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The physiological responses to the use of MDMA whilst clubbing: posterior pituitary function and fluid balance

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It is estimated that there are half a million users of 3.4-methylenedioxymeth-amphetamine (MDMA, "ecstasy") every week in the UK, use being predominantly associated with clubbing. However the metabolic effects of MDMA are not well described. MDMA given to subjects in a laboratory setting stimulated vasopressin (Forsling *et al.* 2001) and a study has now been performed "in the field" on 51 self nominating drug users (18 women, 33 men) with a mean age of 25 years. All recruits were experienced clubbers who on average had been clubbing for 6.6 yrs, the majority (49/51) smoked cigarettes and all had used 'ecstasy' previously.

The study was performed with the consent of the local ethics committee and all participants gave written consent. Subjects attended the study centre before going clubbing and returned at the end of the evening. Pre-and post clubbing measurements of body weight, pulse rate and sitting and standing blood pressure were performed and urine and blood samples obtained to determine parameters of fluid balance and plasma hormone concentrations and to confirm drug use.

Of the 31 subjects whose urine tested positive for a psychoactive substance, 21 clubbers screened positive for MDMA. Eight clubbers had blood alcohol levels ranging from 23–106 mg/dl, of which only one used in combination with MDMA. Two clubbers had tested above the legal limit for driving (80 mg/dl). The other main substance used was cannabis The average, resting pre-clubbing pulse rate was 78 (range 60–120) BPM rising to 99.3 (range 140–170) BPM upon return to the club site. There were 18 post-clubbing subjects who had BPM>100. Five post clubbers who returned to the test site had indications of hypertension. All of these had confirmed use of MDMA during the evening. Plasma sodium fell significantly from 138 ± 0.5 to 136 0.4 mmol/l (S.E.M., $P < 0.05$ paired Student's t test) in those taking MDMA while there was no significant change in the other participants. Post-clubbing the urinary osmolality was 600 ± 83 mOsm/kg in the MDMA group as compared to 368 ± 84 mOsm/kg although this difference failed to reach statistical significance. Plasma cortisol concentrations increased in both the group taking MDMA and those who did not. However the increase in the former group was greater, the concentrations being 670.5 ± 101.6 as compared to 411.5 ± 65 mmol/l. The mean plasma vasopressin concentration in the MDMA group increased from a mean of 2.1 ± 0.6 pmol/l to 2.8 ± 0.9 pmol/l, while the values in the other group fell from 2.5 ± 0.8 to 2.1 ± 0.8 pmol/l. None of these values were significantly different from each other. Overall there was no good correlation of vasopressin with plasma osmolality. Mean plasma oxytocin concentrations rose significantly ($P < 0.05$) after ingestion of MDMA from 3.6 ± 0.52 pmol/ml to 4.9 ± 0.48 pmol/ml. There was no significant change in the other group. Thus the use of MDMA can result in a drop in plasma osmolality which could result from enhanced neurohypopohysial hormone release.

Forsling ML *et al.* (2001). *J Pharm Pharmacol* **53**, 1357–63.

All procedures accord with current local guidelines and the Declaration of Helsinki

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The role of calcitonin gene-related peptide (CGRP) in stress induced suppression of LH pulses in the rat

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CGRP is involved in a variety of stress responses. Central administration of CGRP causes fear related behaviour, activates the sympathetic system and the hypothalamo-pituitary-adrenal (HPA) axis, specially enhancing corticosterone release. CRH antiserum blocks the CGRP-induced rise in corticosterone (Kovacs *et al.* 1995). CRH, which is central to the HPA axis, plays a pivotal role in stress-induced suppression of pulsatile LH secretion. The aims of the present study were to test the hypothesis that CGRP suppresses LH pulses and to determine whether CRH mediates this response.

Ovariectomized (ketamine, 100 mg kg^{-1}, ip) Wistar rats were implanted with intracerebroventricular (icv) and intravenous (iv) cannulae (ketamine, 100 mg kg^{-1}, ip). Blood samples (25μl) were collected every 5 min for 6 h and assayed for LH. After 2 h of sampling CGRP (75, 400, or 1200 pmol) or artificial cerebrospinal fluid (4μl) were administered by icv injection ($n = 6$–12). In addition, CGRP (400 pmol) was co-administered icv with the CGRP antagonist ($CGRP_{8-37}$, 1 nmol, $n = 8$) or CRH antagonist (α-helical CRF_{9-41}, 26 nmol, $n = 11$). Finally rats were given 2 nmol $CGRP_{8-37}$ and 10 min later 0.5 U kg^{-1} insulin was given iv to induce hypoglycaemia; a stress known to suppress LH (Cates & O'Byrne, 2000). Animals were humanely killed.

I.C.V. infusions of CGRP induce a dose dependant suppression of LH pulses. 400 pmol CGRP significantly (paired Student's t-test, $P < 0.05$) increased LH pulse interval from 29 ± 3 min (mean ± S.E.M.) before to 38 ± 4 min after treatment. The higher dose (1200 pmol CGRP) abolished LH pulses for the duration of the 4 h post-treatment period. The $CGRP_{8-37}$ blocked the inhibitory effect of CGRP, whilst the CRH antagonist blocked the inhibitory effect of CGRP on LH pulses for the first 2 h post-infusion. Furthermore, $CGRP_{8-37}$ completely blocked the hypoglycaemic stress-induced suppression of LH pulses. The expression of FOS immunoreactivity following icv CGRP (1.2 nmol) was found to be particularly intense within the paraventricular nucleus (PVN) and the medial preoptic area.

These results suggest that central CGRP suppresses the gonadotropin releasing hormone pulse generator and is mediated, at least in part, by CRH. The ability of a CGRP antagonist to block the effects of hypoglycaemic stress on the pulsatile release of LH indicates that CGRP may be physiologically relevant in mediating metabolic stressors. Neuronal activation in both the PVN and the preoptic area identifies these as brain regions which may be critical in the response to central CGRP.

Cates PS O'Byrne KT, (2000). *Brain Res* **853**, 151–155.

Kovacs A *et al.* (1995). *Neuroendocrinology* **62**, 418–424.

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All procedures accord with current UK legislation