

Action of MDMA (Ecstasy) and Its Metabolites on Arginine Vasopressin Release

J.K. FALLON,^a D. SHAH,^b A.T. KICMAN,^a A.J. HUTT,^a J.A. HENRY,^c
D.A. COWAN,^a AND M. FORSLING^b

^a Drug Control Centre and Department of Pharmacy, King's College London,
Franklin-Wilkins Building, London SE1 9NN, UK

^b Neuroendocrine Laboratories, New Hunts House, King's College London,
Guy's Hospital, London Bridge, London SE1 1UL, UK

^c Academic Department of Accident and Emergency Medicine,
Imperial College School of Medicine, London, W2 1NY, UK

ABSTRACT: 3,4-Methylenedioxymethamphetamine (MDMA) has been reported to cause hyponatraemia, which appears to result from inappropriate secretion of the antidiuretic hormone arginine vasopressin (AVP). After administration of a low dose of (*R,S*)-MDMA (40 mg) to eight healthy drug-free male volunteers, concentrations of AVP in plasma increased significantly at 1, 2, and 4 hours. Although no relation between plasma MDMA and AVP was found on an examination of the entire data set over the 24-hour study period, a statistically significant negative correlation was observed at 1 hour. As this occurred at a time when both AVP and MDMA concentrations were rising, it was postulated that a metabolite, or metabolites, could primarily be responsible for the increase in AVP. To test this hypothesis we examined the effect of MDMA and five of its metabolites, in the dose range 0.1–1,000 nM, on AVP release from the isolated rat hypothalamus. All compounds tested were found to increase AVP release (using 10 nM and 1,000 nM concentrations), with 4-hydroxy-3-methoxymethamphetamine (HMA), the major metabolite of MDMA, being the most potent, and 3,4-dihydroxymethamphetamine (DHMA) the least potent. Each compound (1,000 nM), with the exception of DHMA, also enhanced the response to 40-mM potassium stimulation. Our findings confirm that metabolites of MDMA, in addition to the parent drug, contribute to AVP secretion *in vitro*. Further work will demonstrate whether this is also true *in vivo*.

KEYWORDS: MDMA; ecstasy; arginine vasopressin

INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy," "E," "Adam") ingestion has been associated with disturbances of body water homeostasis. In the 1980s and early 1990s the literature concentrated on hyperthermia and associated complications as the

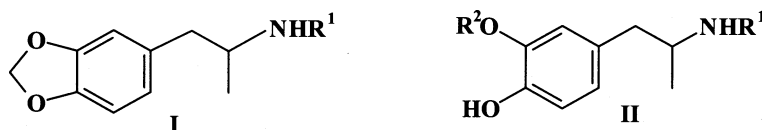
Address for correspondence: Dr Andrew T. Kicman, Drug Control Centre, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NN, UK. Voice: +44-20-78484779; fax: +44-20-78484980.
andrew.kicman@kcl.ac.uk

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main problems of MDMA use.¹⁻⁴ As a result, users were often advised to maintain adequate hydration to help counter these effects. Subsequent reports on the effects of MDMA ingestion described cases of hyponatraemia, sometimes fatal, that were postulated to result from the syndrome of inappropriate antidiuretic hormone secretion (SIADH), especially in young women.⁵⁻⁹ Despite these reports, perhaps because this adverse reaction was considered to be idiosyncratic, the effect of MDMA administration on the underlying mechanism of arginine vasopressin (AVP) release has not been investigated.

Here we describe results from a pharmacokinetic study in healthy MDMA naïve male volunteers in which the effect of a low dose of (*R,S*)-MDMA (40 mg) on AVP release was also examined. Following examination of the data obtained, we advanced the hypothesis that a metabolite (or metabolites) rather than, or together with, the parent drug may be responsible for the observed effects on AVP release. To test this hypothesis we examined the effect of MDMA, and five of its metabolites, on AVP release from the isolated rat hypothalamus.

Demethylenation is the most important pathway of MDMA metabolism in man,¹⁰⁻¹⁴ with *N*-demethylation being a minor pathway. The major cytochrome P-450 (CYP) involved in demethylenation is CYP2D6, and other isoforms, such as 2B6, 3A4, and 1A2, are also believed to make a contribution.¹⁵⁻¹⁸ Hence, the major product of this transformation is 3,4-dihydroxymethamphetamine (DHMA; FIG. 1), with 3,4-dihydroxyamphetamine (DHA) also being formed via demethylenation of the minor product 3,4-methylenedioxyamphetamine (MDA; the demethylated metabolite). These two products (DHMA and DHA) subsequently undergo methylation at the 3-hydroxy group on the phenyl ring by catechol-O-methyl transferase to form 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxy-



Compound	Structure	R ¹	R ²
MDMA	I	CH ₃	-
MDA	I	H	-
HMMA	II	CH ₃	CH ₃
DHMA	II	CH ₃	H
HMA	II	H	CH ₃
DHA	II	H	H

FIGURE 1. Structure of MDMA and its metabolites.

amphetamine (HMA), respectively. HMMA is believed to be the predominant metabolite of MDMA in humans,^{11,12,14,19} and together with HMA, DHMA, and DHA it is excreted as glucuronide or sulfate conjugates in urine. The effect and relative potency of these metabolites, together with the parent drug, on the release of AVP are reported herein.

METHODS

Material. (±)-(R,S)-MDMA hydrochloride and (±)-(R,S)-MDA hydrochloride were obtained from Sigma Chemical Company Ltd, Poole, UK; (–)-(R)- and (+)-(S)-MDMA hydrochloride and (–)-(R)- and (+)-(S)-MDA hydrochloride were generously donated by the Research Technology Branch of the National Institute on Drug Abuse, Rockville, Maryland, USA. Hydrochloride salts of the racemates of HMMA, HMA, DHMA, and DHA were synthesized as described previously.^{20–23}

Analytical Techniques. MDMA and MDA plasma enantiomer concentrations were measured by a validated GC-MS assay.²⁴ AVP concentrations in plasma²⁵ and in Earles balanced salt solution (EBSS, Gibco, Biocult, Paisley, UK) media²⁶ were determined by validated radioimmunoassay using the first International Standard for vasopressin (77/501). Intra- and interassay coefficients of variation for plasma were 7.5 and 11.6% at 2.5 pmol/L, respectively, and the corresponding values in media were 5.0 and 8.9%, respectively. Cortisol was also measured by validated radioimmunoassay (Diagnostic Products Corporation, Coat-A-Count, Gwynedd, UK) and osmolalities by freezing point depression (Microosmometer Model 3MO Plus, Advanced Instruments Inc., Vitec Scientific Ltd.). Sodium concentrations were determined using potentiometric dry slide technology.

Human Study. (±)-(R,S)-MDMA (47.6 mg HCl salt; equivalent to 40 mg free base) was administered in capsule form to eight healthy nondrug-using (MDMA naïve) male volunteers (22–32 years) at 10:00 AM on the study day with ~200 mL of water as described by Fallon *et al.*²⁴ Briefly, blood samples were collected from a forearm vein immediately prior to drug administration and at 0.5, 1, 2, 4, 6, 8, and 24 hours postdose. Immediately after each collection the plasma was separated and rapidly frozen using liquid nitrogen. It was stored at –20°C until required for analysis. Approval to administer the compound was obtained from the UK Home Office and the King's College London Ethics Committee, and each subject received full details prior to giving written informed consent. A control study in which three of the eight volunteers acted as untreated controls was undertaken at least 2 weeks later.

Treatment of data: Repeated measures ANOVA, with time as the within subject factor, was used to test for overall change from basal AVP and MDMA concentrations, using the SPSS software statistics package (SPSS, UK). The simple contrasts were performed to locate differences indicated, comparing mean values at each postadministration time to respective basal values. Regression analysis was applied at each sampling time to examine the relation between MDMA and AVP concentrations as well as between MDA and AVP concentrations.

In Vitro Study. The study was performed on isolated rat hypothalami using a previously validated method.²⁷ Specific pathogen-free male Wistar rats (Banting & Kingman Ltd., Aldeburgh, UK) weighing 225–275 g were used. Animals were given free access to food (Rat and Mouse no 1 maintenance diet; Special Diet Services

Ltd., Witham, Essex, UK) and water, and were housed under conditions of fixed lighting (12 h light: 12 h dark) and constant temperature and humidity.

Hypothalamus dissection: Decapitation of groups of rats took place between 9:00 and 10:00 AM. The brain was removed immediately and a hypothalamic block dissected within the following limits: anterior border of the optic chiasm, anterior border of the mamillary bodies, and lateral hypothalamic sulci. The dissection depth was approximately 3.0 mm. The blocks were bisected longitudinally through the midsagittal plane and the two hypothalamic halves incubated in one vial. Total dissection time was less than 2 minutes from decapitation.

Hypothalamic incubation: Each hypothalamus was incubated in polyethylene vials containing 400 μ L of EBSS. The solution was supplemented with human serum albumin (0.2%), ascorbic acid (60 mg/mL), and aprotinin (concentration in EBSS; 40 kallikrein-inhibiting units [KIU]/mL). The vials were placed in a shaking water bath at 37°C and gassed with 95% O₂ and 5% CO₂. An 80-minute equilibration period was chosen as previously described.²⁸ After equilibration, fresh media were added for a control period of 20 minutes, after which time the media were again replaced by either fresh media (control hypothalami) or media containing MDMA or metabolites (test hypothalami) for a further 20-minute incubation period. Following each incubation period the media were analyzed for AVP. Each compound was examined at concentrations in medium of 0.1, 10, and 1000 nM ($n = 5$). The single enantiomers of MDMA and MDA were also examined at a concentration of 500 nM ($n = 5$). Additionally ($\pm$)-(R,S)-MDMA was reexamined in the presence of ($\pm$)-(R,S)-HMMA, each at a concentration of 500 nM ($n = 5$). Following these steps the hypothalami were also exposed to KCl in EBSS (40 mM) and then to KCl in EBSS also containing the compound under investigation (for the control hypothalami, no compound was added). Hypothalami were bathed in EBSS alone for a 20-minute control period prior to this. At the end of the experiment the viability of the tissue was confirmed by incubation with 56 mM KCl. Hypothalami not responding to the 56 mM KCl stimulation were excluded from the data analysis. EBSS medium from each incubation period was stored at -20°C until analyzed for vasopressin.

Treatment of data: Results were expressed as the ratio of hormone release in the test period with that in the preceding control period, being calculated for basal and stimulated release. These were compared with ratios calculated from the control hypothalami. Overall significance for each series of observations (e.g., test:control ratios, following incubation with ($\pm$)-(R,S)-MDMA at 0.1, 10, and 1000 nM concentrations, in comparison with ratios obtained for control hypothalami) was tested by one-way ANOVA. If statistical significance was found ($p < 0.05$), then sets of data were compared using Student's t test with Dunnett's correction for multiple comparisons.

RESULTS AND DISCUSSION

Human Study. A significant rise in plasma AVP concentrations was observed in all volunteers between 1 and 4 hours after administration of 40 mg (R,S)-MDMA (repeated measures ANOVA, simple contrasts, $p < 0.05$ at 1 and 4 hours, $p < 0.01$ at 2 hours) (Fig. 2).²⁹ Concentrations had returned to basal at 8 and 24 hours ($p > 0.05$). The rise was accompanied by a small but significant decrease in plasma sodi-

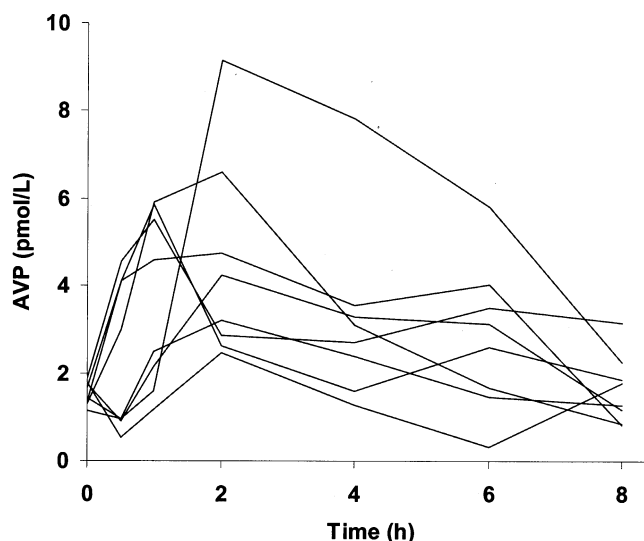


FIGURE 2. Plasma concentrations of AVP after administration of (*R,S*)-MDMA (40 mg) to eight drug-free healthy male volunteers. Mean increases from basal were significant at 1, 2, and 4 hours (repeated measures ANOVA, $p < 0.05$ at 1 and 4 hours, $p < 0.01$ at 2 hours).

um concentration between 0.5 and 2 hours (t test, $p < 0.05$), although plasma osmolality remained unchanged up to 8 hours after drug administration ($p > 0.05$). No marked increase in plasma cortisol concentration was seen ($p > 0.05$), the significant decreases at 6 and 8 hours ($p \leq 0.05$) being representative of a characteristic circadian rhythm. None of the measurements changed significantly in the control subjects ($p > 0.05$) up to 8 hours, with the exception of plasma cortisol, which again showed a characteristic circadian rhythm.

Although plasma total MDMA concentrations (i.e., the sum of the individual enantiomer concentrations) rose to a maximum (geometric mean) of $47.0 \mu\text{g/L} \pm 20.9\%$ at 4 hours (the corresponding value at 2 hours was $45.2 \mu\text{g/L} \pm 18.5\%$), no correlation between (*R,S*)-MDMA and AVP concentrations was seen over the total sampling period (Spearman $r = 0.2$, $p = 0.1$). However, following examination of the data at each sampling time, a highly significant negative correlation was observed between total MDMA and AVP concentrations at 1 hour ($r = -0.94$, $p < 0.001$; $n = 8$) (FIG. 3).³⁰ This was the case whether single or total enantiomer MDMA concentrations and whether actual AVP concentrations or AVP concentration changes from basal ($r < -0.90$, $p < 0.002$) were used for data analysis. At 0.5 hour the correlation tended towards significance in the same direction (for total MDMA versus AVP, $r = 0.61$, $p = 0.11$; for total MDMA versus changes in AVP from basal, $r = 0.66$, $p = 0.11$), whereas at 2, 4, 6, and 8 hours no correlation was seen (e.g., total MDMA versus AVP or AVP concentration changes from basal at 2 hours, $r < 0.09$, $p > 0.84$).

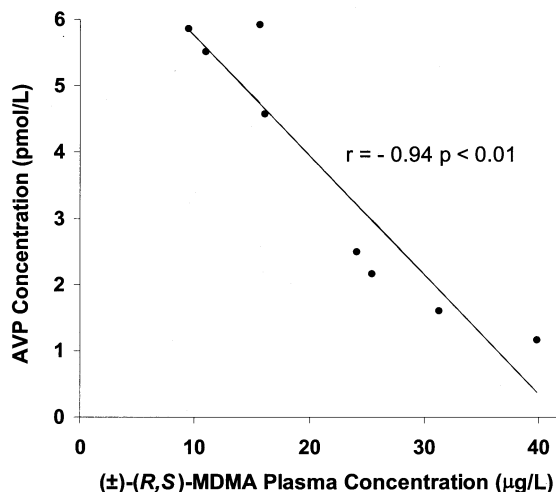


FIGURE 3. Correlation of plasma AVP concentrations with total MDMA enantiomer plasma concentrations at 1 hour after oral administration of 40 mg (*R,S*)-MDMA to eight drug-free healthy male volunteers. Reproduced with kind permission of the *Journal of Pharmacology and Pharmacology*.³⁰

There was no significant correlation between AVP concentration and single or total enantiomer MDA concentrations at any time from 1 to 8 hours after drug administration ($p > 0.05$). The values at 0.5 hour were not examined as some of the enantiomeric concentrations of MDA were below the limit of quantification of 0.025 µg/L at this time.²⁴

The rise in AVP occurred at a time of day when no change in basal AVP would be expected.²⁵ It did not appear to be associated with changes in water homeostasis, as plasma sodium concentrations decreased between 0.5 and 2 hours postadministration. Neither did it appear to be part of a stress response, as plasma cortisol concentrations remained relatively unchanged up to 4 hours postdose.

The lack of overall correlation between MDMA and AVP may have resulted from the short half-life of AVP, which is initially about 6 minutes,³¹ whereas the half-life of MDMA is measured in hours.^{19,24} The negative correlation observed at 1 hour after drug administration may have been a chance occurrence, but nonetheless the possibility that a metabolite (or metabolites) of MDMA rather than, or as well as, the parent compound may be responsible for the AVP release should be considered. Also, although a negative correlation could signify inhibition of AVP release by MDMA, the fact that the relation was seen at 1 hour, at which time AVP concentrations had increased significantly (Fig. 2), suggested that involvement of an active metabolite(s) was more likely. The lack of correlation at 2 hours could be explained by the possible diminishing responsiveness of the magnocellular neurones secreting vasopressin, even though plasma AVP concentrations were significantly greater than basal values at this time (paired *t* test, $p = 0.006$). Because of the lack of correlation between (*R,S*)-MDA and AVP shortly after (*R,S*)-MDMA administration, it was not

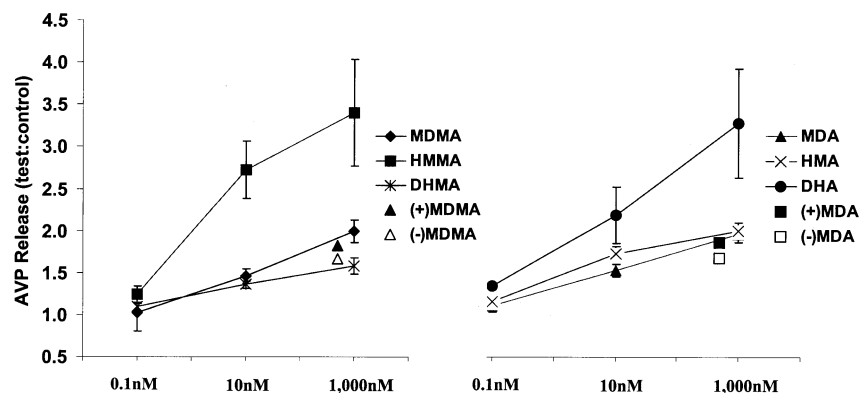


FIGURE 4. Effect of MDMA and five of its metabolites (racemates unless stated) on AVP release from isolated rat hypothalamus *in vitro*. Bars represent mean $\pm$ SEM. Response (ratio of test period:control period) to 10 nM and 1000 nM concentrations was significantly greater for each compound ($p < 0.01$) compared to data obtained from control hypothalami. At 0.1 nM concentrations, only the response to DHA was significant ($p < 0.05$). The response to 500 nM concentrations of the (+)-*S*-enantiomers of MDMA and MDA was significantly greater ($p < 0.05$) than that for their corresponding (–)-*R*-enantiomers.

thought that MDA was the metabolite causing the AVP release. MDA is known, in addition, to be a relatively minor metabolite of MDMA,²⁴ in comparison with catechol-derived products which are major metabolites.^{10,11,14}

To examine the hypothesis that a metabolite, or metabolites, of MDMA, in addition to the parent drug, may influence the AVP release observed in humans, an *in vitro* study using isolated rat hypothalami was undertaken.

In Vitro Study. All compounds (MDMA and five of its metabolites) were found to increase AVP release from the isolated rat hypothalamus in a dose-related manner (FIG. 4). (*R,S*)-HMMA was the most potent compound and (*R,S*)-DHMA the least potent, compared to data from control hypothalami. Each compound, except DHMA, also enhanced the response to 40 mM potassium stimulation at a concentration of 1000 nM ($p < 0.05$). Thus, our previous observations that MDMA administration can stimulate vasopressin release in man were confirmed *in vitro*, and evidence was provided for the involvement of a metabolite or metabolite(s) in the response. The concentrations employed in the experiment covered the range of concentrations of MDMA and MDA found in plasma. They were also similar to those measured by other investigators.¹⁴ The concentrations employed for the drug:metabolite and single enantiomer mixtures also fell within these ranges. In addition, the results confirm that MDMA can act directly on the hypothalamus. If this is also true in humans, then vasopressin release following MDMA ingestion could occur from direct action as well as other changes such as hyperthermia.^{3,4}

The increase in AVP release observed was significant for each compound (parent drug and metabolites) at 10 nM and 1000 nM concentrations. For the 0.1 nM con-

centrations the increase was only significant for the primary amine catechol (*R,S*)-DHA. For the single enantiomer solutions the response to 500 nM of the (+)-*S*-enantiomer was significantly greater than that for the (–)-*R*-enantiomer, at the same concentration, for both MDMA and MDA ($p < 0.05$). This agrees with findings from other animal studies which show (+)-(*S*)-MDMA to have greater neurochemical activity than (–)-(*R*)-MDMA.³² The response in incubates containing equal amounts of (*R,S*)-HMMA and (*R,S*)-MDMA (each 500 nM) was less than for the equivalent concentrations of (*R,S*)-HMMA alone (1000 nM) ($p < 0.05$). This confirmed the observation that (*R,S*)-HMMA was more active than (*R,S*)-MDMA in affecting the AVP response, whether the MDMA acted as an inhibitor for the HMMA or simply reduced the total response by its lower activity.

Stimulation of AVP release could account for the sometimes fatal hyponatremia often observed following MDMA ingestion.^{5,9,33} All cases of hyponatremia and SIADH reported in the literature have occurred in premenopausal women (see, for e.g., Refs. 8 and 34–36). Hyponatremia has a high incidence of morbidity and mortality in premenopausal women (Ref. 35 and references therein) as compared to young men, and some animal studies have suggested that renal responsiveness to AVP is affected by reproductive status in women.³⁷ Combined with any gender-dependent differences in the metabolism of MDMA, it is therefore possible that women are more susceptible than men to abnormalities of body water homeostasis following the ingestion of MDMA.

AVP release is believed to be controlled by both serotonergic and aminergic pathways.^{38–40} Whereas the serotonergic effects of MDMA are well documented,^{32,41,42} aminergic effects have also been reported.^{43–45} Considering the similarity of the MDMA catechol and methoxy metabolite structures to common monoamine neurotransmitters, it is possible that the aminergic actions of MDMA and/or its metabolites are important for the stimulation of AVP release after the ingestion of MDMA. From animal studies it is not clear whether MDMA is metabolized inside the blood-brain barrier.^{46,47} Neither is it known whether it (or its metabolites) is active at the magnocellular neurons (circumventricular organs) *in vivo*. Considering SIADH as a well-known side effect of neuroleptic and other psychoactive drugs,^{48,49} it is perhaps not surprising that MDMA, with its catechol and catechol-like metabolites, has also been associated with SIADH.

In conclusion, we have shown an increase in plasma AVP concentration after administration of (*R,S*)-MDMA to healthy drug-free male volunteers. The observation of a highly significant inverse correlation between plasma drug and hormone at 1 hour postdose suggested the possible involvement of an active metabolite in hormonal release. This hypothesis was confirmed *in vitro* using rat hypothalamic preparations where HMMA, a major metabolite of MDMA in humans, was shown to be a more potent stimulator of AVP release than the parent drug. The significance of this observation to the adverse effects of MDMA in humans awaits further work.

NOTE ADDED IN PROOF: Since the submission of this manuscript, a paper on the effect of MDMA, and its metabolites, on neurohypophyseal hormone release from the isolated rat hypothalamus has been published.⁵⁰ The response to drug and metabolite stimulation on oxytocin release was found to be dose-dependent, but less marked than that for AVP.

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