduction

Amphetamine derivatives such as MDMA (3,4-methylenedioxymethamphetamine), MDEA (3,4-methylenedioxyethylamphetamine) and MDA (3,4-methylenedioxyamphetamine) are now widely abused as recreational drugs resulting in fatalities, but their toxicity has been much less studied than that of cocaine and classical amphetamines. MDMA 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 (Fitz-Gerald 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 to MDMA can be demonstrated in rats (Kelly et al., 1994). Chronic use of methamphetamine may also result in serious cardiovascular changes including tachycardia and palpitations (Chan et al., 1994). Another amphetamine derivative, fenfluramine, has been linked to valvular heart disease and this may involve the serotonin transporter in the heart (Connolly et al., 1997; Brouri et al., in press). In addition, cathinone from the khat plant which has amphetamine-like actions (Kalix and Glennon, 1986), is widely used as a recreational substance, and so may have cardiovascular actions in man similar to those of MDMA.

We have recently shown that MDMA and cocaine potentiate the actions of noradrenaline in 1-Hz-paced rat right ventricle (Al-Sahli et al., 2001). The purpose of this study was to compare the abilities of a series of amphetamine-like agents—MDMA, MDEA, MDA and cathinone—to potentiate the actions of noradrenaline in rat right ventricular strips as models of possible cardiac morbidity. Some of these results have been published in abstract form (Buber et al., 2002).

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## 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 (in mM): NaCl 119; $NaHCO_3$ 25; D-glucose 11.1; KCl 4.7; $CaCl_2$ 2.5; $KH_2PO_4$

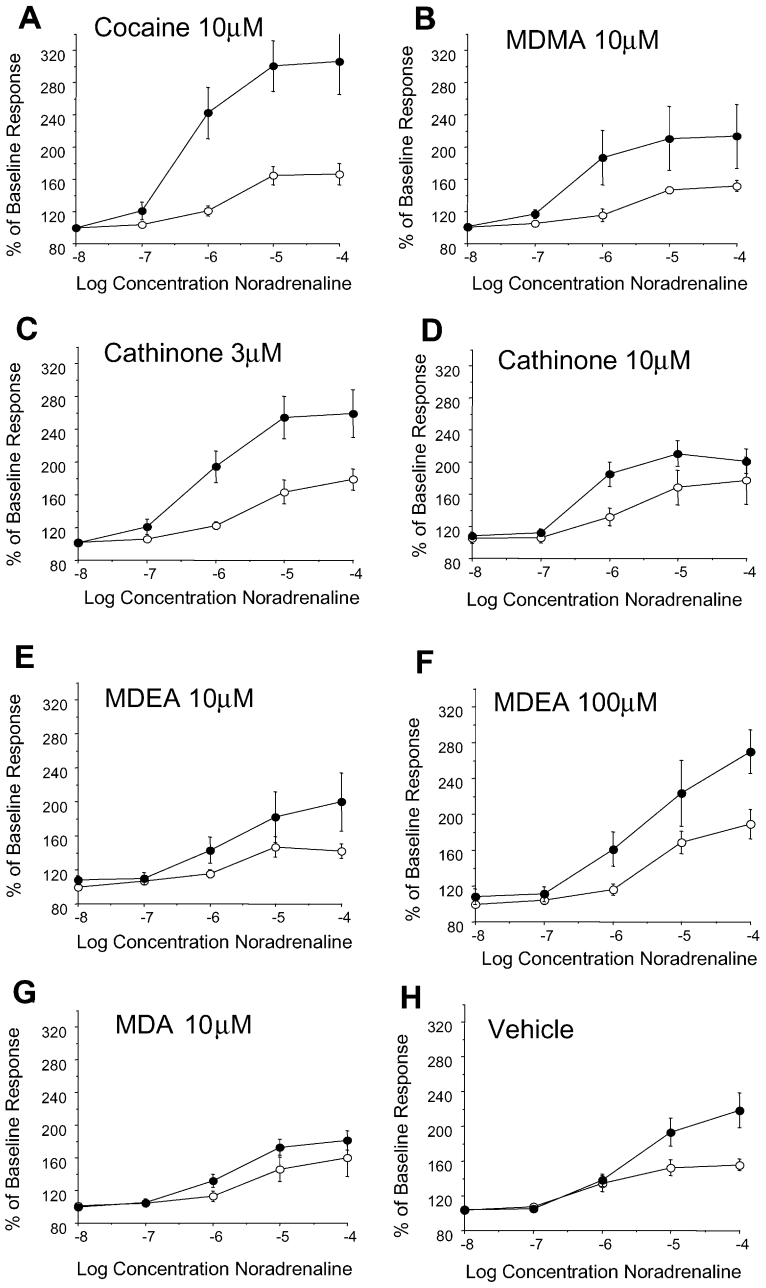


Fig. 1. Effects of (A) cocaine (10 μM), (B) MDMA (10 μM), (C) cathinone (3 μM), (D) cathinone (10 μM), (E) MDEA (10 μM), (F) MDEA (100 μM), (G) MDA (10 μM) and (H) vehicle on contractions to noradrenaline in 1 Hz paced rat right ventricle. Responses to noradrenaline shown are from the first (control) curve (open symbols) and the second (test) concentration–response curve (closed symbols), and are expressed as a percentage of the baseline 1-Hz stimulation-evoked contraction just prior to addition of noradrenaline. Vertical bars represent S.E.M. from 5 to 15 experiments.

1.2; $MgSO_4$ 1.0; EDTA 0.28. The total number of animals employed was 66. Strips of right ventricle were set up between platinum electrodes and isometric force transducers (Grass FT03) under 2 g tension and paced at a frequency of 1 Hz (supramaximal voltage, 0.5 m/s pulses) using a Grass S88 stimulator. Data were recorded on a Grass Polygraph Model 79D. 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 1 log unit increments beginning with 1 nM, until a maximum response was reached. Bathing fluid was then changed every 15 min for the next hour. Tissues were then exposed to test agent or vehicle for 30 min, and the concentration–response curve to noradrenaline or isoprenaline was then repeated in the continuing presence of test agent or vehicle. Two concentration–response curves were obtained per tissue, control and following vehicle or test drug.

### 2.2. Statistics

Values are expressed as mean and standard error of the mean (S.E.M.). Noradrenaline or isoprenaline p$D_2$ ($-\log EC_{50}$) values were calculated using the GraphPad Prism programme for PC. Since control mean p$D_2$ values for noradrenaline and isoprenaline varied between groups, it was necessary to normalize control values. All control group means were shifted to 5.60 (noradrenaline) or 7.50 (isoprenaline), and the test means were shifted accordingly. This allowed direct comparison of test means. Maximum contraction was measured in grams weight. Effects of test agents or vehicle on contractions were expressed as a percentage of initial contraction. Differences between groups and vehicle were compared by 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 test for comparison of effects of vehicle with test drug, or by Tukey's test for comparison of first and second concentration–response curves. Means were considered significantly different when $P$ values were $<0.05$.

Table 1
p$D_2$ values ($-\log EC_{50}$) obtained in first (control) and second (test) concentration–response curves to noradrenaline prior to normalization

| Test agent | Control | Test |
|---|---|---|
| Vehicle ($n=15$) | 5.87 ± 0.09 | 5.69 ± 0.08 |
| Cocaine (10 μM) ($n=6$) | 5.66 ± 0.13 | 6.31 ± 0.11 * |
| MDMA (10 μM) ($n=6$) | 5.54 ± 0.10 | 6.42 ± 0.13 * |
| Cathinone (3 μM) ($n=10$) | 5.57 ± 0.08 | 6.12 ± 0.07 * |
| Cathinone (10 μM) ($n=6$) | 5.60 ± 0.12 | 6.27 ± 0.10 * |
| MDEA (10 μM) ($n=5$) | 5.58 ± 0.22 | 5.76 ± 0.11 |
| MDEA (100 μM) ($n=5$) | 5.52 ± 0.09 | 5.90 ± 0.12 * |
| MDA (10 μM) ($n=6$) | 5.35 ± 0.15 | 5.92 ± 0.05 * |

Values are mean ± S.E.M., from *n* experiments. Asterisks denote significant difference with respect to the corresponding control (analysis of variance and Tukey's test: $P<0.05$).

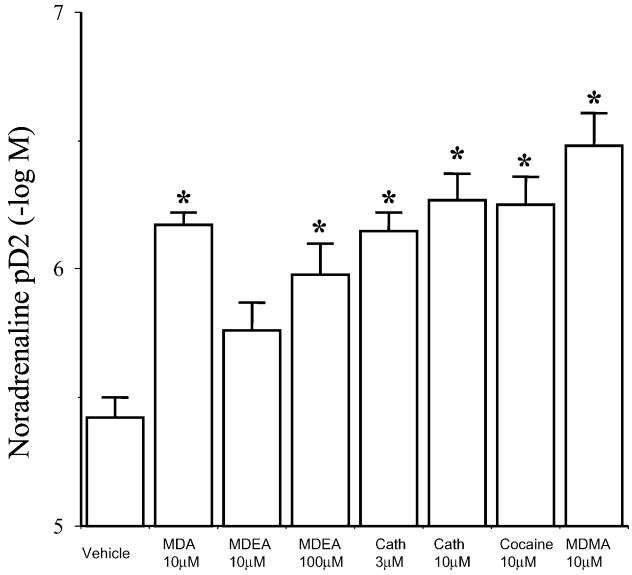


Fig. 2. Effects of vehicle, cocaine (10 μM) MDMA (10 μM), MDA (10 μM), MDEA (10 and 100 μM) and cathinone (3 and 10 μM) on the contractile potency (p$D_2$, $-\log EC_{50}$) of noradrenaline in 1-Hz-paced rat right ventricle. Responses shown are test response to noradrenaline in the second concentration–response curve following vehicle or test drug, normalized as explained in Methods. Vertical bars represent S.E.M. from 5 to 15 experiments. Values for MDMA and cocaine are taken from Al-Sahli et al. (2001). Asterisks denote significance of difference between test drug and vehicle (* $P<0.05$; analysis of variance and Dunnett's test).

### 2.3. Drugs

Cathinone (Sigma); (−)-isoprenaline hydrochloride (Sigma); methylenedioxyamphetamine (MDA: Sigma); methylenedioxyethylamphetamine (MDEA: Sigma); methylenedioxymethamphetamine (MDMA: Research Biochemicals); (−)-noradrenaline hydrochloride (Sigma).

All drugs were dissolved in distilled water.

## 3. Results

In rat right ventricular strips, 1 Hz stimulation produced a contraction of 0.39 ± 0.03 g ($n=74$). Noradrenaline significantly increased stimulation-evoked contractions to 167.5 ± 5.4% of baseline ($P<0.001$), with a p$D_2$ ($-\log EC_{50}$) of 5.64 ± 0.07 (combined mean of all controls ± S.E.M., $n=49$). Control responses and responses following test drugs or vehicle are shown in Fig. 1.

The maximum contractile effect of noradrenaline was not significantly affected by test drugs (vehicle: 215.9 ± 19.6%; cocaine (10 μM): 306.3 ± 40.8%; MDMA (10 μM): 213.4 ± 39.8%; cathinone (3 μM): 262.3 ± 28.6%; cathinone (10 μM): 214.5 ± 14.5%; MDEA (10 μM): 200.0 ± 34.3%; MDEA (100 μM): 244.8 ± 42.7%; MDA (10 μM):

178.9 ± 12.7%), but there was a great variability between experiments in the magnitude of the potentiation (Fig. 1). Furthermore, potency differences between groups in the first (control) concentration–response curve influenced potency in the second concentration–response curve (see Table 1).

To allow comparison between second concentration–response curves, noradrenaline control means for each group were shifted to 5.60 (see Methods). The original $pD_2$ values prior to normalization are shown in Table 1. Cocaine (10 μM), MDMA (10 μM), cathinone (3 and 10 μM) and MDA (10 μM) significantly ($P<0.001$) increased the potency of noradrenaline to 6.25 ± 0.11 ($n=6$), 6.48 ± 0.13 ($n=6$), 6.15 ± 0.07 ($n=10$), 6.27 ± 0.10 ($n=6$) and 6.17 ± 0.05 ($n=6$), respectively, as compared with the effects of vehicle (5.42 ± 0.08, $n=15$) (analysis of variance with Dunnett's test) (Fig. 2). However, MDEA (10 μM, $n=5$) failed to affect the potency of noradrenaline, although MDEA (100 μM) significantly increased noradrenaline potency (5.98 ± 0.12, $n=5$; $P<0.01$) (Fig. 2).

Table 2
$pD_2$ values ($-\log EC_{50}$) obtained in first (control) and second (test) concentration–response curves to isoprenaline prior to normalisation

| Test agent | Control | Test |
|---|---|---|
| Vehicle ($n=7$) | 7.56 ± 0.19 | 7.49 ± 0.29 |
| Cocaine (10 μM) ($n=6$) | 6.95 ± 0.23 | 6.79 ± 0.28 |
| MDMA (10 μM) ($n=6$) | 7.10 ± 0.24 | 7.08 ± 0.19 |
| Cathinone (10 μM) ($n=7$) | 6.99 ± 0.25 | 7.19 ± 0.24 |
| MDEA (100 μM) ($n=6$) | 8.07 ± 0.12 | 7.58 ± 0.12 * |
| MDA (10 μM) ($n=5$) | 7.39 ± 0.09 | 7.03 ± 0.13 |

Values are mean ± S.E.M., from $n$ experiments. Asterisks denote significant difference with respect to the corresponding control (analysis of variance and Tukey's test: $P<0.05$).

Isoprenaline significantly increased stimulation-evoked contractions to 198.0 ± 8.9% of baseline ($P<0.001$), with

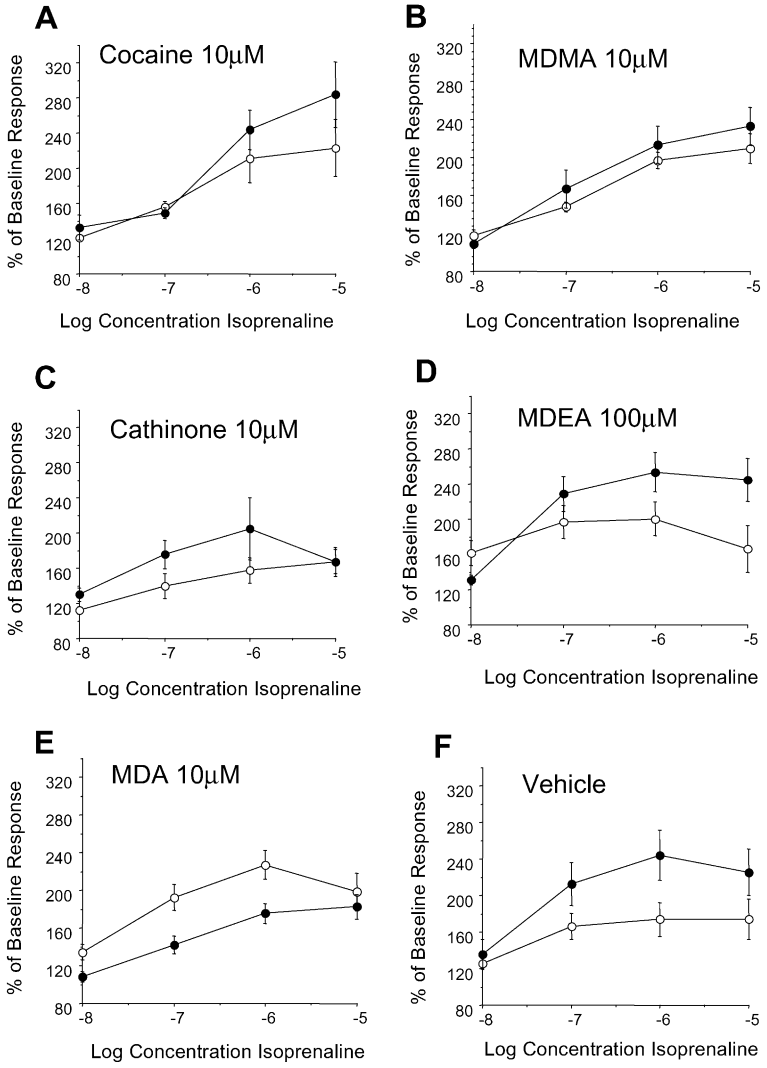


Fig. 3. Effects of (A) cocaine (10 μM), (B) MDMA (10 μM), (C) cathinone (10 μM), (D) MDA (10 μM), (E) MDEA (100 μM) and (F) vehicle on contractions to isoprenaline in 1-Hz-paced rat right ventricle. Responses to isoprenaline shown are from the first (control) curve (open symbols) and the second (test) concentration–response curve (closed symbols), and are expressed as a percentage of the baseline 1-Hz stimulation-evoked contraction just prior to addition of isoprenaline. Vertical bars represent S.E.M. from five to seven experiments.

a p$D_2$ of 7.45 ± 0.12 (combined mean of all controls ± S.E.M., $n$ = 25). Control responses and responses following test drugs or vehicle are shown in Fig. 3. As with noradrenaline, differences between groups in the potency of isoprenaline in the first (control) concentration–response curve influenced potency in the second concentration–response curve (see Table 2).

The maximum contractile effect of isoprenaline was not affected by cocaine, MDMA, cathinone or MDEA (vehicle: 269.7 ± 25.6% of control; cocaine: 302.4 ± 33.1%; MDMA: 252.4 ± 22.3%; cathinone: 216.9 ± 31.0%; MDEA (100 μM): 256.6 ± 24.1%). However, the presence of MDA (182.6 ± 13.0%) caused a significantly lower maximum contractile response to isoprenaline as compared to the presence of vehicle ($P$ < 0.05).

To allow comparison between second concentration–response curves, isoprenaline-control means for each group were shifted to 7.50 (see Methods). The original p$D_2$ values prior to normalization are shown in Table 1. Cocaine (10 μM), MDMA (10 μM), cathinone (10 μM), MDA (10 μM) or MDEA (100 μM) did not significantly affect the response to isoprenaline (7.34 ± 0.28, $n$ = 6; 7.48 ± 0.19, $n$ = 6; 7.70 ± 0.24, $n$ = 7; 7.14 ± 0.13, $n$ = 5; 7.01 ± 0.12, $n$ = 6, respectively) as compared with the effects of vehicle (7.43 ± 0.29, $n$ = 7) (Fig. 4). However, MDEA (100 μM) significantly reduced the potency of isoprenaline as compared to control (first concentration–response curve) ($P$ < 0.05).

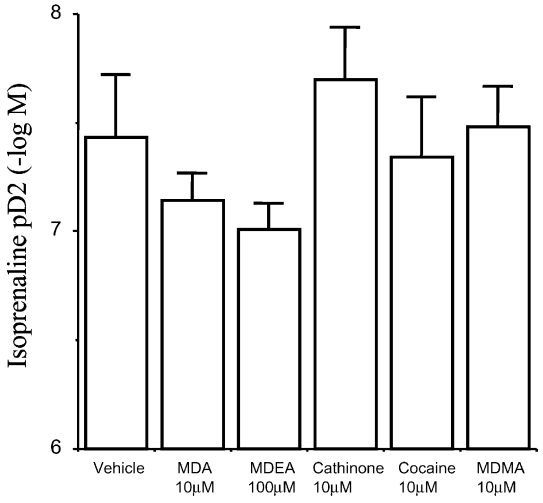


Fig. 4. Effects of vehicle, MDA (10 μM), MDEA (100 μM), cathinone (10 μM), cocaine (10 μM) or MDMA (10 μM) on the contractile potency (p$D_2$, − log $EC_{50}$) of isoprenaline in 1-Hz-paced rat right ventricle. Responses shown are the test response to isoprenaline in the second concentration–response curve following vehicle or test drug, normalized as explained in Methods. Vertical bars represent S.E.M. from five to seven experiments. Values for MDMA and cocaine are taken from Al-Sahli et al. (2001). There were no significant differences between test drug and vehicle (analysis of variance and Dunnett's test).

## 4. Discussion

In this study, we have investigated the effects of MDA, MDEA and cathinone in comparison to MDMA and cocaine on contractile responses to noradrenaline and isoprenaline in paced rat right ventricle, as an index of cardiac morbidity. The right ventricle rather than the left was employed because it is thin-walled and therefore much more viable in vitro. Effects on the right ventricle are likely to be similar to effects on the left ventricle. Potentiation of the actions of noradrenaline is likely to increase the force of ventricular contraction and increase the workload on the heart, increasing the incidence of myocardial infarction. Additionally, any constriction of the coronary arteries caused by this potentiation of the actions of noradrenaline may cause further ischaemia. Arrhythmogenic actions of these agents were not studied, but we are currently carrying out chronic studies in vivo.

We have previously reported that cocaine and MDMA at the concentration of 10 μM had similar actions at potentiating the effects of noradrenaline in rat right ventricular strips (Al-Sahli et al., 2001). Cocaine and MDMA were not additive in their actions: cocaine prevents the actions of MDMA. Not surprisingly, cocaine did not affect the potency of isoprenaline, a beta-adrenoceptor agonist which is not a substrate for the noradrenaline-uptake transporter (Hertting, 1964). The interesting result was obtained with MDMA: MDMA also failed to increase the potency of isoprenaline, suggesting 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.

We have now investigated the amphetamine-like agents MDA (a metabolite of MDMA), MDEA and cathinone (from khat) against contractile responses to noradrenaline and isoprenaline in rat right ventricle. MDA (10 μM) and cathinone (3 and 10 μM) significantly increased the potency of noradrenaline, whereas only MDEA (100 μM) significantly affected responses to noradrenaline. We also confirmed that cathinone, MDA and MDEA do not potentiate the effects of isoprenaline. However, MDEA (10 μM) significantly reduced the potency of isoprenaline. Hence, MDA, cathinone and, to a lesser extent, MDEA share with MDMA and cocaine an ability to potentiate responses to noradrenaline in rat ventricle. The lower potency of MDEA at potentiating the effects of noradrenaline may be due to a postjunctional depressant action rather than any difference in affinity for the noradrenaline transporter.

Test drugs were chosen at a concentration of 10 μM (and lower or higher concentrations depending on the effect or lack of effect of this concentration). This compares with

typical human illegal and pharmacokinetic doses of MDMA of 1–2 mg/kg (O'Loinsigh and O'Boyle, 1998; Mas et al., 1999; De La Torre et al., 2000). Illegal tablets can contain 57–136 mg, approximately 4–8 μmol/kg. Peak plasma levels of MDMA following 125 mg were 1.07 μM (Mas et al., 1999), and peak plasma levels of cathinone following khat 0.8 mg/kg were 0.7 μM (Widler et al., 1994). Likewise, cocaine at a dose of 1 mg/kg (2.9 μmol/kg) is reported to cause cerebrovascular abnormalities (Johnson et al., 1997). Hence, the effects seen in our study of rat ventricle occur in the range of concentrations expected in man, although perhaps at the higher end. Since cocaine is known to increase acutely the risk of myocardial infarction (Mittleman et al., 1999), it might be expected that MDMA, MDA, cathinone and, to a lesser extent, MDEA have similar actions both in terms of ventricular and vasoconstrictor actions. Cocaine, by blocking the noradrenaline transporter, and MDMA, MDA, MDEA and cathinone, 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. Blood flow falls to zero in areas of the left ventricle during systole, the increased oxygen demand and coronary vasoconstrictor actions (Lange et al., 1989) would further compromise ventricular blood flow. Further studies are required to test whether MDEA has lesser cardiac actions than the above agents.

In conclusion, cocaine, MDMA, MDA, cathinone and, to a lesser extent, MDEA potentiate the actions of noradrenaline in rat right ventricular strips by an action which may involve competitive blockade of the noradrenaline transporter, rather than simply displacement of noradrenaline. This action may result in cardiac morbidity as previously shown for cocaine.

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## References

Al-Sahli, W., Ahmad, H., Kheradmand, F., Connolly, C., Docherty, J.R., 2001. Effects of methylenedioxymethamphetamine on noradrenaline-evoked contractions of rat right ventricle and small mesenteric artery. Eur. J. Pharmacol. 422, 169–174.

Brouri, F., Eddahibi, S., Adnot, S., Hamon, M., Lechat, P.H., 2002. Cardiac remodeling in 5-HT transporter knock-out mice. Fundam. Clin. Pharmacol. (Abstract, in press).

Buber, R., Cleary, L., Docherty, J.R., 2002. Effects of MDMA and cathinone on noradrenaline evoked contractions of rat right ventricle. Br. J. Pharmacol. 135 (345 pp.).

Chan, P., Chen, J.H., Lee, M.H., Deng, J.F., 1994. Fatal and nonfatal methamphetamine intoxication in the intensive care unit. J. Toxicol., Clin. Toxicol. 32, 147–155.

Connolly, H.M., Crary, J.L., McGoon, M.D., Hensrud, D.D., Edwards, B.S., Edwards, W.D., Schaff, H.V., 1997. Valvular heart disease associated with fenfluramine-phentermine. N. Engl. J. Med. 337, 581–588.

De La Torre, R., Farre, M., Ortuno, J., Mas, M., Brenneisen, R., Roset, P.N., Segura, J., Cami, J., 2000. Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. Br. J. Clin. Pharmacol. 49, 104–109.

Dowling, G.P., McDonough, E.T., Bost, R.O., 1987. 'Eve' and 'ecstasy'. A report of five deaths associated with the use of MDEA and MDMA. J. Am. Med. Assoc. 257, 1615–1617.

FitzGerald, J.L., Reid, J.J., 1994. Sympathomimetic actions of methylenedioxymethamphetamine in rat and rabbit isolated cardiovascular tissues. J. Pharm. Pharmacol. 46, 826–832.

Gordon, C.J., Watkinson, W.P., O'Callaghan, J.P., Miller, D.B., 1991. Effects of 3,4-methylenedioxymethamphetamine on autonomic thermoregulatory responses of the rat. Pharmacol. Biochem. Behav. 38, 339–344.

Harries, D.P., De Silva, R., 1992. 'Ecstasy' and intracerebral haemorrhage. Scott. Med. J. 37, 150–152.

Hayner, G.N., McKinney, H., 1986. The dark side of ecstasy. J. Psychoact. Drugs 18, 341–346.

Hertting, G., 1964. Fate of [$^3$H]-isoproterenol in the rat. Biochem. Pharmacol. 13, 1119–1128.

Johnson, B., Lamki, L., Barron, B., Spiga, R., Chen, R., Meisch, R., Khilnani, N., 1997. Brain blood flow abnormalities associated with oral cocaine use. Ir. J. Psychol. Med. 14, 72–73.

Kalix, P., Glennon, R.A., 1986. Further evidence for an amphetamine-like mechanism of action of the alkaloid cathinone. Biochem. Pharmacol. 35, 3015–3019.

Kelly, P.A.T., Ritchie, I.M., Sangra, M., Cursham, M.J.A., Dickson, E.M., Kelly, B., Neilson, R.F.P., Reidy, M.J., Stevens, M.C., 1994. Hyperaemia in rat neocortex produced by acute exposure to methylenedioxymethamphetamine. Brain Res. 665, 315–318.

Lange, R.A., Cigarroa, R.G., Yancy, C.W., Willard, J.E., Popma, J.J., Sills, M.N., McBride, W., Kim, A.S., Hillis, L.D., 1989. Cocaine-induced coronary-artery vasoconstriction. N. Engl. J. Med. 321, 1557–1562.

Mas, M., Farre, M., De La Torre, R., Roset, P.N., Ortuno, J., Segura, J., Cami, J., 1999. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. J. Pharmacol. Exp. Ther. 290, 136–145.

Mittleman, M.A., Mintzer, D., MacLure, M., Tofler, G.H., Sherwood, J.B., Muller, J.E., 1999. Triggering of myocardial infarction by cocaine. Circulation 99, 2737–2741.

O'Loinsigh, E., O'Boyle, K., 1998. Pure ecstasy? Ir. Sci. 6, 162.

Steele, T.D., Nichols, D.E., Yim, G.K.W., 1987. Stereochemical effects of 3,4-methylenedioxymethamphetamine (MDMA) and related amphetamine derivatives on inhibition of uptake of [$^3$H]-monoamines into synaptosomes from different regions of rat brain. Biochem. Pharmacol. 36, 2297–2303.

Widler, P., Mathys, K., Brenneisen, R., Kalix, P., Fisch, H.U., 1994. Pharmacodynamics and pharmacokinetics of khat: a controlled study. Clin. Pharmacol. Ther. 55, 556–562.