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Arginine vasopressin release in response to the administration of 3,4-methylenedioxymethamphetamine (''ecstasy''): is metabolism a contributory factor?

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Abstract

The aim of this investigation was to examine the effect of 3,4-methylenedioxymethamphetamine (MDMA) administration on arginine vasopressin (AVP) release. (*R*,*S*)-MDMA (40 mg) was administered to eight normally hydrated healthy male volunteers (22–32 years) and blood samples were collected up to 24 h. Plasma was assayed for AVP and cortisol by radioimmunoassays, and for MDMA and the *N*-demethylated metabolite, MDA, by gas chromatography-mass spectrometry. Sodium concentrations and osmolality were also determined. Plasma AVP increased in all subjects after MDMA administration and a significant negative correlation was observed between concentrations of AVP and both single and total enantiomer MDMA at 1 h ($r < -0.91$, $P < 0.01$). This had disappeared by 2 h ($P > 0.7$). Compared with basal values, no significant change was observed for osmolality or cortisol at 1 h after drug administration. In conclusion, plasma AVP concentrations increase after MDMA administration, but the increase is not part of a generalized stress response since cortisol did not increase concurrently. A significant negative correlation between plasma MDMA and AVP was observed soon after administration. The possibility that a pharmacological effect of MDMA is primarily mediated via one or more metabolites, rather than by the parent drug, should be considered.

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA), originally developed as an appetite suppressant, is now a widely used ''recreational'' drug commonly known as ''ecstasy''. It is an indirectly acting sympathomimetic agent and can produce a number of complications including hyponatraemia with accompanying headache, vomiting and convulsions (Maxwell et al 1993). The hyponatraemia appears to result from increased arginine vasopressin (AVP) secretion as case reports show that it is accompanied by hyperosmolar urine (Parr et al 1997) and raised plasma AVP (Holden & Jackson 1996). Stimuli for AVP release also induce drinking, and excessive water intake has been reported after taking MDMA (Matthai et al 1996). As part of a pharmacokinetic study, the opportunity arose to investigate the effects of MDMA on AVP secretion in healthy subjects under controlled conditions. The ethical and safety issues associated with the administration of neurotoxic agents, such as MDMA to man, is the subject of considerable debate, for example see

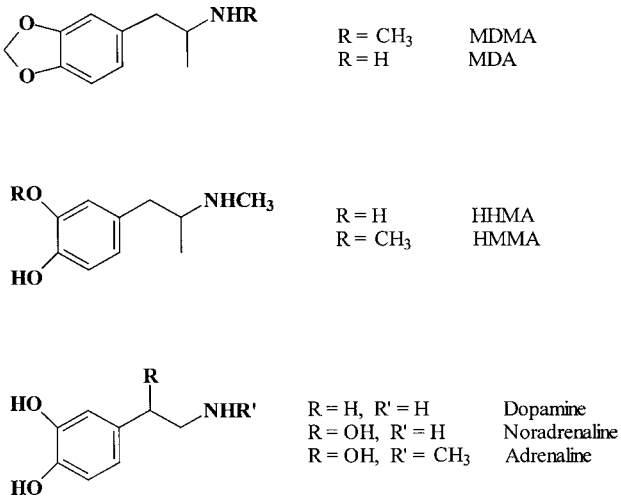

Figure 1 Structures of 3,4-methylenedioxymethamphetamine (MDMA), metabolites and similarly related catecholamine neurotransmitters.

Vollenweider et al (2001) and references therein. The dose of MDMA (40 mg) selected in this investigation is equivalent to between 0.5–0.7 mg kg^{-1}, which is well below any single dose shown to be neurotoxic in both animals and man, and much lower than that typically used recreationally (75–150 mg) (Steele et al 1994). We have previously reported, in a research letter, that oral administration of racemic MDMA to healthy male volunteers, results in an increase in plasma AVP concentrations (Henry et al 1998). Here we describe in full the results of that investigation and examine the relationship between plasma concentrations of MDMA and AVP. It is not known whether the effect is owing to the parent drug or a metabolite (or metabolites), or whether the effect is stereoselective. In view of the structural resemblance of the catechol and related metabolites of MDMA to endogenous catecholamine neurotransmitters (Figure 1), the potential exists for MDMA metabolites to exert pharmacological effects (Lim & Foltz 1988).

Materials and Methods

Administration study

The protocol was as described by Fallon et al (1999). Briefly, eight healthy non-drug-using (MDMA naive) male volunteers (22–32 years) participated in the study. Three of the volunteers acted as untreated controls at least two weeks later. Approval to administer MDMA was obtained from the UK Home Office and the King's College London Ethics Committee, and each subject gave written informed consent. Part of the study exclusion criteria included a history of drug abuse, psychosis or alcoholism and the subjects were specifically asked if they had used illicit drugs or MDMA in the past. Medical examination revealed that all volunteers were in good general health; all had normal pulse rates and blood pressure, and liver function tests (plasma aspartate transaminase, alanine transaminase and γ-glutamyl transferase) were within reference ranges. All subjects were required to abstain from alcoholic beverages for 24 h before and during the study, and normal water intake was maintained from 2200 h on the night before the investigation.

Each subject received (*R*,*S*)-MDMA hydrochloride (47.6 mg; equiv. 40 mg free base) in capsule form with approximately 200 mL of water at 1000 h after a light caffeine-free breakfast. Volunteers rested under medical supervision, for the first 8 h of the study, in a designated area. Blood samples (20 mL) were collected from a cannulated forearm vein into heparinized tubes immediately before and at 0.5, 1, 2, 4, 6, 8 and 24 h after drug administration. Pulse rate and blood pressure were monitored at each sampling time. After collection, samples were immediately centrifuged at 4°C for 15 min. The plasma was separated and rapidly frozen using liquid nitrogen. It was then stored at −20°C until required for further analysis.

Analysis of plasma samples

Plasma concentrations of the enantiomers of MDMA and 3,4-methylenedioxymethamphetamine (MDA) were measured by gas chromatography-mass spectrometry, as validated elsewhere (Fallon et al 1999). AVP was determined using a validated radioimmunoassay (Forsling et al 1998), as was cortisol (Diagnostic Products Corporation, Coat-A-Count, Gwynedd, UK) (Kicman et al 1999). MDMA does not interfere in the AVP assay. Osmolality was measured by freezing-point depression (Microosmometer model 3MO Plus; Advanced Instruments Inc., Vitec Scientific Ltd). Sodium concentrations were determined using potentiometric dry-slide technology.

Treatment of data

Each individual's values for analytes after administration were compared with the respective basal values

by repeated-measures analysis of variance. This incorporated univariate analysis with time as the within-subject factor using the statistical software program SPSS 9.0 (SPSS, UK). To locate differences indicated by repeated-measures analysis of variance ($P < 0.05$), the simple contrasts were performed to compare post-drug administration values with their respective basal values.

Regression analysis was applied to AVP concentrations and MDMA combined, or individual enantiomer concentrations, at each sampling time. In addition, regression analysis was carried out using the increase in AVP concentrations (i.e. the post-drug administration value minus the basal value). The above analysis was then repeated using MDA combined and single enantiomer concentrations instead of those of the MDMA. Pearson correlation (r) and significance (P) values were calculated.

Results

Plasma (*R*,*S*)-MDMA, AVP, cortisol and sodium concentrations together with osmolality after (*R*,*S*)-MDMA administration are summarized in Figure 2. There was a significant increase in plasma AVP concentrations compared with basal values between 1 and 4 h after drug administration in all subjects. Sodium concentrations showed a small, but significant, decrease between 0.5 and 2 h after administration (at 1 h, a decrease of 1–2 mM from basal values was observed in six of the eight volunteers; the remaining two volunteers showed no decrease at that time). Plasma osmolality remained unchanged up to 8 h after MDMA ingestion. At 24 h, the plasma osmolality and sodium concentrations were significantly above basal values and no marked increase in mean cortisol concentrations was observed after drug administration. In the control subjects, none of the measurements changed significantly ($P > 0.05$), with the exception of plasma cortisol, which showed a characteristic circadian rhythm. All the control data obtained were within the reference ranges for each analyte. There was no significant change in pulse or blood pressure for treated or control subjects throughout the study.

The mean plasma AVP increased from basal (geometric mean $\pm$ s.e.m.) (1.5 pM $\pm$ 6%) to a maximum concentration at 2 h (4.0 pM $\pm$ 18%) after MDMA ingestion, at which time the total observed MDMA enantiomer concentrations in plasma were 45.2 μg L^{-1} $\pm$ 18.5%, reaching a maximum of 47.0 μg L^{-1} $\pm$ 20.9% at

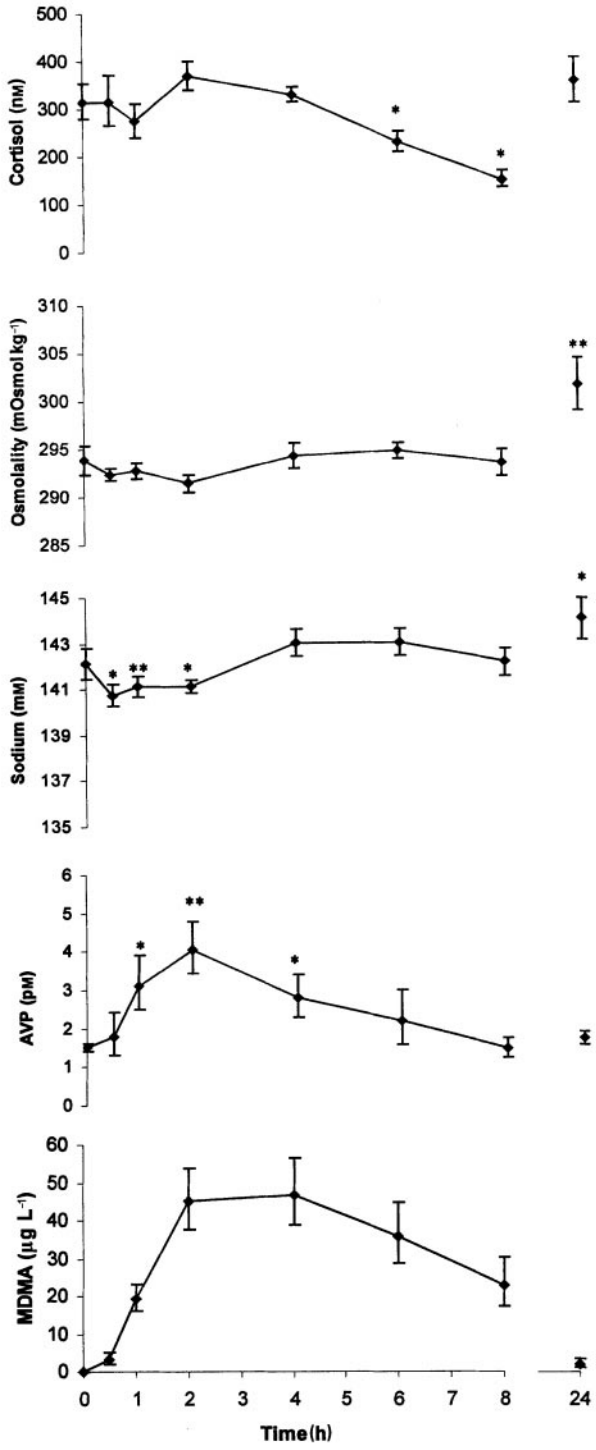

Figure 2 Plasma concentrations (mean $\pm$ s.e.m.) of MDMA (total enantiomer), arginine vasopressin (AVP), sodium and cortisol, together with osmolality, before and after administration of 40 mg (*R*,*S*)-MDMA to eight healthy male volunteers (*$P < 0.05$, **$P < 0.01$). Results are expressed as geometric means for MDMA, AVP and cortisol.

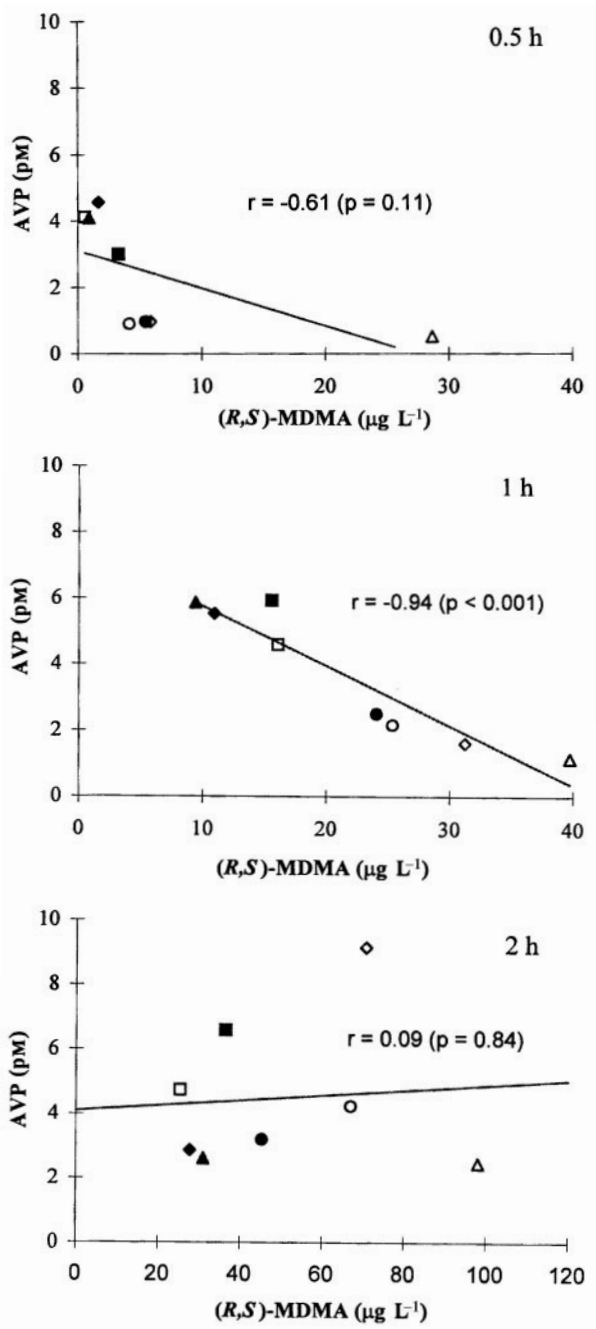

Figure 3 Correlation of plasma arginine vasopressin (AVP) concentrations with total MDMA enantiomer plasma concentrations at 0.5, 1 and 2 h after oral administration of 40 mg (*R*,*S*)-MDMA to eight healthy male volunteers. For ease of comparison, the y-axis scale has been kept constant throughout and a different symbol is used for each volunteer.

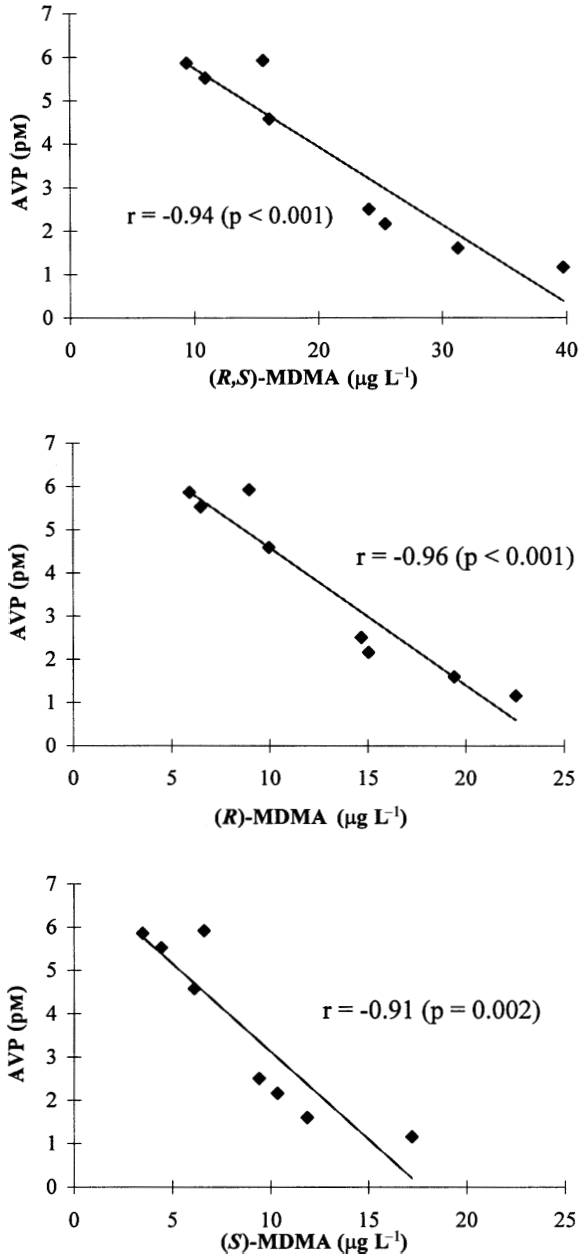

Figure 4 Correlation of plasma arginine vasopressin (AVP) concentrations with total and single enantiomer MDMA plasma concentrations at 1 h after oral administration of 40 mg (*R*,*S*)-MDMA to eight healthy male volunteers.

4 h (Figure 2). Figure 3 shows plasma AVP concentrations corresponding to total enantiomeric MDMA concentrations in plasma for each individual at 0.5, 1 and 2 h after MDMA administration. Of particular note is that the individual with the highest concentration of MDMA over this time period (0.5–2 h), concurrently had the lowest AVP concentration (0.5 pM at 0.5 h increasing to 2.5 pM at 2 h) among the volunteers (represented by the open triangle in Figure 3).

At 1 h after MDMA administration, plasma AVP concentrations were significantly negatively correlated with total MDMA ($r = -0.94$; $P < 0.001$). This was also the case when AVP concentration changes from basal were used instead of the measured concentrations ($r = -0.94$; $P < 0.001$). The lowest MDMA concentrations at 1 h corresponded to the highest concentrations of AVP and also showed the largest increases in AVP compared with the corresponding respective basal values (e.g. the subject with the lowest total MDMA concentration of 9.4 μg L^{-1} at 1 h had one of the highest AVP concentrations of 5.9 pM, a 4.5-fold increase from his basal AVP value of 1.3 pM). At 2 h after administration, there was no significant correlation, whether actual AVP concentrations (Figure 3) or differences in AVP concentrations from basal values for each subject ($r < 0.09$; $P > 0.84$), were used. At 0.5 h, the corresponding data was tending towards significant correlation in the same direction, whether using actual AVP concentrations ($r = -0.61$, $P = 0.11$) or changes in AVP concentrations from basal ($r = -0.66$, $P = 0.08$); the values of P being much smaller than those calculated for data at 2, 4, 6 and 8 h ($P > 0.5$).

The AVP concentrations versus the single enantiomer plasma MDMA concentrations at 1 h are shown in Figure 4; these plots can be compared with that of the total MDMA. All data was highly significantly negatively correlated (the smallest r value being -0.91, $P < 0.01$; $n = 8$), albeit that the plasma concentrations of (*R*)-MDMA (mean $\pm$ s.e.m., 12.9 ± 2.1 μg L^{-1}) were significantly greater than those of the *S*-enantiomer (mean $\pm$ s.e.m., 8.7 ± 1.6 μg L^{-1}; paired *t*-test $P < 0.001$) at this time. Significant negative correlations were also observed when the differences in AVP concentrations with respect to basal values for each subject were used instead of the measured concentrations (data is not shown).

The plasma concentrations of (*S*)-MDA exceeded those of the (*R*)-MDA in all volunteers up to 8 h after drug administration, with the observed mean C_{max} of (*S*)-MDA (2.9 ± 0.4 μg L^{-1}) being significantly greater than that of the *R*-enantiomer (1.0 ± 0.1 μg L^{-1}; $P < 0.01$, paired *t*-test) (Fallon et al 1999). No statistically significant correlation was seen between AVP concentrations and single or total enantiomer concentrations of MDA at 1 or 2 h (all P values > 0.15). For values at 0.5 h, regression analysis was not performed because some of the enantiomeric concentrations of MDA were below the limit of quantification of 0.025 μg L^{-1} (Fallon et al 1999).

Discussion

An acute increase in plasma AVP concentration compared with control was observed after administration of a relatively small dose (40 mg) of (*R*,*S*)-MDMA to human volunteers. An increase in AVP secretion would not be expected at this time of day (Forsling et al 1998). The rise did not appear to be part of a generalized stress response since no marked increase in plasma cortisol concentrations was observed, nor did it appear to occur as a result of changes in water homeostasis, as plasma sodium concentrations decreased, rather than increased, between 0.5 and 2 h after drug administration. However, it is interesting to note that at 24 h after drug administration, the plasma sodium and osmolality were significantly greater than basal values, consistent with an altered hydration status after participation in the study.

Plasma MDMA and AVP concentrations tended towards a significant negative correlation at 30 min post-drug administration and at 1 h the correlation was highly significant. Although the observed negative correlation might be a chance occurrence, the possibility that a metabolite of MDMA, rather than the parent compound, is responsible for the stimulation of AVP release, should be considered (results from this study encouraged us to use a rat model in which the metabolites were found to be active – see later). Given the difference in clearance rates between MDMA (Fallon et al 1999) and AVP (Fabian et al 1969), together with the possible diminishing responsiveness of the magnocellular neurones during the study, one would only expect to see any clear relationship soon after drug administration. This could explain why the relationship was lost at 2 h, even though the AVP concentrations were significantly greater than basal values ($P = 0.006$, paired *t*-test, one-tail).

As the negative correlations were observed so soon (1 h) after administration of the racemate, it was not possible to determine whether the relationship with AVP was exclusive to one enantiomer of MDMA. Although the plasma concentrations of (*R*)-MDMA were significantly greater than those of the *S*-enantiomer at 1 h, the difference in the plasma profiles of the enantiomers may not have been sufficient to prevent a highly significant negative correlation being observed concurrently for each enantiomer. Administration of the single enantiomers of MDMA and its metabolites to new volunteers would help resolve this issue.

In contrast to observations with the parent compound, no statistically significant correlation was seen between AVP concentration, or changes in AVP con-

centration from basal values, and single or total enantiomer concentrations of the *N*-demethylated metabolite (MDA). Therefore, it may be concluded that MDA is not involved in the stimulation of AVP release. This should probably not be surprising, as we have shown that MDA is a relatively minor metabolite of MDMA (Fallon et al 1999). Similarly, de la Torre et al (2000) have recently shown that MDA is a relatively minor metabolite compared with the catechol-derived products, even at doses of 150 mg.

The increase in AVP concentrations observed in this study, occurred as a result of the acute (0–6 h) effects of MDMA administration. From animal studies, MDMA is known to stimulate serotonin (5-HT) release and inhibit its reuptake (Johnson et al 1986; Steele et al 1987), while serotonergic pathways have been shown to regulate AVP secretion (Iovino & Steardo 1985). However, the significant negative correlation between plasma AVP and MDMA concentrations observed 1 h after administration, suggests that a metabolite of MDMA, rather than the parent drug, may be an important factor. 4-Hydroxy-3-methoxymethamphetamine (HMMA) (Lim & Foltz 1989; Helmlin et al 1996; Lanz et al 1997; de la Torre et al 2000), a major metabolite of MDMA, is formed via methylation of a catechol intermediate, 3,4-dihydroxymethamphetamine (3,4-HHMA; Figure 1), presumably by catechol *O*-methyltransferase. Due consideration should be given to the possibility that HMMA and related metabolites are agonists that stimulate AVP release. Unfortunately, we did not have sufficient plasma remaining from the study to determine these metabolites. However, in order to examine this possibility we recently undertook an in-vitro study in male Wistar rats to determine whether MDMA and HMMA stimulate neurohypophysial hormone release. The preliminary results indicate that HMMA is a more potent in-vitro stimulator of vasopressin release than the parent compound (Fallon et al 2000) and the effect has subsequenly been shown to be reproducible. These data support the hypothesis that a metabolite(s) of MDMA contributes to AVP release in-vivo. However, further work is necessary to establish the hypothesis that the metabolism of MDMA is a contributory factor to AVP release in humans. Also, there is a possible involvement of the metabolites of MDMA, rather than the parent drug, in serotonergic neurotoxicity associated with MDMA use (Bai et al 1999 and references therein).

While the stimulatory effect would be consistent with activation of serotoninergic pathways, dopaminergic or adrenergic mechanisms could also be involved as effects on monoaminergic transmission have been described (White et al 1996). However, the action of dopamine on vasopressin release in man is not clear, both stimulation (Coiro et al 1995) and inhibition (Lightman & Forsling 1980) having been reported depending on the experimental protocol adopted. The response to noradrenaline is also unclear in man, the earliest reports suggested no effect (Milsom et al 1986). The stimulatory effect of MDMA on prolactin release would argue against dopamine involvement in the neuroendocrine response (Nash et al 1988).

If the metabolism of MDMA is significant for the stimulation of AVP release, that may mean that certain individuals are more prone to MDMA-induced AVP effects than others. For example, the demethylenation of MDMA to HHMA is known to be mediated by cytochrome P450 2D6 (Kumagai et al 1994; Tucker et al 1994; Lin et al 1997) and therefore the metabolizer status (extensive or poor) of an individual may be expected to influence AVP release, with the extensive metabolizers producing a greater increase. Drug dose may also be expected to influence AVP release, as de la Torre et al (2000) have recently reported on the non-linearity of MDMA pharmacokinetics in man. This could have wider implications when situations of over-hydration and hyponatraemia are encountered (Maxwell et al 1993). The present investigation was undertaken only in male volunteers and it is not known whether gender influences the metabolism of MDMA. Interestingly, all reported cases of hyponatraemia associated with MDMA ingestion found in the literature, occurred in premenopausal women (Maxwell et al 1993; Holden & Jackson 1996; Matthai et al 1996; Parr et al 1997). As pointed out by Watson et al (1997), acute hyponatraemia as a result of water overload has a high incidence of morbidity and mortality in premenopausal women (Arieff 1986, 1993). From animal studies, it appears that renal responsiveness to AVP is affected by reproductive status in females, Forsling et al (1996) having shown that the renal action of vasopressin varies over the 4-day oestrus cycle of the female rat. These factors, combined with possible gender differences in the metabolism of MDMA, could mean that women are more susceptible than men to hyponatraemia and abnormalities of body water homeostasis after ingestion of MDMA.

In conclusion, MDMA administration increases plasma AVP concentrations and this effect is not mediated by stress since cortisol did not increase concurrently. A significant negative correlation between plasma MDMA and AVP was observed soon after drug administration. The possibility that a pharmacological effect of MDMA is primarily mediated via one or more

metabolites, rather than by the parent drug, should be considered.

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