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Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population

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Abstract

Despite the common use of MDMA (ecstasy) in the UK, the mechanism underlying associated potentially fatal cerebral oedema is unclear. We used a new experimental approach working directly with clubbers to perform a study on 30 (17 male) experienced clubbers (mean 6.6 years of clubbing). Pre- and post-clubbing measurements were performed to compare plasma levels of pituitary hormones (vasopressin, oxytocin), plasma and urine osmolality, urinary pH, and plasma sodium and urea. Ecstasy consumption was confirmed by using urinary drug screening pre- and post-clubbing. MDMA was detected in the urine samples of 17 subjects, three of which tested positive during pre-clubbing tests. Mean plasma vasopressin concentration increased in the MDMA group (1.28 ± 0.29 to 1.43 ± 0.41 pmol/l), but fell in other participants (1.23 ± 0.42 to 1.16 ± 0.0.34 pmol/l). Similarly, mean plasma oxytocin concentrations increased after ingestion of MDMA (2.02 ± 0.29 to 2.43 ± 0.24 pmol/l), but fell in the group that did not use MDMA (2.17 ± 0.36 pmol/l to 1.89 ± 0.37 pmol/l). There was a significant group by time interaction for plasma osmolality and plasma sodium ($p = 0.001$ and $p = 0.003$, respectively) and between change in urinary osmolality ($p < 0.001$) and MDMA use, with the pattern of change being consistent with the induction of inappropriate vasopressin secretion (also known as SIADH) by MDMA. This report demonstrates SIADH in ecstasy-using 'clubbers', which has important clinical implications.

Keywords

MDMA, ecstasy, water homeostasis, pituitary hormones, vasopressin, oxytocin, clubbing

Introduction

Ecstasy is the common name for 3,4-methylenedioxymethamphetamine (MDMA), an amphetamine analogue and generic term for tablets, capsules or powder, which are believed to contain MDMA. There is no common shape, name or colour to the tablets or capsules being sold as ecstasy. These are illicitly manufactured, given 'trade' names and, as new batches become available, others disappear from the market. Although there is no absolute guarantee of the content, the majority of tablets sold as ecstasy are thought to contain moderate doses (75–125 mg) of MDMA (Ayus *et al*., 1992; Box *et al*., 1997). Recreational ecstasy users normally consume about 1.9 mg/kg orally (Forsling *et al*., 2001). The British Crime survey indicates that around two million people in the UK have used ecstasy and that there is an estimated half a million users of ecstasy every week. Use is predominantly associated with the dance scene ('clubbing'), which encompasses a range of behaviours that have been widely explored by researchers over the last decade (Schuckit, 1994; Forsling *et al*., 2002).

The metabolic consequences of the specific effects of MDMA use are, however, less well described. The clubbing environment, being invariably overcrowded, hot and noisy, has frequently been identified as a key variable affecting various biological parameters. Similarly, activities of the clubbers themselves during the evening, such as prolonged repetitive dancing, lack of rest, or altered sleep/wake cycle, comprise a significantly different picture

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from other recreational pursuits of young adults (Henry *et al*., 1998). It is possible that the interactions of biological, psychological and environmental events may result in a unique and potentially pathological combination of forces (Gore, 1999; Cole *et al*., 2005).

MDMA itself produces a spectrum of responses. In the environment in which the drug is most commonly consumed (the 'nightclub'), the underlying mechanisms remain only partially understood. Like other stimulants, MDMA has cardiovascular effects, including increasing systolic and diastolic blood pressure, and elevation in heart rate, with myocardial oxygen consumption peaking at approximately 1 hour (Henry *et al*., 1998; Mas *et al*., 1999); however these usually disappear 6 hours post-ingestion (Holmes *et al*., 1999). However, unlike other stimulant use, MDMA use has been associated with many high profile deaths (Martin, 2001; Kraner *et al*., 2001; Schifano *et al*., 2003).

Several investigators have highlighted the importance of markedly elevated body temperature in a number of fatal cases (Henry *et al*., 1992; O'Connor, 1994; Simantov, 2004), and profuse sweating as a result of both the vigorous physical activity undertaken in dance venues and the pharmacological action of the drug on thermoregulatory mechanisms. Both excessive sweating and inadequate water intake have been associated with clubbing and produce well-known physiological events (Kalant, 2001). Considerable amounts of sodium may be lost in sweat, and it has been suggested that the ingestion of large amounts of water to avoid overheating by clubbers may be at least partly responsible for cerebral oedema and haemodilution (Matthai *et al*., 1996). In turn, this could lead to hyponatraemia, with plasma sodium concentrations being reported to reach less than 120 mmol/l (Watson *et al*., 1997; Holmes *et al*., 1999).

Inappropriate secretion of pituitary antidiuretic (ADH) hormone, also known as arginine vasopressin (AVP), leading to retention of water by the kidneys (Satchell and Connaughton, 1994), has also been postulated to be involved. In the case of Leah Betts, excessive AVP secretion was thought to result in hyponatraemia and consequent water intoxication (Laurence, 1995). However, data are not available regarding the prevalence of this effect in a regular clubbing population. Whether or not the predominant mechanism in those presenting with hyponatraemia following ingestion of MDMA is elevated plasma vasopressin levels (Schifano *et al*., 1998), or excessive water intake following profuse sweating (Maxwell *et al*., 1993; Kessel, 1994) is therefore unclear. We tested the following hypothesis: that ecstasy use would be associated with inappropriate secretion of AVP (also known as the syndrome of inappropriate secretion of antidiuretic hormone, or SIADH), with the accompanying hallmarks of increased urinary osmolality with plasma hypo-osmolality and hyponatraemia, in a clubbing population.

MDMA is also known to elicit large increases in the synaptic concentrations of dopamine and serotonin (5-HT), which are both involved in the control of vasopressin and other pituitary hormones (Jorgensen *et al*., 2002; Jorgensen *et al*., 2003; Galfi *et al*., 2005). Increased hormone release could also involve active metabolites of MDMA such as 3,4-methylenedioxyamphetamine (MDA, Forsling *et al*., 1999). Ingestion of MDMA also results in the release of anterior pituitary hormones such as prolactin and ACTH (Dafters, 1995; Henry, 2000).

Most of the scientific papers pertaining to MDMA comprise case reports or studies on volunteers under control conditions. This may relate to the practical difficulties in sampling the clubbing population. We attempted to address this issue by performing a biological 'before and after' investigation ('pre-' clubbing vs. 'post-' clubbing) study 'in the field'. Identifying and engaging drug users from non-treatment ('hidden') populations in research studies is problematic and obtaining access to a large sample is often difficult. Previous studies have used snowballing techniques (Callow, 1996; Topp *et al*., 1999), privileged access interviewing (Beck and Rosenbaum, 1994; Brown *et al*., 1995; Williamson *et al*., 1996) research advertisements and questionnaires in magazines (Winstock *et al*., 2001). All of these methodologies have their limitations and conventional survey techniques also tend to perform poorly in this area (Griffiths *et al*., 2000). Thus, convincing random samples of 'hidden drug users' are rarely available; a strength of this study is that it was performed 'in the field' on those regularly engaging in clubbing.

Methods

Recruitment

Our subjects were a self-nominated sample of regular MDMA users who responded to an advertisement placed in 'Mixmag', a popular UK media publication whose primary target audience is one interested in the dance music scene (Petridis and Sherlock, 1996). This publication with a circulation of about 50 000 (one of the UK's largest) is targeted at those involved in the dance music scene, which has been previously shown to be associated with the use of recreational drugs such as MDMA and other stimulant drugs (Forsyth *et al*., 1997; Saunders, 1997).

Procedures

Pre- and post-clubbing measures of pulse rate, sitting and standing BP measures were performed in combination with blood (5 mL) and urine (20 mL) sampling. Standard biochemical tests were undertaken to assess changes in fluid balance including plasma sodium (mmol/L), urea (mmol/l), plasma and urinary osmolality (mosmol/kg), and urinary pH. Pre- and post-clubbing qualitative urinary drug screening for common drugs of abuse, MDMA, MDEA (methylenedioxyethylamphetamine) and MDA (methylenedioxyamphetamine) was also undertaken.

Plasma AVP and oxytocin concentrations were determined by Radio Immuno Assay (RIA) after prior extraction using Sep Pak C18 cartridges (Water Associates Inc., Milford, MA, USA). The standard employed for AVP was the first International Standard for AVP (77/501); the lower limit of detection was 0.08 pmol/l, and intra- and inter-assay coefficients of variation were 5.0 and 8.9% respectively at 2.5 pmol/l. The cross reactivity of the antiserum with oxytocin was less than 1%. The standard employed for oxytocin assay was the first International Standard for oxytocin

(76/575); the lower limit of detection was 0.1 pmol/l, and intra- and inter-assay coefficients of variation were 5.1 and 7.8% respectively at 2.5 pmol/l. The cross-reactivity of the antiserum with AVP was less than 0.1%.

Subjects

Thirty clubbers (17 males), aged 18–41 (mean 25) years participated in the study. The group predominantly of Caucasian ethnicity (87%) were largely from London (36%) or within the M25 boundary (7/30), the rest travelling from major cities (5/30) or towns (7/30) around the United Kingdom. Male clubbers were marginally older than the female clubbers (mean age 26, range 22–40 years; mean age 24 years, 18–41 years respectively). All were experienced in the 'dance-scene': clubbing on average three times per month (range 0–10/month). Over half the cohort reported clubbing on a monthly (17/30) basis; others once (4/30) or twice (5/30) weekly and some less frequently (< monthly, 4). Recruits had no past medical or psychiatric history that contraindicated participation, and gave written consent to be investigated in line with local (South London and Maudsley NHS Trust and King's College London, Institute of Psychiatry, Ref No: 272/00) research ethical committee guidelines. Compensation was available to those who successfully returned to the post-clubbing test site for any inconvenience caused by agreeing to participate.

Statistical analysis

Data were analysed using SPSS for Windows (version 12.0, SPSS Inc., Chicago, IL, USA), with means and standard errors of the means being given. A t-test was used to compare means for normally distributed data. Linear regression analysis was used to investigate associations between variables and ecstasy use status. A p value of less than 0.05 was considered statistically significant in all analyses.

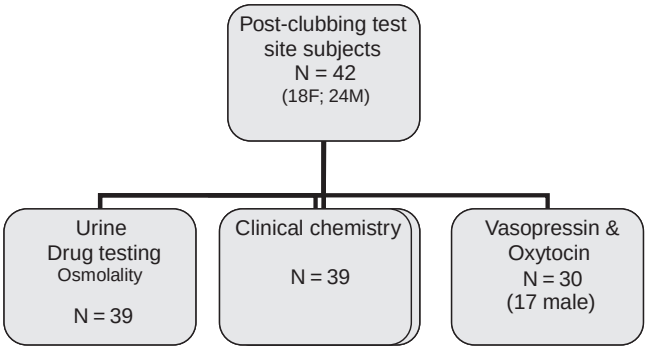
Results

Response rate

Potential recruits were asked to present for testing at the study centre (pre-test) before going clubbing. Transport was arranged for participants to return after leaving the clubbing environment at the end of the evening (post-test). Not all of the original 51 volunteers returned. Nine clubbers all male, mean age 27.8 (range 25–35) years did not return, one of whom had used MDMA. Not all of those returning to the test site (n=42) were able to provide biological samples for all tests (Organisational chart 1).

Ecstasy use

Subjects were recorded as having taken ecstasy pre- or post-clubbing on the basis of qualitative urinalysis. Thirty clubbers provided biological samples (both pre- and post-) for the analysis of neurohypophysial hormones. Three quarters of these (77%) had



Organisational chart 1 Description of the subjects who participated in testing procedures

positive drug tests which detected: cannabis in nine pre- and ten post-clubbers (five positive at both time points; 40%, 12/30), MDMA in 17 clubbers (three positive at both time points; 57%, 17/30), cocaine 0.1% (3/30) and amphetamine 0.03% (1/30), with nearly half of the cohort (47%) demonstrating consumption of more than one drug, though only two clubbers had consumed more than two psychoactive substances during the evening (cannabis, cocaine and MDMA). Three clubbers had blood alcohol levels ranging from 24 mg/dL to 97 mg/dL.

Water homeostasis

Water homeostasis measures were completed in 30 study participants (Table 1), with the oxytocin and pH measurements being incomplete in one. Of these, 17 had MDMA detected in their urine post-clubbing (i.e. three had tested positive on initial entry to the test site). The mean plasma AVP concentration in those with an MDMA-positive urine post-clubbing (n=17) increased, while values in those with a negative urine result for NMDA post-clubbing (n=13) fell (Fig. 1). Similarly, mean plasma oxytocin concentrations increased after ingestion of MDMA, but fell in the group that did not use MDMA (Fig. 2), and the pattern of change was more marked for oxytocin than for vasopressin. However, in both cases, the change in vasopressin or oxytocin (i.e. differences between pre- and post-rave values) for those with a positive urine sample post-clubbing versus those with a negative urine post-clubbing were not significant (independent samples t-test).

Urine osmolality (an indication of the degree of dehydration) fell in those with a negative MDMA post-clubbing urine test result (n=13), but did not fall in those with urinary MDMA detected post-clubbing (n=17, Fig. 3); there was a highly significant association between change in urine osmolality and evidence of ecstasy use that evening (independent samples t-test, comparing change in urine osmolality for the 13 with MDMA-negative post-clubbing urines with change in urine osmolality for the 17 MDMA-positive post-clubbing urines, $t=-4.078$, $df=28$, $p<0.001$). The change in urine osmolality was reflected by a

Table 1 Pituitary hormone levels and indicators of water homeostasis in the whole sample, and subdivided according to MDMA consumption

		Whole sample			Those who consumed MDMA			Those who did not consume MDMA		
Measure		N	Range	Mean ± SEM	N	Range	Mean ± SEM	N	Range	Mean ± SEM
Vasopressin	Pre (pmol/l)	30	0.12–5.56	1.26 ± 0.24	17	0.12–3.21	1.28 ± 0.29	13	0.12–5.56	1.23 ± 0.42
	Post (pmol/l)	30	0.10–4.69	1.31 ± 0.27	17	0.10–4.69	1.43 ± 0.41	13	0.10–3.98	1.16 ± 0.34
Oxytocin	Pre (pmol/l)	29	0.11–4.35	2.09 ± 0.22	16	0.22–4.10	2.02 ± 0.29	13	0.11–4.35	2.17 ± 0.36
	Post (pmol/l)	29	0.17–4.95	2.18 ± 0.21	16	1.43–4.95	2.43 ± 0.24	13	0.17–4.87	1.89 ± 0.37
Urinary osmolality	Pre (pmol/l)	30	109–1152	597.33 ± 54.11	17	109–949	585.53 ± 61.89	13	164–1152	612.77 ± 98.06
	Post (pmol/l)	30	101–1185	529.57 ± 63.33	17	101–1185	589.29 ± 90.79	13	105–1073	451.46 ± 84.23
Plasma osmolality	Pre (msom/kg)	30	291–320	299.07 ± 1.35	17	291–320	300.83 ± 2.04	13	292–308	296.77 ± 1.46
	Post (mosm/kg)	30	282–334	296.23 ± 1.80	17	284–300	292.00 ± 1.17	13	282–334	301.77 ± 3.34
Plasma sodium	Pre (mmol/l)	30	134–142	137.40 ± 0.37	17	135–142	137.71 ± 0.50	13	134–140	137.00 ± 0.55
	Post (mmol/l)	30	132–139	136.63 ± 0.30	17	132–138	135.94 ± 0.38	13	135–139	137.54 ± 0.35
Plasma urea	Pre (mmol/l)	30	3.5–7.8	5.30 ± 0.20	17	3.5–6.6	5.14 ± 0.23	13	4.0–7.8	5.51 ± 0.35
	Post (mmol/l)	30	3.0–7.1	4.63 ± 0.16	17	3.0–6.2	4.50 ± 0.22	13	3.8–7.1	4.81 ± 0.25
Urinary pH	Pre	29	5.0–8.0	6.59 ± 0.20	16	5.0–8.0	6.63 ± 0.26	13	5.0–8.0	6.53 ± 0.31
	Post	30	5.0–9.0	5.93 ± 0.17	17	5.0–9.0	6.12 ± 0.26	13	5.0–7.0	5.69 ± 0.17

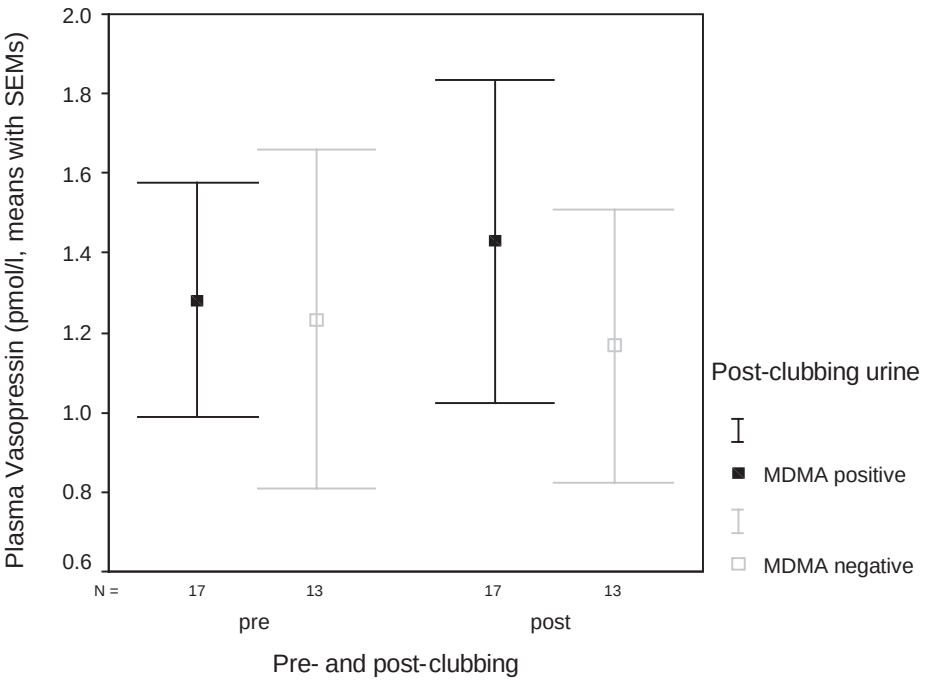


Figure 1 Change in plasma vasopressin (n=30) pre- and post-clubbing, grouped according to presence of MDMA in the post-clubbing urine sample

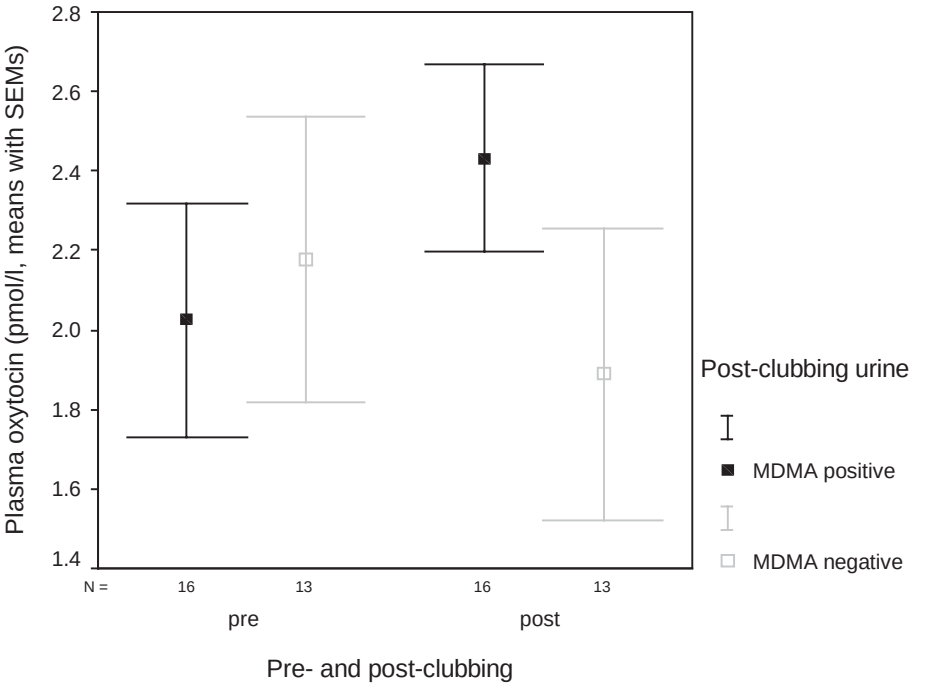


Figure 2 Change in plasma oxytocin (n=29) pre- and post-clubbing, grouped according to presence of MDMA in the post-clubbing urine sample

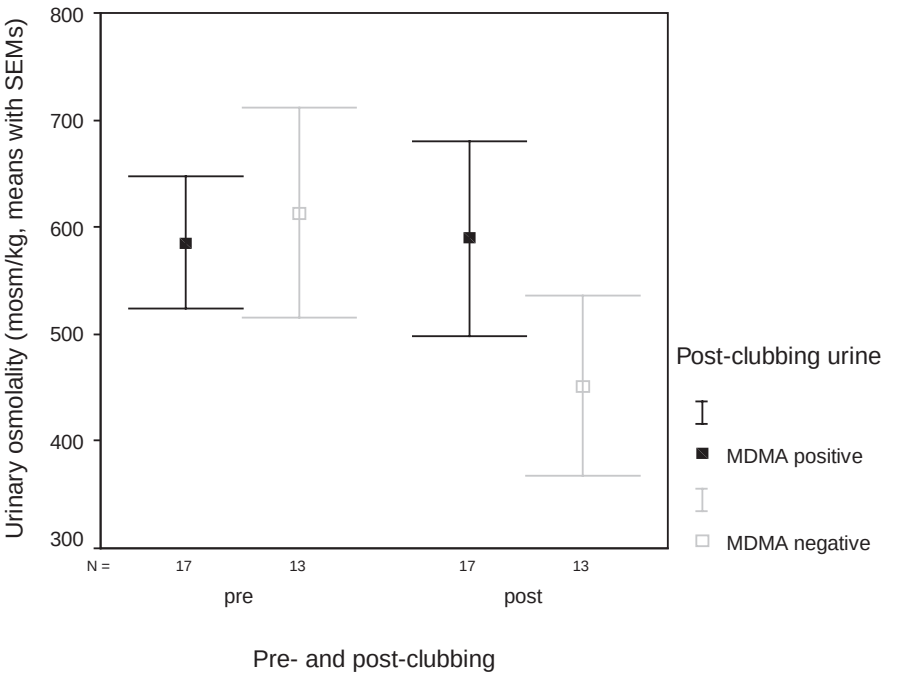


Figure 3 Change in urine osmolality pre- and post-clubbing (n=30), grouped according to presence of MDMA in the post-clubbing urine sample

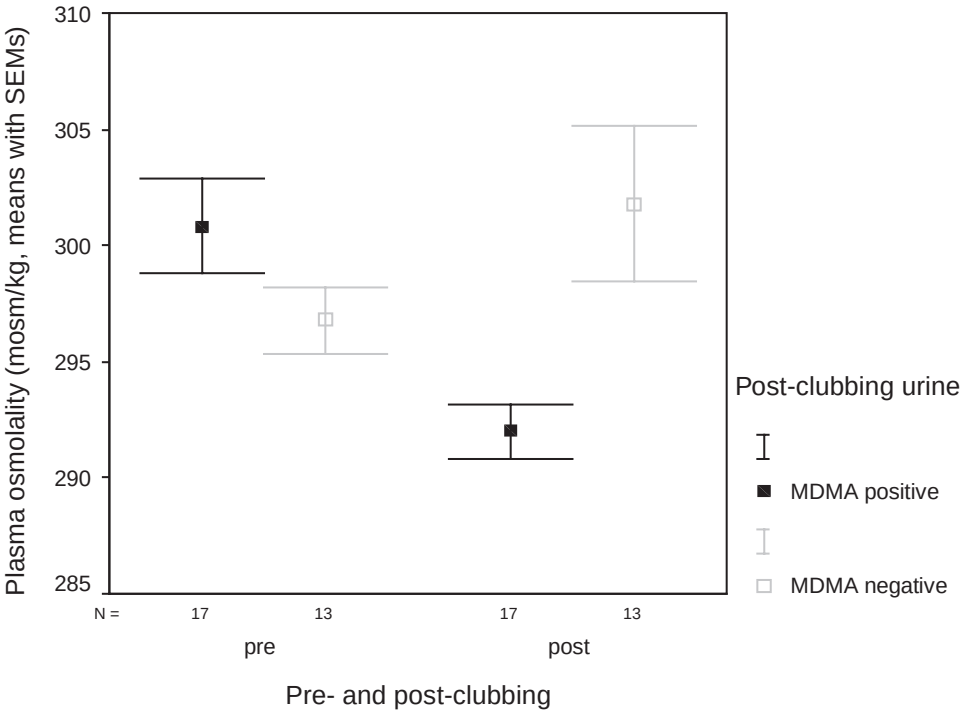


Figure 4 Change in plasma osmolality pre- and post-clubbing (n=30), grouped according to presence of MDMA in the post-clubbing urine sample

change in plasma osmolality, with this falling in the group who used MDMA, and rising in those who did not, and again, there was an association between the change in plasma osmolality and MDMA use of the same magnitude (independent samples t-test, comparing change in plasma osmolality for the 17 with an MDMA-positive urine with change in plasma osmolality for the 13 with an MDMA-negative urine, t = −4.078, df = 28, $p < 0.001$, Fig. 4).

Plasma sodium levels fell significantly in those who had taken MDMA, whilst there was no significant change in those who had not (Fig. 5); an independent samples t-test, comparing change in plasma sodium for the 17 with an MDMA-positive post-clubbing urinalysis with the 13 with an MDMA-negative post-clubbing urine test, gave a p value of 0.003 (t = 3.271, df = 28). On exclusion of the three subjects that had had a pre-clubbing MDMA-positive urinalysis, the above associations all remained significant ($p < 0.001$, t = −4.129; $p < 0.001$, t = −4.129; and $p = 0.002$, t = 3.45; change in urine osmolality, change in plasma osmolality, and change in plasma sodium, respectively).

In addition, there was a significant group by time interaction for plasma osmolality and plasma sodium (general linear model, repeated measures analysis, factor 1 = time (pre- and post-), within-subjects factor = plasma osmolality pre-/post-clubbing or plasma sodium pre-/post-clubbing, between-subjects factor = presence/absence of MDMA in the post-clubbing urine), $p < 0.001$ (F = 16.6), and $p = 0.003$ (F = 10.7), respectively (Figs 7 and 8). Multiple linear regression with change in urine osmolality as the dependent variable and change in AVP and in plasma sodium as the independents revealed a significant association in both the overall sample ($p < 0.001$, standardised β coefficient = −0.641, t = −4.196) and in the sub-sample with an MDMA-positive post-clubbing urine ($p < 0.001$, standardised β coefficient = −0.807, t = −4.999). This pattern of an increase in plasma AVP in response to MDMA consumption, with accompanying increased urine osmolality, and plasma hypo-osmolality and hyponatraemia is consistent with SIADH.

Mean plasma urea values fell both in those who had taken ecstasy and in those who had not, with six individuals having abnormal plasma urea levels (range 6.5–7.8 mmol/L, five pre-clubbing, and one post-clubbing). Urinary pH also fell in both those who consumed ecstasy and in those who did not.

Discussion

Identifying and engaging drug users from non-treatment ('hidden') populations in research studies is problematic and obtaining access to a large sample is often difficult, particularly if biological sampling is to be undertaken. There has, therefore, been an increased use of non-random sampling methods in studying drug use within the dance scene. Thus, as part of a wider study exploring current patterns of drug misuse employed by 'clubbers', we have investigated change in mechanisms of water homeostasis in response to MDMA use in a self-nominating sample of regular 'clubbers'.

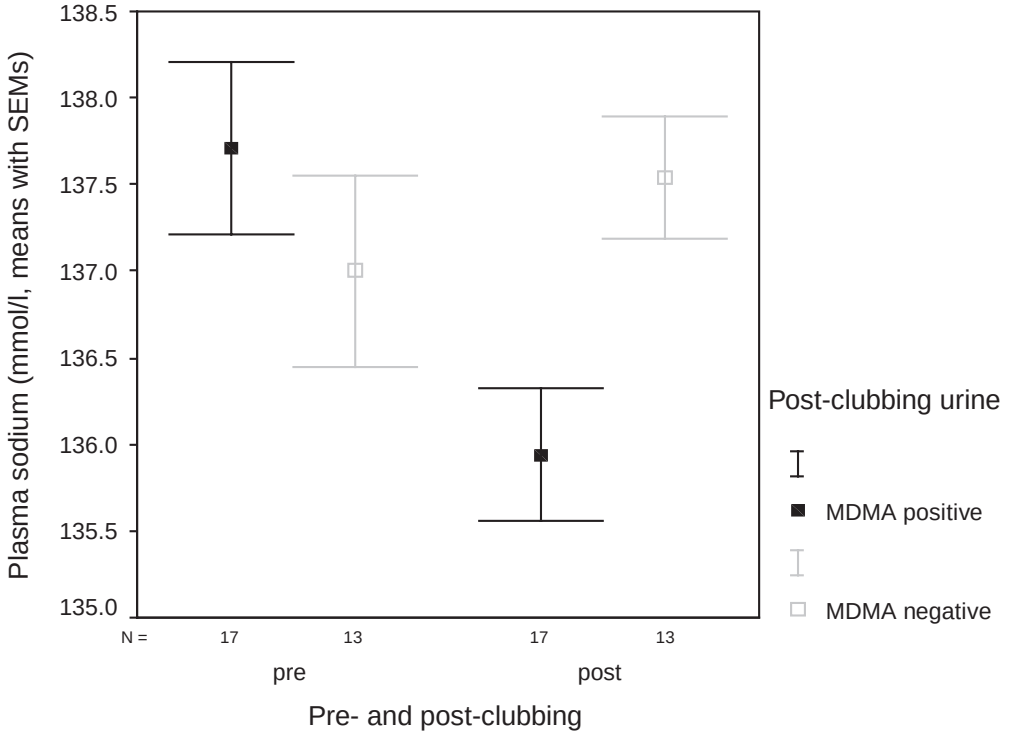


Figure 5 Change in plasma sodium pre- and post-clubbing (n = 30), grouped according to presence of MDMA in the post-clubbing urine sample

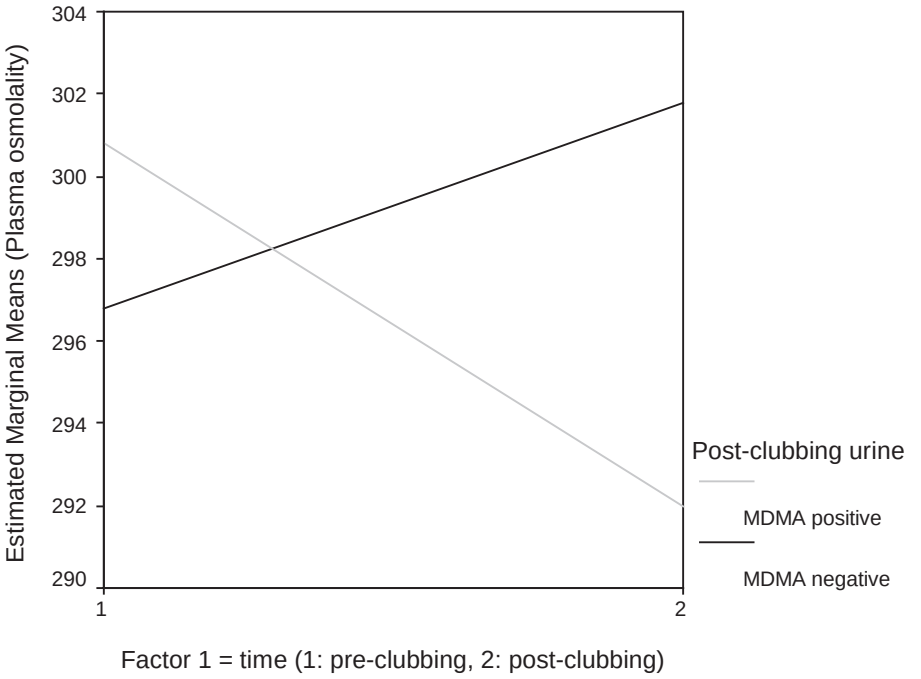


Figure 6 Repeated measures analysis for plasma osmolality (estimated marginal means by time, grouped according to the presence of MDMA in the post-clubbing urine, n = 17) illustrating significant group by time interaction

In this sample, those that had consumed MDMA showed an increase in AVP secretion, with accompanying increased urine osmolality, and decreased plasma osmolality and plasma sodium. AVP acts on the renal tubule collecting duct, to increase water reabsorption at this site, hence leading to the production of urine with an increased concentration, and, if water intake is normal, hyponatraemia and hypo-osmolality.

It has been previously described that concentrations of vasopressin peak 1–2 h after MDMA ingestion (Forsling *et al*., 2001) and then decline, although the renal effects of the hormone are maintained for longer. Just under half of our post-clubbers had elevated urine osmolality levels, and there was a highly significant association between change in urinary osmolality and MDMA consumption ($p < 0.001$, standardised β coefficient = −0.807, t = −4.999). This pattern of change in indicators of water homeostasis is consistent with the induction of SIADH by MDMA, and therefore our hypothesis is upheld. The pattern of change is not consistent with psychogenic polydipsia, in which a primary increase in water ingestion leads to a dilution of the extracellular fluids, inhibition of AVP secretion and a water diuresis; hence, in this condition, although plasma osmolality is low, urine osmolality is also low. The fall in plasma urea in the whole sample is also not consistent with dehydration secondary to excessive sweating and leading to excessive water consumption being a primary mechanism. Nevertheless profuse sweating and copious drinking could well be an additional contributing factor.

There are other psychotropic drugs known to stimulate AVP release, for example, phenothiazines and carbamazepine, and also non-psychotropics (e.g. cyclophosphamide, vincristine, clofibrate and diclofenac (Cheung *et al*., 1993)). Other conditions associated with SIADH include neoplasia (especially bronchial carcinoma), central nervous system (CNS) trauma and infections, and endocrine disease (e.g. pituitary insufficiency). In this sample, a variety of other measures not reported in this paper were also taken (including pupil size and neuropsychological measures, data not shown); from these we can rule out major CNS trauma as a cause of SIADH.

We observed a significant association between change in plasma sodium and MDMA consumption ($p = 0.003$). Many of the case reports concerning ecstasy have been in females (Kessell, 1994; Box *et al*., 1997; Watson *et al*., 1997), and it has been reported that women of reproductive age are more likely to suffer adverse effects following a reduction in plasma sodium (Ayus *et al*., 1982). In our sample, there were three (two male, one female) individuals (10%) who had plasma sodium levels below 135 mM (defining hyponatraemia) post-clubbing, all of whom had consumed MDMA.

There are other factors that could influence vasopressin release on taking MDMA whilst clubbing, such as hyperthermia (Forsling *et al*., 1976; Gordon *et al*., 1991), and exercise (Landgraf *et al*., 1982). Amphetamine-type drugs such as MDMA (amphetamine itself and cocaine) increase muscular activity, which may contribute to the development of hyperthermia. MDMA-induced hyperthermia also results from a direct pharmacological effect of the drug, with the response being subject to environmental modification (Dafters, 1995).

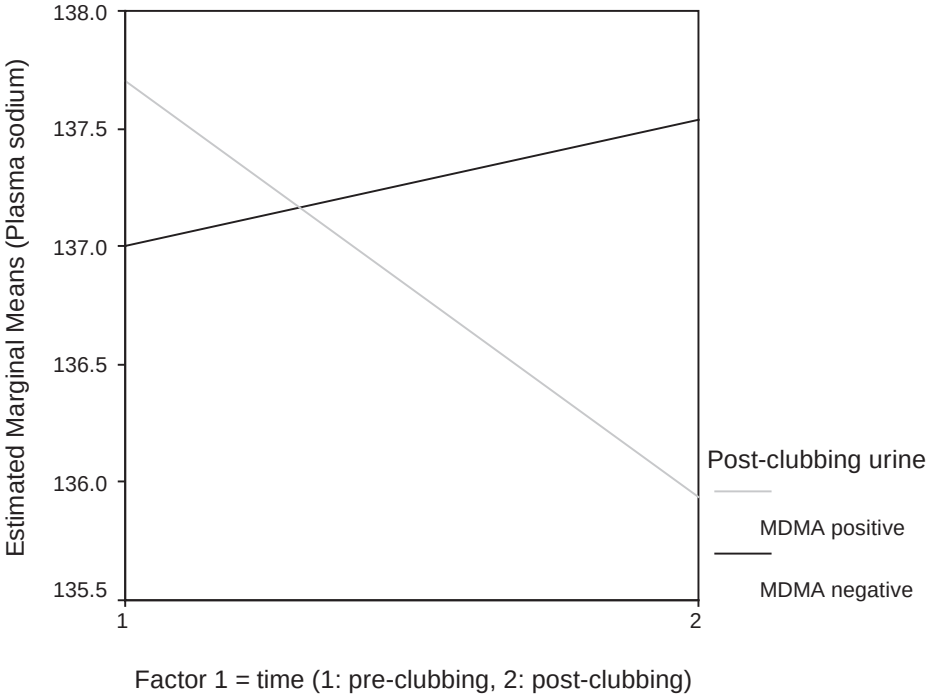


Figure 7 Repeated measures analysis for plasma sodium (estimated marginal means by time, grouped according to the presence of MDMA in the post-clubbing urine, n=17), illustrating significant group by time interaction

It was the association between high body temperature and a fatal outcome (O'Connor, 1994) that led to the recommendation that adequate fluid replacement be taken during 'clubbing'. However, if MDMA leads to SIADH, ingestion of water will only worsen the hyponatraemia, and increase the risk of cerebral oedema. It is possible that cerebral oedema has been exacerbated or even precipitated by the injudicious use of hypotonic fluid replacement in an accident and emergency situation, in 'clubbers' presenting in a state of collapse. The clinical manifestations of hyponatraemia include headache, anorexia, nausea, vomiting, muscle cramps and aches (Rabinstein and Wijdicks, 2003). Acute symptomatic hyponatraemia requires cautious administration of hypertonic saline (Ayus *et al*., 1982; Sterns, 1991), with minimization of free water intake, and consideration of the use of furosemide to induce a hypotonic diuresis (Rabinstein and Wijdicks, 2003); if left untreated, patients may rapidly develop complications from cerebral oedema. The infusion of hypertonic saline must be tightly controlled, as there is a risk of inducing osmotic demyelination if the hyponatraemia is corrected too rapidly (Laureno and Karp, 1997).

The increase in oxytocin release in response to MDMA was more marked than that in AVP, which may be due to the fact that oxytocin appears to be modulated by fewer variables outside its role in reproduction. That is, the effect of MDMA on oxytocin may not be subject to moderation by other factors to the same extent as AVP. Although stimulation of oxytocin release by MDMA in rats has been demonstrated previously (Forsling *et al*., 2002), this is, to our knowledge, the first demonstration in man. It has also been shown that release of both oxytocin and AVP can be stimulated by metabolites of MDMA; both MDA and HMMA (4-hydroxy-3-methoxymethamphetamine) affect release of these hormones (Fallon *et al*., 2002). HMMA is more potent than the parent compound, so that the rate of its production would also affect the response. MDA was detected in the urine of four subjects in addition to MDMA and all but one of these had elevated AVP. A further subject with abnormal AVP had both MDMA and MDEA detected post-clubbing by urinalysis; HMMA was not analysed.

Although both oxytocin and AVP show a nocturnal peak (Kostogloo-Athanassiou *et al*., 1998a), this would not account for the opposite direction of change for both oxytocin and AVP between those consuming and those not consuming MDMA. In addition the sleep deprivation in the night would be associated with a reduced hormone peak (Kostoglou-Athanassiou *et al*., 1998), rather than an increase, so this would also not account for our findings. The increased oxytocin in those who consumed MDMA could contribute to the hyponatraemia (Fieldman and Forsling, 1985; Kostoglou-Athanssiou *et al*., 1998a).

Hormone secretion is also altered by illicit substances like cocaine (direct effect on regulation) and alcohol (pharmacological interaction). Use of cocaine and alcohol however was limited in our population, although a third of those returning to the test site had used cannabis. Clubbers frequently use more than one psychoactive substance at a time and combinations of psychoactive substances are likely to produce significant endocrine and

electrolyte effects. Further field studies of clubbing populations are required to investigate pituitary hormone levels and water homeostasis in the polysubstance user.

In summary, we have shown that ingestion of MDMA is associated with the induction of SIADH in a sample of regular 'clubbers', with associated dysregulation of the HPA axis. This has important clinical implications, notably that 'clubbers' with early signs of hyponatraemia should in fact restrict their free water intake, and that those presenting to accident and emergency departments should have their plasma and urine osmolality investigated urgently, together with assessments of their cardiovascular volume status, and if these results are consistent with SIADH, that they should be treated appropriately. As a public health intervention, encouraging the availability of commercially available oral rehydration salts containing sodium in clubbing venues should perhaps be considered. Such measures could be life-saving, and, conversely, inappropriate administration of water without knowledge of the water homeostatic state of the patient could be fatal.

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