Sex Differences in the Effects of MDMA (Ecstasy) on Plasma Copeptin in Healthy Subjects

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Background: 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) misuse is associated with hyponatremia particularly in women. Hyponatremia is possibly due to inappropriate secretion of plasma arginine vasopressin (AVP).

Objective: To assess whether MDMA increases plasma AVP and copeptin in healthy male and female subjects and whether effects depend on MDMA-induced release of serotonin and norepinephrine. Copeptin, the C-terminal part of the AVP precursor preprovasopressin, is cosecreted with AVP and can be determined more reliably.

Methods: We used a randomized placebo-controlled crossover design. Plasma and urine osmolalities as well as AVP and copeptin levels were measured in 16 healthy subjects (eight female, eight male) at baseline and after MDMA (125 mg) administration. In addition, we tested whether effects of MDMA on AVP and copeptin secretion can be prevented by pretreatment with the serotonin and norepinephrine transporter inhibitor duloxetine (120 mg), which blocks MDMA-induced transporter-mediated release of serotonin and norepinephrine.

Results: MDMA significantly elevated plasma copeptin levels at 60 min and at 120 min compared with placebo in women but not in men. The copeptin response to MDMA in women was prevented by duloxetine. MDMA also nonsignificantly increased plasma AVP levels in women, and the effect was prevented by duloxetine. Although subjects drank more water after MDMA compared with placebo administration, MDMA tended to increase urine sodium levels and urine osmolality compared with placebo, indicating increased renal water retention.

Conclusion: MDMA increased plasma copeptin, a marker for AVP secretion, in women but not in men. This sex difference in MDMA-induced AVP secretion may explain why hyponatremia is typically reported in female ecstasy users. The copeptin response to MDMA is likely mediated via MDMA-induced release of serotonin and/or norepinephrine because it was prevented by duloxetine, which blocks the interaction of MDMA with the serotonergic and noradrenergic system. **(*J Clin Endocrinol Metab* 96: 2844–2850, 2011)**

Abuse of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) has been associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1, 2) and symptomatic hyponatremia particularly in women (3, 4). Specifically, a case series of ecstasy-associated hyponatremia included 18 cases, of which 17 were women (4). Another larger retrospective series of ecstasy exposures reported to a poison center found hyponatremia (Na <130 mmol/liter) in 73 (38.8%) of 188 cases (3). Of the 73 cases with hyponatremia, 55 (75.3%) were women and 18 (24.7%) men (3). Thus, female sex was significantly associated with increased odds of hypona-

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Abbreviations: AVP, Arginine vasopressin; MDMA, 3,4-methylenedioxymethamphetamine; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

tremia and increased odds of associated coma among these cases (3). A small nonblinded laboratory study showed that MDMA significantly increased plasma concentrations of arginine vasopressin (AVP) at 1–4 h after controlled MDMA administration in eight healthy male volunteers (5, 6). This study provides evidence for a stimulatory effect of MDMA on AVP secretion. However, no female subjects were included. We assessed MDMA effects on AVP system activation and associated changes in plasma and urine osmolality as well as sodium levels in resting healthy subjects with *ad libitum* water intake in a controlled laboratory setting.

MDMA is a substrate of both the serotonin and norepinephrine transporter (7). It enters presynaptic nerve terminals and potently releases serotonin and norepinephrine through the transporter (7). AVP secretion is thought to be regulated by serotonergic (8) and noradrenergic (9) pathways, and these monoamines could act as mediators for the effects of MDMA on the AVP system. The MDMA-induced carrier-mediated release of serotonin and norepinephrine can be reduced by serotonin and norepinephrine transporter inhibitors, respectively (10, 11). We therefore assessed whether blockade of both the serotonin and norepinephrine transporter with duloxetine would prevent potential effects of MDMA on AVP secretion in the present study.

The reliable determination of plasma AVP is problematic. We therefore measured copeptin in addition to AVP levels. Copeptin is the C-terminal part of the AVP precursor preprovasopressin. Copeptin is produced together with AVP in equimolar ratio and exhibits similar kinetics in response to osmotic changes (12–14). In contrast to AVP, copeptin levels remain stable in serum or plasma samples and can easily and reliably be measured (12).

We hypothesized that MDMA would increase AVP and copeptin levels, particularly in women, and that pretreatment with the serotonin-norepinephrine transport inhibitor duloxetine would prevent this effect.

Subjects and Methods

Study subjects

The study was performed in 16 healthy subjects (eight women, eight men). Women were (mean ± SD) 29.0 ± 7.1 yr old. Body weight was 59.0 ± 6.9 kg. Men were 23.3 ± 3.1 yr old. Body weight was 79.5 ± 9.8 kg. Exclusion criteria included age under 18 or over 45 yr, pregnancy (urine pregnancy test before each test session), body mass index below 18.5 or over 25 kg/m^2, personal or family (first-degree relatives) history of psychiatric disorder, regular use of medications, chronic or acute physical illness (normal physical exam, normal electrocardiogram, and standard hematological and chemical blood analyses), smoking, lifetime prevalence of illicit drug use over five times (except for tetrahydrocannabinol), illicit drug use within the last 2 months, and illicit drug use during the study (urine tests before test sessions). Subjects were asked to abstain from excessive alcohol consumption between test sessions and in particular to limit their use to one glass on the day before the test sessions. Subjects abstained from caffeinated beverages on the test days. Female subjects were investigated during the follicular phase (d 2–14) of their menstrual cycle when the reactivity to amphetamines (15) and osmotic sensitivity (16) are expected to be similar to men. All subjects gave their written informed consent before participating in the study, and subjects were paid for participation.

Study procedures

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Basel, Switzerland. The use of MDMA in healthy subjects was authorized by the Swiss Federal Office of Public Health, Bern, Switzerland. The study was registered at www.clinicaltrials.gov (number NCT00990067) with neuroendocrine measures as a secondary outcome. We used a randomized placebo-controlled crossover design with four conditions (placebo-MDMA, placebo-duloxetine, duloxetine-MDMA, and placebo-placebo) in balanced order. Washout periods between sessions lasted 10–14 d. Duloxetine (120 mg) or placebo was administered twice 16 and 4 h before MDMA (125 mg) or placebo, respectively. We assessed plasma and urine osmolality as well as plasma and urine sodium 4 h before and 120 min after MDMA/placebo administration. Plasma levels of copeptin were assessed 4 h before and at 60 and 120 min after MDMA/placebo. Plasma levels of AVP were assessed 4 h before and 120 min after MDMA/placebo. Subjects were not engaged in any physical activity and were resting in hospital beds during the test session. Subjects had a small standardized breakfast at the beginning of each test session. Fluid consumption was not restricted up to a total intake of 2000 ml water during the session and was recorded from 4 h before to 120 min after MDMA/placebo administration when the last hormone measurement was performed. In addition, saline was administered via an iv catheter to keep catheters open for blood sampling at a rate of 100 ml/h from 0–120 min after MDMA/placebo administration. The study design also included additional assessments of subjective and cardiovascular effects, blood drawings for pharmacokinetics, and monitoring of adverse events for 6 h after MDMA/placebo administration as will be described elsewhere (Simmler, L. D., C. M. Hysek, J. Huwyler, M. E. Liechti, unpublished data).

Measurements

Measurements were done in duplicates in a blinded fashion in a single batch. AVP was assessed in EDTA plasma using a RIA (Direct Vasopressin RIA; Bühlmann Laboratories AG, Schönenbuch/Basel, Switzerland). The lower detection limit was 0.82 pmol/liter, and the intraassay precision was 6.0%. Copeptin levels were assessed using an immunoassay (LIA CT-proAVP; B.R.A.H.M.S./ThermoFisher Scientific, Hennigsdorf/Berlin, Germany) as described previously (12) and modified as described previously (14). The lower detection limit was 0.4 pmol/liter, and the intraassay coefficient of variation was less than 5%. Sodium concentrations were measured by indirect potentiometry (Hitachi 917; Roche Diagnostics, Rotkreuz, Switzerland). Osmolality was measured by cryoscopy (Micro Osmometer; Advances Instruments for Switzerland Instruments, Zurich, Switzerland).

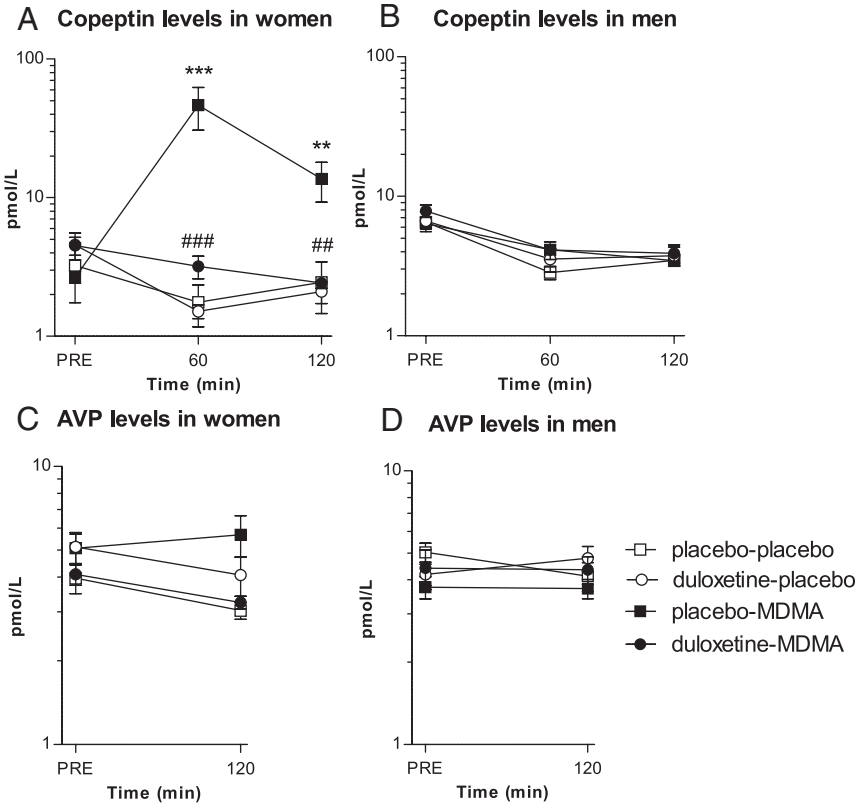

FIG. 1. Mean values ± SEM for plasma levels of copeptin and AVP in eight female and eight male healthy subjects 4 h before (PRE) and 60 and 120 min after MDMA (125 mg) or placebo. A, MDMA significantly increased copeptin levels in women at 60 and 120 min after drug administration compared with placebo. Duloxetine pretreatment prevented the MDMA-induced elevation in circulating copeptin in women. B, MDMA did not alter copeptin levels in men. C, Similar to its effects on MDMA-induced copeptin increases, duloxetine also prevented the nonsignificant increase in AVP at 120 min after MDMA administration in women. D, There were no drug effects on AVP levels in men. **, $P < 0.01$; ***, $P < 0.001$ *vs.* placebo-placebo; ##, $P < 0.01$; ###, $P < 0.001$ *vs.* placebo-MDMA.

Study drugs

(±)MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was obtained from the Swiss Federal Office of Public Health and prepared as gelatin capsules (100 and 25 mg). Identical placebo (lactose) capsules were prepared. MDMA was administered in a single absolute dose of 125 mg. This dose of MDMA corresponds to a typical recreational dose of ecstasy, and comparable doses of MDMA have previously been used in controlled settings. Because MDMA was dosed in an absolute dose of 125 mg, differences in body weight resulted in different weight-adjusted relative MDMA doses of 1.6 ± 0.23 mg/kg (range, 1.4–2.1 mg/kg) in men and 2.1 ± 0.25 mg/kg (range, 1.8–2.5 mg/kg) in women. Duloxetine (Cymbalta; Eli Lilly SA, Vernier, Switzerland) was prepared as 60-mg gelatin capsules, and identically looking placebo (lactose) capsules were similarly prepared.

Statistical analysis

Repeated-measures ANOVA with the factors drug (placebo-placebo, duloxetine-placebo, placebo-MDMA, and duloxetine-MDMA) and time (baseline, 60 min, and 120 min) stratified for sex and followed by pairwise Tukey *post hoc* tests was used to assess differences in the effects of the different drugs. Nonnormally distributed variables were log normalized before the ANOVA. Correlation analyses were performed using Spearman's rank correlations using the total of all values (n = 128). All tests were two tailed, and the significance level was set to $P = 0.05$.

Results

ANOVA on plasma copeptin levels yielded a significant drug × time × sex interaction [$F_{(6,84)} = 3.93$; $P = 0.0017$]. MDMA significantly elevated plasma copeptin levels at 60 min ($P < 0.001$) and at 120 min ($P < 0.01$) compared with placebo in women (Fig. 1A) but not in men (Fig. 1B). The MDMA-induced increase in plasma copeptin in women was prevented by duloxetine pretreatment both at 60 min ($P < 0.001$) and 120 min ($P < 0.01$) (Fig. 1A). A similar trend was observed for AVP levels but drug effects did not reach significance (Fig. 1, C and D). Oral liquid intake varied across drug treatments, but there were no sex differences [main effect of drug: $F_{(3,42)} = 8.62$; $P < 0.001$, no drug × sex interaction]. Oral liquid intake (mean ± SEM) was 612 ± 50 ml after placebo-placebo, 1267 ± 118 ml after duloxetine-placebo ($P < 0.001$ *vs.* placebo-placebo), 1198 ± 130 ml after placebo-MDMA ($P = 0.001$ *vs.* placebo-placebo), and 807 ± 83 ml after duloxetine-MDMA ($P = 0.02$ *vs.* duloxetine-placebo, and $P = 0.051$ *vs.* placebo-MDMA). Urine osmolality decreased significantly over time [main effect of time: $F_{(1,14)} = 62.69$; $P < 0.001$]. Urine osmolality tended to be higher after placebo-MDMA or duloxetine-MDMA compared with placebo-placebo or duloxetine-placebo as evidenced by a near-significant drug × time interaction in the ANOVA [$F_{(3,42)} = 2.70$; $P = 0.058$] (Fig. 2, A and B). A similar trend was observed for urine sodium levels [drug × time interaction: $F_{(3,42)} = 2.33$; $P = 0.088$] (Fig. 2, C and D). There were no significant drug effects on plasma sodium levels or plasma osmolality (Fig. 2, E–H). Circulating copeptin levels correlated with AVP levels (all: $r_s = 0.34$, $P < 0.001$; women: $r_s = 0.53$, $P < 0.001$; men: $r_s = 0.28$, $P < 0.05$]. Copeptin levels were also correlated with plasma and urine osmolality [$r_s = 0.22$; $P < 0.05$ and $r_s = 0.68$; $P < 0.001$, respectively] as well as with plasma and urine sodium [$r_s = 0.18$; $P <$

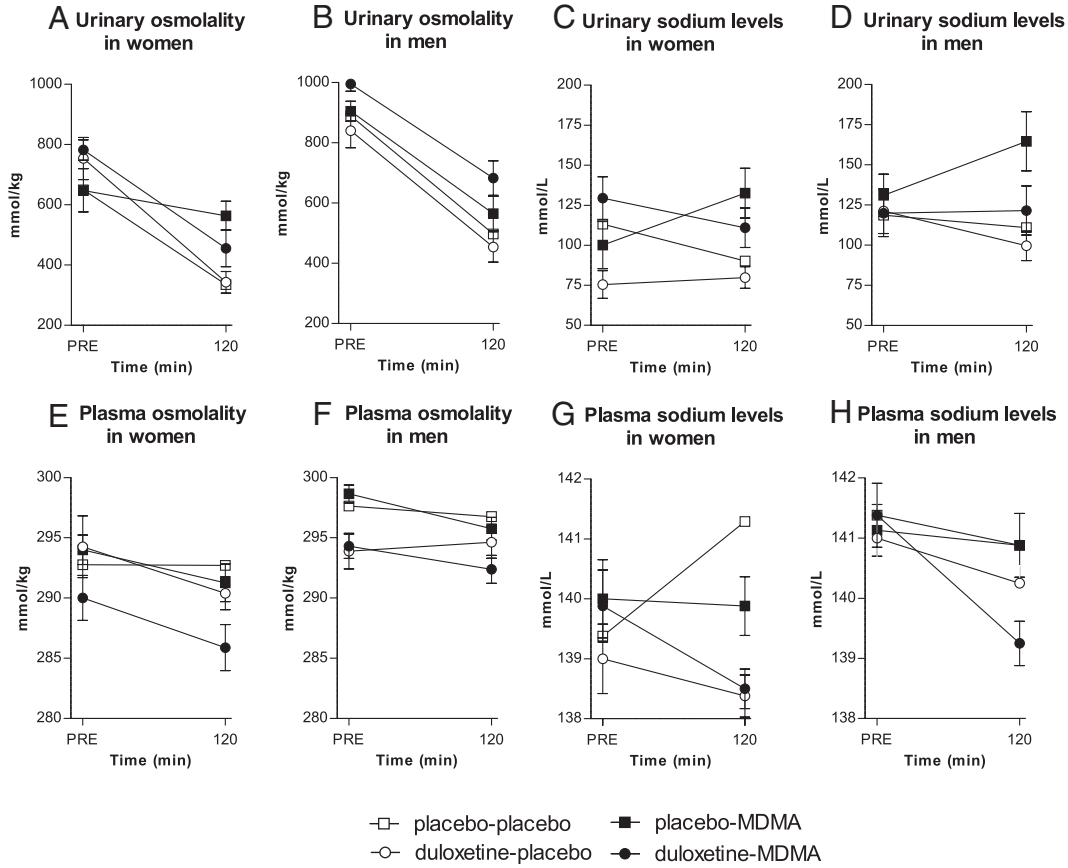

FIG. 2. Mean values ± SEM for sodium and osmolality in urine and plasma in eight female and eight male healthy subjects 4 h before (PRE) and 120 min after MDMA (125 mg) or placebo. The two treatment conditions including MDMA (placebo-MDMA and duloxetine-MDMA) tended to increase both urine osmolality (A and B) and urine sodium levels (C and D) in both sexes. There were no treatment effects on plasma osmolality or plasma sodium levels (E–H).

0.05 and $r_s = 0.28$; $P < 0.01$, respectively]. Baseline copeptin levels were significantly lower in women than men [$F_{(1,14)} = 8.38$; $P = 0.012$]. The relative dose of MDMA (in milligrams per kilogram body weight) did not correlate with the MDMA-induced increase in plasma copeptin within the two sex groups. In the present study, MDMA also produced marked subjective and cardiovascular stimulant effects as will be reported separately elsewhere (Simmler, L. D., C. M. Hysek, J. Huwyler, M. E. Liechti, unpublished data).

Discussion

We found that MDMA increased circulating copeptin, a marker for AVP secretion, in women but not in men. This sex difference in MDMA-induced AVP secretion is in line with the clinical observation that ecstasy-associated hyponatremia is typically reported in female users (3, 4). Other sex differences in the response to MDMA or ecstasy have previously been reported and include increased subjective effects in women compared with men to equal weight-adjusted doses of MDMA (18), more pronounced depression after ecstasy use (19), and a potential increase in serotonergic neurotoxicty in association with long-term use of ecstasy in women (20). The present findings indicate that women may be at increased risk for developing hyponatremia and associated neurotoxicity due to their sex-specific stronger AVP response to MDMA. In addition, the threshold levels of plasma sodium at which neurological complications occur appear to be higher in women than men (21, 22), and woman are more likely than men to die from hyponatremic encephalopathy after surgery (21, 23). Seizures and coma were also more frequently reported in female cases of ecstasy-associated hyponatremia compared with men (3). However, ecstasy-associated hyponatremia may have multiple causes, and MDMA-induced AVP secretion may be only one of several contributing factors. Dry mouth and physical exertion with sweating followed by hyperhydration with electrolyte-free water may all contribute to the development of hyponatremic states in recreational ecstasy users. Even loss of sodium into the gastrointestinal tract has been discussed (24).

The AVP system is activated by factors typically associated with MDMA consumption in a party setting in-

cluding dehydration (12–14), heat (25), and physical activity (12, 26), all of which are potentially increasing the risk of SIADH. Our results indicate that direct activation of the AVP system by MDMA may play a crucial facilitating role in the development of ecstasy-associated SIADH, in particular in women, because we controlled carefully for confounding factors that may increase AVP. Subjects were well hydrated orally and iv and resting comfortably in hospital beds in a temperature-controlled research environment. Of note, our subjects drank more water after MDMA than after placebo administration possibly due to a dry mouth and increased thirst after MDMA administration (18). Fluid consumption would be expected to decrease copeptin secretion (13), counteracting the effects of MDMA. However, copeptin levels were actually increased during the MDMA condition, which further supports the concept that MDMA activated the AVP system via pharmacological stimulation, although we cannot exclude an indirect effect via increased thirst perception (14). Furthermore, urine osmolality and urine sodium levels tended to be higher after MDMA compared with placebo administration despite the increase in oral fluid intake. This finding indicates that MDMA increased renal fluid retention, which is consistent with an elevated secretion of AVP.

The AVP response to MDMA in women was blocked by duloxetine pretreatment. Duloxetine prevents the transporter-mediated release of serotonin and norepinephrine by MDMA. Thus, MDMA-induced AVP secretion appears to be mediated by serotonin and norepinephrine. This clinical finding is in line with preclinical studies indicating a role for central serotonin (8) and norepinephrine (9) systems in AVP secretion. The mediating role of the serotonin system in AVP regulation is also supported by the fact that several serotonergic medications are typically associated with an increased risk of SIADH (22). The precise mechanism of the serotonin/norepinephrine-AVP system interaction is not known. AVP and copeptin are also hypothalamic stress hormones (27, 28), and MDMA is a pharmacological stressor. MDMA activates the hypothalamo-pituitary-adrenal axis and increases plasma corticotropin and cortisol (29, 30). In addition, MDMA increases aldosterone secretion in rats. Cortisol and mineralocorticoids also influence the electrolyte and body fluid balance. We did not assess the role of steroids in the present study. However, steroids increase renal sodium reabsorption and would thereby antagonize AVP effects on plasma osmolality.

In our study, MDMA (125 mg) had no effect on AVP or copeptin plasma levels in male subjects, whereas an earlier study showed an increase in AVP after a lower dose of MDMA (47.5 mg) in eight healthy men (5, 6). This discrepancy is likely due to differences in the study design and setting. Importantly, subjects were free to drink as much as they wanted in our study, and fluid consumption was higher after MDMA than after placebo which could have counteracted any MDMA effects on AVP secretion and even abolished any MDMA effects in men. In addition, our subjects were resting in hospital beds, eliminating any contributing effects of physical activity on AVP secretion. Nevertheless, it is surprising that our comparatively high dose of MDMA did not affect AVP or copeptin secretion despite pronounced subjective and cardiovascular stimulant effects of MDMA in the same subjects (Simmler, L. D., C. M. Hysek, J. Huwyler, M. E. Liechti, unpublished data). Interestingly, similar inconsistencies are seen in the clinical reports on ecstasy-associated hyponatremia. Hyponatremia was found in 55 (52.4%) of 105 women and 18 (21.7%) of 83 men in ecstasy exposures reported to the California Poison Control System (3). However, other reports indicate that hyponatremia is a relatively rare complication of ecstasy use. Ecstasy-associated hyponatremia was observed in only two (5%) of 40 monointoxications (31) or was not reported (32) according to other poison center studies. Hyponatremia was also a rare medical complication according to a series of intoxication cases presenting to emergency rooms (17, 33, 34). Taken together, the available data point toward an important role of additional contributing personal (sex, menstrual phase, and genetic factors) and/or environmental (heat and hydration) factors that may contribute and modulate the effects of MDMA on AVP secretion and osmotic regulation.

Our study has several limitations. The study sample size is relatively small. Only single doses of MDMA and duloxetine were used. However, the doses were selected in the upper dose range and produced pronounced effects on a variety of outcomes. Importantly, the absolute dose of MDMA was the same in both sexes and was not adjusted for body weight, resulting in higher relative doses of MDMA per kilogram of body weight in women compared with men. Thus, we cannot exclude that the observed sex difference was in fact a dose effect with women receiving higher relative doses of MDMA than men. However, relative MDMA doses did not correlate with MDMA-induced changes in copeptin levels within the male and female groups, supporting the view that our finding represents a true sex difference and not a dose effect. Furthermore, fluid consumption was different across treatment conditions, which may have counteracted effects of MDMA on AVP secretion because subjects consumed more liquids after MDMA than after placebo administration. Finally, urine osmolality and associated AVP system activation was higher in men than women at the beginning

of the study, which may have differentially affected the response to MDMA.

With regard to the validity of the outcome measures, we documented a correlation of plasma AVP and copeptin, confirming previous studies (12, 14). In addition, copeptin plasma concentrations also weakly correlated with plasma and urine osmolalities as expected based on osmoregulation and as previously documented in hypo-, iso-, and hyperosmolar states in healthy subjects (14). We also confirmed the previously reported sex differences in basal plasma copeptin concentration (12, 13).

In conclusion, we found that MDMA increased copeptin plasma levels reflecting AVP system stimulation in women but not in men. The finding is consistent with an increased risk for the development of hyponatremia and associated complications after recreational ecstasy use in women compared with men. AVP system activation by MDMA is likely due to the serotonin- and norepinephrine-releasing properties of MDMA.

Acknowledgments

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