Oxytocin in response to MDMA provocation test in patients with arginine vasopressin deficiency (central diabetes insipidus): a single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial

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Summary

Background Disruptions of the hypothalamic–pituitary axis can cause an arginine vasopressin deficiency, also known as central diabetes insipidus. Patients with this condition are at high risk of additional oxytocin deficiency owing to the close anatomical proximity of oxytocin-producing neurons; however, no conclusive evidence for such a deficiency has been reported. We aimed to use 3,4-methylenedioxymethamphetamine (MDMA, also known as ecstasy), a strong activator of the central oxytocinergic system, as a biochemical and psychoactive provocation test to investigate oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus).

Methods This single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial included patients with arginine vasopressin deficiency (central diabetes insipidus) and healthy controls (matched 1:1 by age, sex, and BMI) and was conducted at the University Hospital Basel, Basel, Switzerland. We used block randomisation to assign participants to receive either a single oral dose of MDMA (100 mg) or placebo in the first experimental session; patients received the opposite treatment at the next session, with a wash-out period of at least 2 weeks between the two sessions. Participants and investigators assessing the outcomes were masked to assignment. Oxytocin concentrations were measured at 0, 90, 120, 150, 180, and 300 min after MDMA or placebo. The primary outcome was the area under the plasma oxytocin concentration curve (AUC) after drug intake. The AUC was compared between groups and conditions using a linear mixed-effects model. Subjective drug effects were assessed throughout the study using ten-point visual analogue scales. Acute adverse effects were assessed before and 360 min after drug intake using a 66-item list of complaints. This trial is registered with ClinicalTrials.gov, NCT04648137.

Findings Between Feb 1, 2021, and May 1, 2022, we recruited 15 patients with arginine vasopressin deficiency (central diabetes insipidus) and 15 healthy controls. All participants completed the study and were included in the analyses. In healthy controls, median plasma oxytocin concentration was 77 pg/mL (IQR 59–94) at baseline and increased by 659 pg/mL (355–914) in response to MDMA, resulting in an AUC of 102 095 pg/mL (41 782–129 565); in patients, baseline oxytocin concentration was 60 pg/mL (51–74) and only slightly increased by 66 pg/mL (16–94) in response to MDMA, resulting in an AUC of 6446 pg/mL (1291–11 577). The effect of MDMA on oxytocin was significantly different between groups: the AUC for oxytocin was 82% (95% CI 70–186) higher in healthy controls than in patients (difference 85 678 pg/mL [95% CI 63 356–108 000], p<0·0001). The increase in oxytocin in healthy controls was associated with typical strong subjective prosocial, empathic, and anxiolytic effects, whereas only minimal subjective effects were observed in patients, in agreement with the lack of increase in oxytocin concentrations. The most frequently reported adverse effects were fatigue (eight [53%] healthy controls and eight [53%] patients), lack of appetite (ten [67%] healthy controls and eight [53%] patients), lack of concentration (eight [53%] healthy controls and seven [47%] patients), and dry mouth (eight [53%] healthy controls and eight [53%] patients). In addition, two (13%) healthy controls and four (27%) patients developed transient mild hypokalaemia.

Interpretation These findings are highly suggestive of clinically meaningful oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus), laying the groundwork for a new hypothalamic–pituitary disease entity.

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Research in context

Evidence before this study

Arginine vasopressin deficiency, also known as central diabetes insipidus, is a rare neuroendocrine condition that is clinically characterised by polyuria and polydipsia. Despite treatment with desmopressin (a vasopressin receptor 2 agonist), patients often report residual psychological symptoms such as heightened anxiety levels, difficulties describing or expressing emotions, and depressed mood. Owing to their anatomical proximity, disruptions leading to arginine vasopressin deficiency (central diabetes insipidus) could also affect oxytocin-producing neurons. The central oxytocinergic system promotes prosocial effects—such as in-group favouritism and protection against social threats, trust, attachment, and empathy—and is involved in emotion recognition. An additional oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus) could explain, at least partly, the observed socioemotional changes. We searched PubMed from database inception to Jan 1, 2023, for articles published in English using the terms "diabetes insipidus", "arginine vasopressin deficiency", "oxytocin", "oxytocin deficiency", "hypopituitarism", "provocation test", "stimulation test", "psychological comorbidities", "quality of life", "anxiety", and "depression". Few studies have attempted to measure oxytocin concentrations in patients with arginine vasopressin deficiency (central diabetes insipidus), and those that have mainly focused on basal measurements, giving inconclusive results. For other pituitary hormones, a provocation test to stimulate the respective hormone is often used in the case of a suspected deficiency. So far, no standard provocation test for oxytocin has been established to provide evidence for this disease entity.

Added value of this study

Using 3,4-methylenedioxymethamphetamine (MDMA, also known as ecstasy) as a psychoactive and biochemical provocation test, our findings suggest—for the first time to our knowledge—a clinically relevant oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus). In healthy controls, we observed the expected increase in plasma oxytocin concentrations in response to MDMA stimulation, with typical prosocial, empathic, and anxiolytic effects. By contrast, in patients with arginine vasopressin deficiency (central diabetes insipidus), we found no notable increase in plasma oxytocin concentrations and, in agreement, lower MDMA-induced subjective effects, reflecting the lack of activation of central key regions important for socioemotional processing.

Implications of all the available evidence

We provide evidence for an additional oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus), laying the groundwork for a new hypothalamic–pituitary disease entity. Furthermore, these findings further our understanding of oxytocin as a key hormone in centrally generated socioemotional effects. Future intervention studies should address the potential benefits of oxytocin replacement as a treatment option for patients with arginine vasopressin deficiency (central diabetes insipidus).

Introduction

Arginine vasopressin and oxytocin are both nine-amino-acid neuropeptides that are produced in the hypothalamic supraoptic and paraventricular nuclei (SON/PVN) and released into the circulation from axon terminals projecting to the posterior pituitary.[1] A disrupted hypothalamic–pituitary axis—caused by inflammation, tumours, or head trauma—can cause arginine vasopressin deficiency, a condition that is also known as central diabetes insipidus and is characterised by polyuria and consecutive polydipsia.[2] After diagnosis, desmopressin—a selective arginine vasopressin receptor 2 agonist—is prescribed to treat the symptoms of arginine vasopressin deficiency (central diabetes insipidus).[2] However, despite adequate treatment with desmopressin, patients often report residual psychological symptoms such as heightened anxiety levels, difficulties describing or expressing emotions, and depressed mood, leading to a reduced quality of life.[3–8]

Owing to anatomical proximity, the disruption of the arginine vasopressin system that results in arginine vasopressin deficiency (central diabetes insipidus) could also disturb the oxytocin system, leading to oxytocin deficiency. The central oxytocinergic system is key in regulating socioemotional functioning, including attachment and pair bonding, fear extinction, emotion recognition, and empathy.[1] Therefore, increased psychopathological findings in patients with arginine vasopressin deficiency (central diabetes insipidus) could be caused, at least in part, by an additional oxytocin deficiency. However, there is no conclusive evidence for such a deficiency in these patients and it has not been established as a disease entity, as basal oxytocin concentrations are unreliable and ideal sampling methods are controversial.[9–11] For other pituitary hormones, a provocation test to stimulate the respective hormone is often used in the case of a suspected deficiency. However, no standard provocation test for oxytocin has been established, and testing attempts or physiological stimuli (eg, exercise) have not revealed a consistently strong increase in oxytocin concentrations.[5,12]

3,4-Methylenedioxymethamphetamine (MDMA, also known as ecstasy) is used recreationally for its effects on empathic feelings and sociability. Several studies have reported marked increases in circulating oxytocin concentrations in response to MDMA in healthy adults.[13–15] The prosocial effects of MDMA on emotion processing and social interaction—such as increased trust, closeness to others, identification of facial emotions, and fear extinction—are mediated partly by a strong oxytocin release.[14]

Given the residual psychopathological symptoms in patients with arginine vasopressin deficiency (central diabetes insipidus) and an oxytocin deficiency as a potential underlying cause, we investigated the use of MDMA as a biochemical and psychoactive provocation test to reveal an oxytocin deficiency in these patients. We hypothesised that, in response to MDMA, we would observe a robust increase in oxytocin concentrations in healthy controls and a blunted response in patients with arginine vasopressin deficiency (central diabetes insipidus).

Methods

Study design

This case-control study with nested, randomised, double-blind, placebo-controlled crossover trial was conducted in patients with arginine vasopressin deficiency (central diabetes insipidus) and healthy controls at the University Hospital Basel, Basel, Switzerland. The study conformed with the Declaration of Helsinki and was approved by the Ethics Committee Northwest Switzerland (EKNZ, number 2020-02147). The use of MDMA was authorised by the Swiss Federal Office for Public Health, Bern, Switzerland (BAG, number 2020/013366). All participants provided written informed consent before participating in the study. The study was registered at ClinicalTrials.gov, NCT04648137.

Participants

Adult patients (18–65 years) with a confirmed diagnosis of arginine vasopressin deficiency (central diabetes insipidus) and healthy controls were included in the study. Healthy controls were matched according to factors known to affect oxytocin concentrations: age (±3 years), sex, BMI (±2 kg/m²), menopausal status, and use of hormonal contraceptives. All patients and healthy controls were screened and examined for somatic and psychological comorbidities and were included only if no such illnesses were present. The main exclusion criteria were regular consumption of alcoholic beverages (≥15 standard glasses per week), tobacco smoking (>10 cigarettes per day), documented cardiovascular disease or uncontrolled arterial hypertension, current or previous major psychiatric disorder or psychotic disorder in first-degree relatives (assessed by the Semi-structured Clinical Interview for DSM-IV, Axis I disorders), lifetime prevalence of illicit substance use (except for tetrahydrocannabinol) of more than ten times or any time within the previous 2 months and during the study period, and the use of medications that could interfere with the study medications (eg, any psychiatric medication). Full inclusion and exclusion criteria are provided in the appendix (p 3).

Randomisation

Participants were assigned to receive either MDMA or placebo first, using block randomisation (blocks of four) to counterbalance the intervention order according to a predefined randomisation list. The Good Manufacturing Practice (GMP) facility generated the allocation sequence, the study investigators did the randomisation, and an intervention order was assigned to each participant number. Only the GMP facility and the principal investigator had access to the code (sealed opaque envelopes). The randomisation list was unknown to the participants, the investigators, and the study nurses involved in the trial.

Procedures

This study consisted of a screening visit followed by a baseline evaluation on the same day, two 7-h main visits, and telephone calls 3 days after each visit to inquire about subacute adverse events. The wash-out period between both main visits was at least 14 days.

At baseline, participants had a detailed psychological evaluation that consisted of assessing anxiety levels using the trait subscale of the Spielberger's State-Trait Anxiety Inventory (STAI-T), scoring mood using Beck's Depression Inventory (BDI II), assessing the degree of alexithymia using the Toronto Alexithymia Scale (TAS-20), and establishing general health status using the Short Form 36 Health Survey (SF-36). Detailed descriptions of and references for the questionnaires are provided in the appendix (p 4).

At the main visits, participants presented in the morning after an 8-h food-fasting state. Alcohol intake was prohibited for 24 h before each visit. Participants were also asked to refrain from other substance use during the study and their urine was screened for opiates, cocaine, amphetamines, methamphetamines, and tetrahydrocannabinol at the beginning of each visit. The experimental visits were conducted in a quiet standard hospital patient room. Only one participant and one investigator were present during the experimental visits. An intravenous catheter was placed in an antecubital vein for blood sampling. Patients with additional secondary adrenal insufficiency who were on hydrocortisone substitution were asked to take 50 mg hydrocortisone (30 mg morning dose and 20 mg noon dose) instead of the usual dose at the experimental visits and all patients were asked to take desmopressin as normal. Female participants were screened for pregnancy before each visit, and the visits were conducted during the follicular phase of the menstrual cycle to account for cyclic changes. Each main visit lasted for 360 min after drug administration, and participants were under continuous medical supervision until any subjective effects had completely subsided. A standardised breakfast was served before drug intake, and lunch was served 3 h after drug intake.

See Online for appendix

Autonomic and adverse effects of special interest, and adverse events

Blood pressure, heart rate, and tympanic body temperature were measured 60 min before drug intake, at drug intake, and every 30 min after drug intake for the remainder of the visit. Adverse effects of special interest were assessed

60 min before and 360 min after drug administration using a predefined 66-item list of complaints. Additional adverse events were assessed during and 3 days after each main visit. All events were handled in accordance with the Swiss legal framework and reported if necessary. An annual safety report was provided to the local ethics committee and independent monitoring was conducted.

Subjective drug effects

Subjective effects were assessed throughout the treatment visit (at 0, 30, 60, 90, 120, 150, 180, 240, 300, and 360 min) using visual analogue scales. The scales were presented as 10 cm horizontal lines and ranged either from 0 to 10 (with not at all [0] on the left and extremely [10] on the right) or from −5 to +5 (with 0 being the neutral measure; ie, no effect). We used the following items known to be sensitive to the acute subjective effects induced by MDMA: any effect, good effect, bad effect, liking effect, feeling high, stimulation, fear, satisfaction, happiness, trust, talkative, openness, want to be close to others, want to be embraced, want to embrace someone, want to be with others, and feeling close to others.[13,16–18] Acute anxiety was assessed using the STAI-State subscale (STAI-S) immediately before drug intake (0 min) and was reassessed 180 min after drug administration.

Study drugs

Oral MDMA was prepared as opaque gelatine capsules containing 25 mg of pharmaceutically pure MDMA hydrochloride (ReseaChem, Burgdorf, Switzerland) with mannitol filler and administered as a single dose of 100 mg (four capsules of 25 mg). Oral placebo was prepared as identical opaque gelatine capsules filled with mannitol only. All products were prepared and quality-controlled according to GMP guidelines. On the basis of previous pharmacokinetic studies, the psychoactive effects of MDMA were expected to last 6 h, with peak psychoactive effects after 2·5 h.[13]

Blood samples

Samples were collected at 0, 90, 120, 150, 180, and 300 min to measure oxytocin and sodium concentrations, and at 0 min and 120 min to measure plasma copeptin concentrations. Samples were taken as aliquots (EDTA [edetic acid] plasma, lithium-heparin, and serum), immediately centrifuged at 4°C at 3000 rpm for 10 min, then stored at −80°C until batch analysis. Sodium concentrations were measured by analysing venous blood gas. Copeptin concentrations were measured in serum using a commercial automated immunofluorescence assay (B·R·A·H·M·S CopeptinproAVP KRYPTOR, Thermo Scientific B·R·A·H·M·S Biomarkers, Thermo Fisher Scientific, Hennigsdorf, Germany). EDTA plasma oxytocin was extracted using Oasis PRiME HLB 96-well plate, 30 mg sorbent (Waters Corporation, Milford, MA, USA). Oxytocin concentrations were measured using the Oxytocin ELISA kit (Enzo Life Sciences, Ann Arbor, MI, USA; sensitivity 15 pg/mL [range 15·6–1000·0 pg/mL]) and prolactin concentrations were measured using an electrochemiluminescence assay. The intra-assay coefficient of variation for our oxytocin measurements is 1·59%, and the inter-assay coefficient of variation is 4·97%. The antiserum displays cross-reactivity with mesotocin of 7%, arginine vasotocin of 7.5%, and less than 0·02% for other related molecules. Copeptin, oxytocin, and prolactin were analysed blinded at the end of the study in one batch.

MDMA and its primary metabolite 3,4-methylenedioxyamphetamine (MDA) were measured in human plasma using high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS). The lower limits of quantification were 0·5 ng/mL for MDMA and 1 ng/mL for MDA. A validated bioanalytical method was used for the analysis.[17] Pharmacokinetic parameters were estimated using non-compartmental methods in Phoenix WinNonlin 8.3 (Certara, Princeton, NJ, USA).

Emotion recognition and empathy tasks

At the expected peak concentration of oxytocin (timepoint 150 min),[13] participants did the Multifaceted Empathy Test and Facial Emotion Recognition Task. The Multifaceted Empathy Test is a reliable and valid task to assess the cognitive and emotional aspects of empathy[19] and has shown to be sensitive to the effects of oxytocin[20] and MDMA.[16] The Facial Emotion Recognition Task assesses the recognition of basic emotions, featuring ten neutral faces and 160 faces that express one of four basic emotions (happiness, sadness, anger, and fear), with pictures morphed between 0% (ie, neutral) and 100% in 10% increments. A detailed description of the tasks is provided in the appendix (p 4).

Outcomes

The primary outcome was the change in oxytocin concentrations between 0 min and 300 min in response to MDMA compared with placebo in patients with arginine vasopressin deficiency (central diabetes insipidus) and healthy controls. The secondary outcomes were baseline psychological characteristics and physical and mental health measures in both groups, evaluated using the questionnaires STAI-T, TAS-20, BDI-II, and SF-36. Other outcomes were descriptive in nature. We aimed to evaluate the time course of 20 subjective effects, emotion recognition and empathy at 150 min, and acute anxiety levels at 180 min after drug intake.

Statistical analysis

Given the absence of data on oxytocin concentrations after the administration of MDMA in patients with arginine vasopressin deficiency (central diabetes insipidus), assumptions for sample size calculation were discussed by a panel of expert neuroendocrinologists. According to available data from healthy adults on oxytocin concentrations after a single oral dose of MDMA,[13] we assumed a mean maximum increase in plasma oxytocin con-

centrations after MDMA of 810 pg/mL (SD 330) in healthy controls. A 30% reduced response (ie, plasma oxytocin concentrations after MDMA of 550 pg/mL [SD 100]) in patients with arginine vasopressin deficiency (central diabetes insipidus) was considered a minimum clinically meaningful difference. With a power of 80%, a two-sided significance level α of 0.05, and assuming a pooled SD of 240 pg/mL (according to Cohen's calculation), we estimated that 15 participants were required in each group.

Demographic information was described using mean (SD), median (IQR), or absolute (relative) frequency as appropriate. The plasma oxytocin concentration after MDMA administration was reported as mean (SD) at each time point and the time course was plotted. The primary endpoint, net incremental area under the curve (AUC) in both directions (positive and negative), was calculated to evaluate the change in oxytocin concentrations between 0 min and 300 min.[21] The continuous primary endpoint, AUC, was analysed using a restricted maximum-likelihood-based repeated measures approach (linear mixed-effects regression model) using the R-package "nlme" (version 3.1-160). We analysed treatment (MDMA *vs* placebo) and participant (control *vs* patient) group and the interaction between both as fixed effects, and the oxytocin concentration at timepoint 0 min (ie, immediately before the administration of the study drug) at each visit was included as a continuous covariate. A random intercept for study participants was added to the model to account for the correlation between measures within the same participant, and a general unstructured variance–covariance structure was used to model the within-patient errors. The degrees of freedom were approximated with the Newton-Raphson algorithm. Significance tests were based on the Wald statistic using a two-sided α of 0·05. We calculated the percentage difference between groups under the MDMA condition on the basis of the estimates of the model using a bootstrapping method with 1000 bootstrap replicates, and used a percentile method to calculate the 95% CI from all obtained estimates.

The baseline psychological characteristics were compared using Wilcoxon rank-sum tests as a post-hoc analysis. The p values were corrected for multiple testing using the conservative Bonferroni method. Other secondary endpoints (ie, Multifaceted Empathy Test, Facial Emotion Recognition Task, STAI-S, and subjective effects) were described using median (IQR) and visualised using boxplots. We used mean (SD) to show the time course of the subjective effects. For each subjective effect, we calculated the maximal change (either positive or negative) and the net incremental AUC as a measure of the total effect. Finally, we calculated the Pearson's correlation coefficient for the maximal change in each subjective effect and the maximum concentration of oxytocin. We described the time course of each safety outcome (blood pressure, heart rate, and tympanic body temperature) and calculated the time to maximum increase. The total number of adverse effects reported on the 66-item list of complaints was stated as mean (SD) at the end of each study visit and during the telephone interview 3 days after the study visit. No data imputation was foreseen for missing data. No participants dropped out of the study or were lost to follow-up. Only the full analysis set was used for statistical analysis. All analyses were performed in R (version 4.2.2).

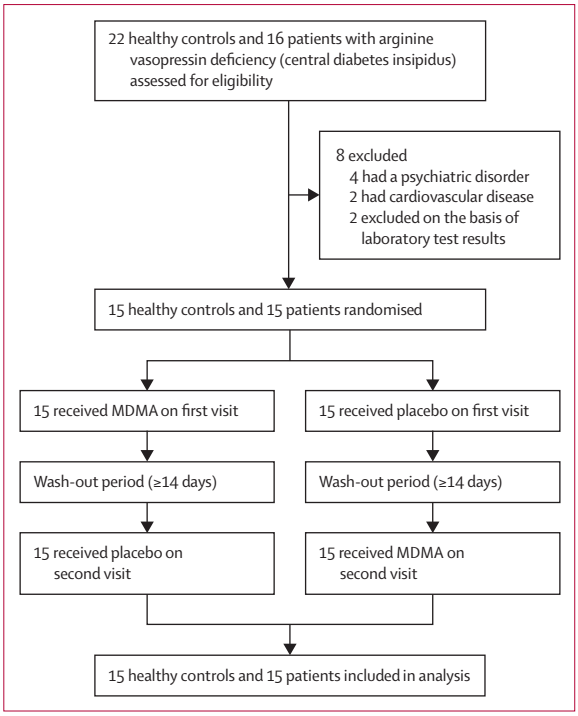

Figure 1: **Trial profile**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 1, 2021, and May 1, 2022, 15 patients with arginine vasopressin deficiency (central diabetes insipidus) and 15 matched healthy controls were recruited to this study (figure 1). The median age was 34 years (IQR 25–46; eight [53%] female and seven [47%] male) in the patient group and 35 years (26–48; eight [53%] female and seven [47%] male) in the control group. Eight (53%) patients had an isolated posterior pituitary dysfunction and seven (47%) patients had a combined pituitary dysfunction. The baseline characteristics of the study population are summarised in table 1.

We observed significantly higher total median scores in trait anxiety (STAI-T: 41 points [IQR 34–48] *vs* 28 points [24–31]; p=0·0143), alexithymia levels (TAS-20: 47 points [38–59] *vs* 30 points [29–37; p=0·0365), and depression symptoms (BDI-II: 6 points [3–17] *vs* 1 point [0–2];

	Patients with arginine vasopressin deficiency (central diabetes insipidus; n=15)		Healthy controls (n=15)	
	Placebo	MDMA	Placebo	MDMA
Age, years	34 (25–46)	34 (25–46)	35 (26–48)	35 (26–48)
Sex				
Male	7 (47%)	7 (47%)	7 (47%)	7 (47%)
Female	8 (53%)	8 (53%)	8 (53%)	8 (53%)
Ethnicity				
Caucasian	14 (93%)	14 (93%)	15 (100%)	15 (100%)
Indian	1 (7%)	1 (7%)	0	0
Weight, kg	74 (13)	74 (13)	70 (10)	70 (10)
Height, cm	174 (11)	174 (11)	173 (10)	173 (10)
BMI, kg/m²	24·4 (3·1)	24·4 (3·1)	23·2 (2·1)	23·2 (2·1)
Cause of central diabetes insipidus				
Idiopathic or unknown	5 (33%)	5 (33%)	NA	NA
Pituitary adenoma (post-surgery)	3 (20%)	3 (20%)	NA	NA
Hypothalamic or pituitary tumour or cyst (eg, craniopharyngioma or Rathke cleft cyst)	3 (20%)	3 (20%)	NA	NA
Inflammatory or autoimmune (eg, hypophysitis)	3 (20%)	3 (20%)	NA	NA
Genetic or hereditary	1 (7%)	1 (7%)	NA	NA
Anterior pituitary deficiency	7 (47%)	7 (47%)	NA	NA
Partial arginine vasopressin deficiency	3 (20%)	3 (20%)	NA	NA

Data are mean (SD), median (IQR), or n (%). NA=not applicable. MDMA=3,4-methylenedioxymethamphetamine.

Table 1: **Baseline characteristics**

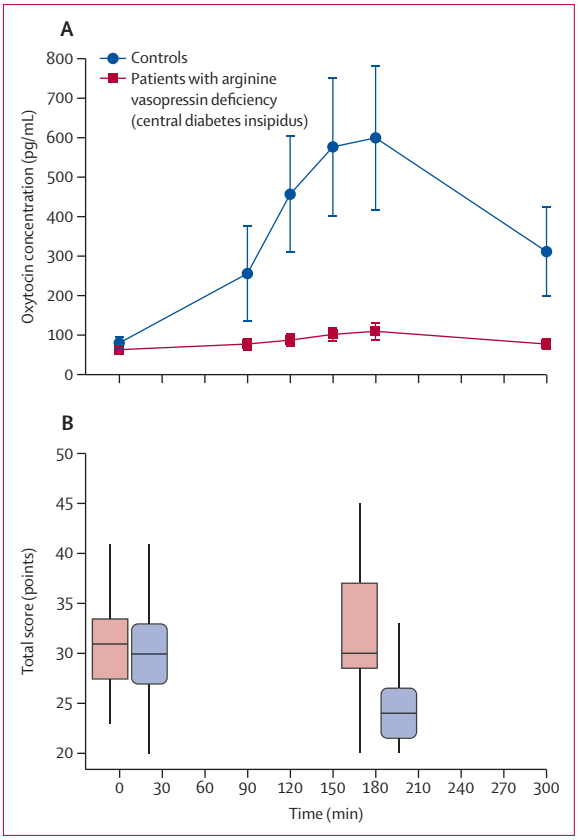

Figure 2: **Plasma oxytocin concentrations and anxiety symptoms in response to MDMA stimulation**

(A) Change in oxytocin concentration after MDMA stimulation. Oxytocin concentration increased in healthy controls, whereas no change was observed in patients with arginine vasopressin deficiency (central diabetes insipidus). Data are mean (SD). (B) State anxiety levels after MDMA stimulation. Heightened state anxiety was observed at baseline (0 min) in both healthy controls and patients. In response to MDMA stimulation, state anxiety decreased at 180 min in healthy controls, whereas no such anxiolytic effect was observed in patients and their anxiety levels remained stable. The horizontal line shows the median, boxes are IQR, whiskers are the most extreme values lying within the box edge and 1·5 × IQR.

p=0·0437) in patients than in healthy controls (appendix pp 6, 20). In the SF-36, patients had lower self-reported mental health scores than healthy controls (mental health subscale: 49 points [43–52] *vs* 54 points [52–55]; p=0·0199; appendix pp 6, 20).

The time course of plasma oxytocin concentrations after MDMA administration is shown in figure 2 and table 2. Maximum changes in oxytocin concentrations from the baseline (ie, immediately before study drug intake) and the time to peak concentration are shown in table 2. In healthy controls, the median oxytocin concentration at baseline was 77 pg/mL (IQR 59–94) and peaked in response to MDMA stimulation at 624 pg/mL (235–959) after 180 min; the resulting maximum change in oxytocin concentration was 659 pg/mL (355–914). In patients with arginine vasopressin deficiency (central diabetes insipidus), oxytocin concentration at baseline was 60 pg/mL (51–74) and peaked in response to MDMA at 92 pg/mL (79–110) after 150 min; the resulting maximum change in oxytocin concentration was 66 pg/mL (16–94). Neither group showed any notable changes in plasma oxytocin concentration with placebo (appendix p 8).

The plasma oxytocin AUC is stated in table 2 and shown in the appendix (p 8). In response to MDMA administration, an eight-fold increase in oxytocin concentration was observed in healthy controls, with a median AUC of 102 095 pg/mL (IQR 41 782 to 129 565), whereas no notable increase was observed in patients with arginine vasopressin deficiency (central diabetes insipidus), with an AUC of 6446 pg/mL (1291 to 11 577). In response to placebo, the plasma oxytocin AUC was 2175 pg/mL (–3750 to 3754) in healthy controls and –1343 pg/mL (–3860 to –580) in patients (appendix pp 8, 21).

The effect of MDMA on oxytocin concentration was significantly different in healthy controls and patients. The net incremental AUC was 85 678 pg/mL (95% CI 63 356–108 000, p<0·0001) higher in healthy controls than in patients (adjusted for baseline oxytocin concentrations). Given the estimates of the oxytocin concentrations of both groups after MDMA administration, healthy controls had an 82% (95% CI 70–186) higher AUC than patients. Additional subgroup analyses are provided in the appendix (p 9–11). Copeptin

concentrations remained stable from 0 min to 120 min in response to MDMA and placebo in both groups (appendix pp 12–13). Prolactin concentrations increased slightly and equally in both groups in response to MDMA (appendix p 14).

At the beginning of the experimental session, a similar level of heightened state anxiety was observed in both healthy controls and patients (STAI-S: 30 points [IQR 27–33] *vs* 31 points [28–34]). In response to MDMA stimulation, at the expected peak concentration of oxytocin (180 min) the anxiety score decreased to 24 points (22–27) in healthy controls, whereas no anxiolytic effect was observed in patients and their anxiety levels remained stable at 30 points (29–37; figure 2).

In patients, MDMA-induced acute subjective effects assessed by visual analogue scales were either absent or were lower than in healthy controls (appendix p 22). Specifically, patients exhibited lower effects for any effect, good effect, bad effect, liking effect, feeling high, stimulation, fear reduction, satisfaction, happiness, trust, talkative, and openness (figure 3). Moderate correlations were found between the maximum change in some subjective effects and the maximum change in oxytocin concentrations (appendix p 22). The assessment of additional subjective effects is shown in the appendix (p 15).

In healthy controls, MDMA impaired the recognition of faces displaying negative emotions—such as anger, sadness, and fear—with no alteration in the correct identification of happy or neutral faces (appendix p 16). By contrast, in patients with arginine vasopressin deficiency (central diabetes insipidus), MDMA differentially impaired the recognition of faces displaying happy and sad emotions without an effect on the recognition of faces displaying anger or fear or neutral faces (appendix p 16). In healthy controls, MDMA increased explicit and implicit emotional empathy ratings for positive valence stimuli, whereas in patients contradirectional effect was observed with lower ratings. MDMA decreased explicit and implicit emotional empathy ratings for negative valence stimuli in healthy controls and patients, with a larger decrease in healthy controls. MDMA showed no effect on cognitive empathy scores in both groups compared with placebo (appendix p 17).

MDMA moderately increased blood pressure, heart rate, and body temperature, with no major differences between healthy controls and patients (table 3, appendix p 18). MDMA increased the acute (360 min after drug intake) and subacute (3 days after the experimental session) number of adverse effects assessed using the 66-item list of complaints to a similar extent in both groups (acute number of adverse effects: 6·6 [SD 2·5] for patients and 6·3 [3·5] for healthy controls; subacute number of adverse effects: 3·6 [2·5] for patients and 3·6 [2·7] for healthy controls; table 3, appendix pp 23–25). The most frequent acute adverse effects after MDMA administration included headache, tiredness, and lack of appetite (table 3). In addition, two (13%) healthy controls and four (27%) patients developed transient mild hypokalaemia; no episodes of new onset hyponatremia were recorded in healthy controls and patients throughout the sessions. One patient presented with mild hyponatremia at the beginning of the experimental session due to a slight desmopressin overdose and remained stable throughout the session. No serious adverse events were reported.

	Patients with arginine vasopressin deficiency (central diabetes insipidus) (n=15)		Healthy controls (n=15)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Oxytocin concentration, pg/ml				
0 min	62 (18)	60 (51–74)	79 (35)	77 (59–94)
90 min	76 (31)	68 (52–96)	255 (244)	141 (121–341)
120 min	86 (35)	73 (62–110)	456 (297)	504 (192–589)
150 min	101 (37)	92 (79–110)	575 (352)	540 (273–844)
180 min	109 (47)	90 (72–134)	598 (367)	624 (235–959)
300 min	76 (28)	70 (62–89)	310 (230)	203 (181–391)
AUC*	7093 (8938)	6446 (1291–11 577)	89 532 (57 149)	102 095 (41 782–129 565)
Maximum change in oxytocin concentration, pg/mL	60 (48)	66 (16–94)	609 (336)	659 (355–914)
Time to peak oxytocin concentration, min	140 (53)	150 (105–180)	166 (47)	180 (150–180)

Data are mean (SD) or median (IQR). MDMA=3,4-methylenedioxymethamphetamine. AUC=area under the oxytocin concentration curve. *Mean difference in AUC between groups 85 678 (95% CI 63 356–108 000).

Table 2: **Response to MDMA stimulation in the full analysis set**

Discussion

This study has three main findings. First, in response to MDMA stimulation, we found an expected eight-fold increase in plasma oxytocin concentrations in healthy controls but no notable increase in patients with arginine vasopressin deficiency (central diabetes insipidus). Second, this lack of increase of oxytocin concentrations in patients was associated with lower MDMA-induced subjective prosocial, empathic, and anxiolytic effects. Third, even at baseline, patients exhibited significantly higher anxiety, alexithymia, and depression symptoms than healthy controls. Together, these findings suggest—for the first time to our knowledge—a clinically relevant oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus).

The central oxytocinergic system and related limbic networks affect complex neural circuits of socioemotional behaviour and promote prosocial effects such as in-group favouritism and protection against social threats, trust and attachment, empathy, and emotion recognition.[1] Previously, little research has been devoted to a potential oxytocin deficiency in patients with hypothalamic–pituitary dysfunction. Few studies attempted to measure oxytocin in these patients, and those that did mainly

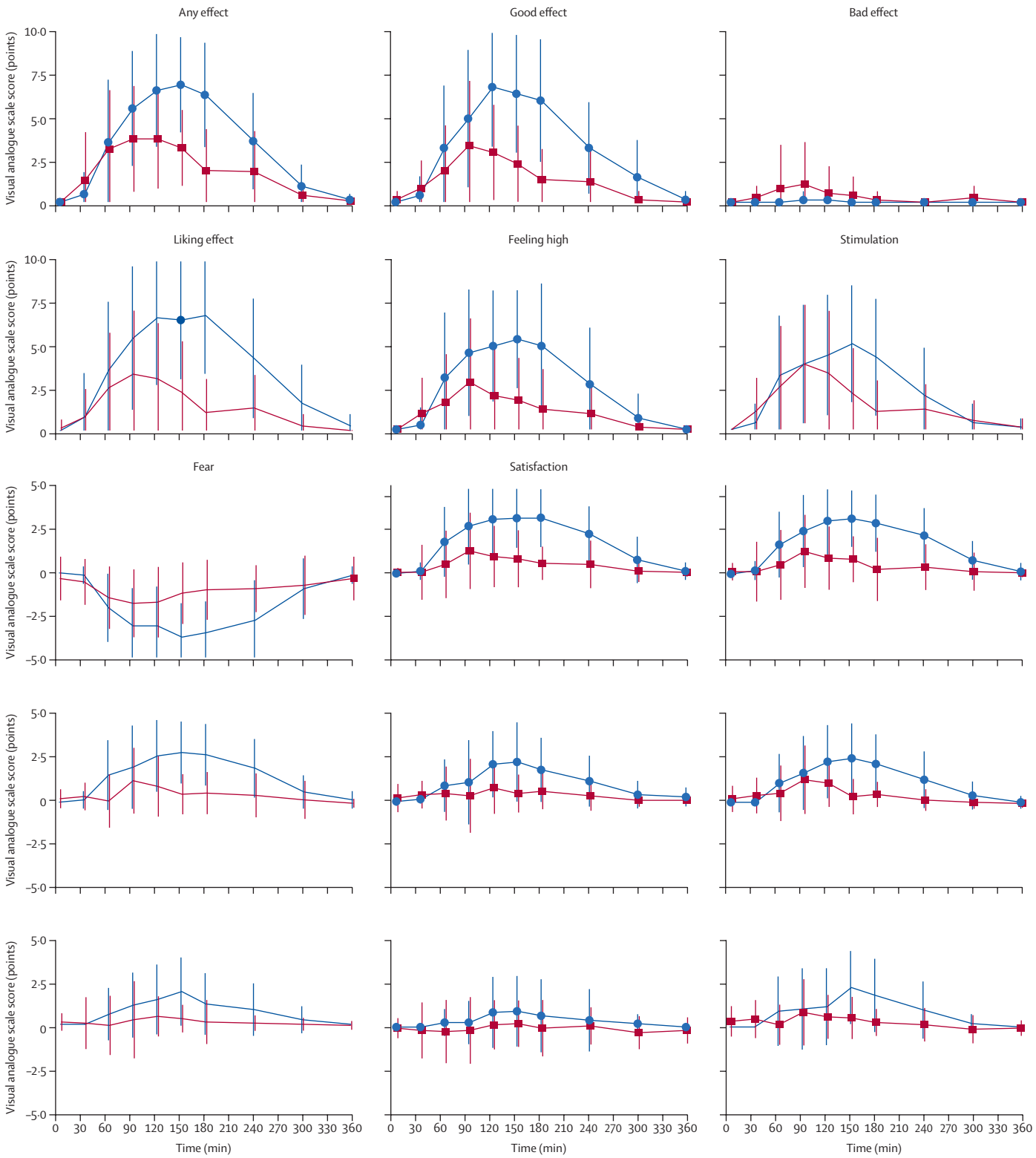

Figure 3: **Acute subjective effects in response to MDMA stimulation**
In patients with arginine vasopressin deficiency (central diabetes insipidus), subjective effects after MDMA stimulation were either absent or were lower than in healthy controls. Effects were assessed using visual analogue scales; data are mean (SD).

focused on basal measurements, providing inconclusive results. Although some studies showed slightly lower basal oxytocin concentrations in patients with arginine vasopressin deficiency (central diabetes insipidus), others could not confirm these findings or even showed contradirectional higher oxytocin concentrations in patients than in healthy controls.[4-6,8] Notably, as for other pituitary hormones, single basal concentrations are unreliable in identifying a deficiency in this context.[11] According to a meta-analysis,[22] peripheral oxytocin concentrations correlate with central concentrations only after stimulation and not at baseline. Using a provocation test, our results clearly indicate an oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus), laying the groundwork for a new hypothalamic–pituitary disease entity. An important question, however, is whether this deficiency is related to alterations or dysfunctions in socioemotional behaviour.

The few studies investigating psychological comorbidities in patients with arginine vasopressin deficiency (central diabetes insipidus) have suggested heightened anxiety and alexithymia, reduced empathic abilities, higher levels of self-reported autistic traits, lower levels of joy when socialising, and lower scores in an emotion recognition task.[3,4,6,23] Studies in patients with craniopharyngioma—a condition that carries a high risk of developing arginine vasopressin deficiency (central diabetes insipidus), either through direct tumour-induced damage or post-surgical damage to the SON/PVN—revealed personality changes (31%) and increased psychosocial comorbidities (47%), including anxiety, depression, and social withdrawal.[24,25] Consistent with these observations, we show high levels of anxiety and alexithymia in patients with arginine vasopressin deficiency (central diabetes insipidus) at baseline. Notably, despite the selection of patients without actively treated psychological co-morbidities, about half exhibited clinically relevant anxiety and alexithymia symptoms. The cause could be multifactorial; however, it is tempting to suggest that some of these symptoms could be attributable to undiagnosed oxytocin deficiency. Consistent with this, we found that the lack of increase in oxytocin concentrations in patients with arginine vasopressin deficiency (central diabetes insipidus) was associated with increased anxiety.

Over the past two decades, oxytocin-knockout models have been used to identify dysfunctional aspects of social behaviour in an oxytocin-deficient state. Generally, an impairment in forming social memories and increased anxiety-related behaviours were observed.[26,27] Some mental health conditions—such as autism spectrum disorder, anxiety, and depressive disorders—have been linked to lower endogenous oxytocin concentrations or impaired signalling.[28] Intranasal oxytocin has been experimentally administered to ameliorate symptoms of social impairment, for example in autism spectrum disorder; however, results have been inconsistent.[29] Notably, in contrast to arginine vasopressin deficiency (central diabetes insipidus), the evidence for oxytocin deficiency in such conditions is not conclusive as it is largely based on reports of individual variations in peripheral basal oxytocin concentrations or in genes involved in oxytocin signalling or oxytocin receptor expression.[30] The effects of oxytocin administration in arginine vasopressin deficiency (central diabetes insipidus) have been described in only one case report and a small study: after pituitary surgery, the parents of a 6-year-old patient recognised personality changes such as increased social isolation and decreased interest in physical contact with family members. After treatment with intranasal oxytocin, the patient re-engaged in play with family members and positive social interactions with peers.[31] A study of ten patients with childhood-onset craniopharyngioma (of whom nine had arginine vasopressin deficiency [central diabetes insipidus]) showed an improvement in the previously impaired ability of the patients to categorise negative emotions after a single dose of intranasal oxytocin.[32] Future studies in a larger patient population should investigate the potential therapeutic use of intranasal oxytocin.

We used MDMA as a stimulus for oxytocin, the release of which is linked to the empathic and prosocial profile of MDMA, including closeness to others, openness, trust, happiness, and feelings of wellbeing.[13,14,17,33] By stimulating the oxytocinergic neurons, MDMA induces an increase

	Patients with arginine vasopressin deficiency (central diabetes insipidus; n=15)		Healthy controls (n=15)	
	MDMA	Placebo	MDMA	Placebo
Clinical safety measures				
Maximum systolic blood pleasure, mm Hg	143 (10)	131 (7)	146 (13)	129 (9)
Maximum diastolic blood pleasure, mm Hg	84 (7)	78 (9)	84 (9)	78 (9)
Maximum heart rate, beats per min	93 (12)	83 (8)	92 (14)	78 (9)
Maximum tympanic temperature, °C	36·9 (0·2)	36·9 (0·2)	37·1 (0·3)	37·0 (0·3)
Adverse effects of special interest				
Total acute reported complaints*	6·6 (2·5)	1·9 (1·5)	6·3 (3·5)	2·0 (1·5)
Fatigue	8 (53%)	2 (13%)	8 (53%)	4 (27%)
Lack of appetite	8 (53%)	0	10 (67%)	0
Lack of concentration	7 (47%)	0	8 (53%)	1 (7%)
Dry mouth	8 (53%)	0	8 (53%)	0
Total subacute reported complaints†	3·6 (2·5)	2·5 (2·9)	3·6 (2·7)	1·4 (0·8)
Headache	7 (47%)	2 (13%)	5 (33%)	1 (7%)
Fatigue	7 (47%)	3 (20%)	6 (40%)	1 (7%)
Lack of energy	4 (27%)	1 (7%)	2 (13%)	0
Dullness	1 (7%)	4 (27%)	5 (33%)	1 (7%)
Adverse events				
Transient mild hypokalaemia	4 (27%)	0	2 (13%)	0

Data are mean (SD) or n (%). MDMA=3,4-methylenedioxymethamphetamine. *Assessed with the 66-item list of complaints. Change from the assessed complaints at 360 min after drug administration. †Assessed with the 66-item list of complaints, 3 days after each visit by telephone call; see full list of complaints in the appendix (pp 23–25).

Table 3: **Safety outcomes in response to MDMA and placebo stimulation in the full analysis set**

not only in peripheral oxytocin concentrations (via the posterior pituitary) but also in central oxytocin-mediated behavioural effects. In rats, arginine vasopressin was not affected by MDMA,[34] a finding also reflected in this study by unchanged copeptin concentrations.[34] The anxiolytic effects observed after MDMA stimulation might be due to the strong increase and consequent action of oxytocin within core regions for fear processing, such as the amygdala. In support of this, we have provided evidence of the anxiolytic effects and of reduced recognition of negative emotions (ie, anger, fear, and sadness) in the Facial Emotion Recognition Task in response to MDMA in healthy controls. By contrast, anxiolytic effects and reduced recognition of fearful emotions were not observed in patients with arginine vasopressin deficiency (central diabetes insipidus) in response to MDMA. Evidence suggests that both MDMA and intranasal oxytocin enhance effects of emotional empathy in response to positive stimuli in the Multifaceted Empathy Test.[20,35] Although the study was not powered for this task, in patients with arginine vasopressin deficiency (central diabetes insipidus) we observed contradirectional effects after MDMA stimulation with no increase in positive empathy—ie, the ability to share, celebrate, and enjoy the positive emotions of others, a state that correlates with increased prosocial behaviour, social closeness, and wellbeing. This lack of positive empathy might contribute to the psychological findings observed in our study.

Taken together, our data show that, compared with the expected effects in healthy controls, almost all subjective effects of MDMA were reduced or even absent in patients with arginine vasopressin deficiency (central diabetes insipidus), reflecting the absence of the hormone and the consequent lack of function in central key regions important for socioemotional processing. These findings contradict the previous theory that oxytocin stimulation has only a secondary role in the effects of MDMA. Our results, by contrast, suggest a paradigm shift and underline the importance of oxytocin as a key feature of the effects of MDMA.

Our study has limitations. First, this was a single-centre trial, the sample size was small and did not allow for appropriate subgroup analysis, and the trial was not blinded with respect to both groups. Second, 100 mg MDMA had pronounced cardiostimulatory effects, and a lower dose could probably be used if this approach is further developed into a routine clinical test. Third, there are ongoing discussions about the accuracy and reliability of currently available enzyme immunoassays and radioimmunoassays for oxytocin. However, all samples were measured in one batch, and an equally large relative increase in oxytocin concentrations upon MDMA stimulation has been shown and reproduced with both assays in different laboratories. Finally, possible selection bias of patients prone to psychological conditions cannot be excluded. However, due to our strict eligibility criteria, we included only patients without current active mental illness and with no somatic illness other than pituitary dysfunction. Therefore, the psychological assessment might even show higher values in the general population of patients with arginine vasopressin deficiency (central diabetes insipidus).

In conclusion, this study provides evidence of a clinically relevant oxytocin deficiency in our population of patients with arginine vasopressin deficiency (central diabetes insipidus). These findings are suggestive of a new hypothalamic–pituitary disease entity and contribute to deepening our understanding of oxytocin as a key hormone in centrally generated socioemotional effects, as reflected by reduced prosocial, empathic, and anxiolytic effects in patients with an oxytocin deficiency. Future studies should evaluate whether oxytocin replacement therapy can alleviate residual symptoms related to oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus).

Contributors

CA, RM, and NH collected the data. NR covered all statistical aspects of the study and planned and conducted the data analysis. CA, MC-C, MEL, FH, COS, NV, AE, and MG contributed to the analysis and interpretation of the data. CA and MC-C did the literature search. CA, MEL, and MC-C designed the study. CA wrote the protocol, which was edited by MC-C, MEL, and COS. CA wrote the manuscript and MC-C, MEL, NR, FH, NV, AE, RM, NH, COS, and MH revised the manuscript. MC-C supervised the study. MC-C, CA, FH, MEL, NR, and NH verified the data. MC-C, CA, NR, and NH had access to all raw data, and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

MEL has received consulting and license fees and funding from MindMed for patents and knowledge related to MDMA; the received fees and funding are not related to the present study. MEL owns stocks of MindMed. All other authors declare no competing interests.

Data sharing

We may share deidentified, individual participant-level data that underlie the results reported in this Article and related documents, including the study protocol and the statistical analysis plan. Data will be available with the publication of the Article on receipt of a request detailing the study hypothesis and statistical analysis plan. All requests should be sent to MC-C. The steering committee of this study will discuss all requests and decide, on the basis of the scientific rigor of the proposal, whether data sharing is appropriate. All applicants are asked to sign a data access agreement.

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References

1 Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci* 2011; **12:** 524–38.

2 Christ-Crain M, Bichet DG, Fenske WK, et al. Diabetes insipidus. *Nat Rev Dis Primers* 2019; **5:** 54.

3 Aulinas A, Plessow F, Asanza E, et al. Low plasma oxytocin levels and increased psychopathology in hypopituitary men with diabetes insipidus. *J Clin Endocrinol Metab* 2019; **104:** 3181–91.

4 Eisenberg Y, Murad S, Casagrande A, et al. Oxytocin alterations and neurocognitive domains in patients with hypopituitarism. *Pituitary* 2019; **22:** 105–12.

5 Gebert D, Auer MK, Stieg MR, et al. De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function. *Psychoneuroendocrinology* 2018; **88:** 61–69.

6 Daughters K, Manstead ASR, Rees DA. Hypopituitarism is associated with lower oxytocin concentrations and reduced empathic ability. *Endocrine* 2017; **57:** 166–74.

7 Atila C, Loughrey PB, Garrahy A, et al. Central diabetes insipidus from a patient's perspective: management, psychological co-morbidities, and renaming of the condition: results from an international web-based survey. *Lancet Diabetes Endocrinol* 2022; **10:** 700–09.

8 Daubenbüchel AM, Hoffmann A, Eveslage M, et al. Oxytocin in survivors of childhood-onset craniopharyngioma. *Endocrine* 2016; **54:** 524–31.

9 Baskaran C, Plessow F, Silva L, et al. Oxytocin secretion is pulsatile in men and is related to social-emotional functioning. *Psychoneuroendocrinology* 2017; **85:** 28–34.

10 Leng G, Sabatier N. Measuring oxytocin and vasopressin: bioassays, immunoassays and random numbers. *J Neuroendocrinol* 2016; **28:** jne.12413.

11 McCullough ME, Churchland PS, Mendez AJ. Problems with measuring peripheral oxytocin: can the data on oxytocin and human behavior be trusted? *Neurosci Biobehav Rev* 2013; **37:** 1485–92.

12 Sailer CO, Winzeler B, Urwyler SA, et al. Oxytocin levels in response to pituitary provocation tests in healthy volunteers. *Eur J Endocrinol* 2021; **185:** 355–64.

13 Holze F, Vizeli P, Müller F, et al. Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacology* 2020; **45:** 462–71.

14 Kirkpatrick MG, Lee R, Wardle MC, Jacob S, de Wit H. Effects of MDMA and Intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology* 2014; **39:** 1654–63.

15 Hysek CM, Domes G, Liechti ME. MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. *Psychopharmacology (Berl)* 2012; **222:** 293–302.

16 Schmid Y, Hysek CM, Simmler LD, Crockett MJ, Quednow BB, Liechti ME. Differential effects of MDMA and methylphenidate on social cognition. *J Psychopharmacol* 2014; **28:** 847–56.

17 Dolder PC, Müller F, Schmid Y, Borgwardt SJ, Liechti ME. Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. *Psychopharmacology (Berl)* 2018; **235:** 467–79.

18 Hysek CM, Schmid Y, Simmler LD, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci* 2014; **9:** 1645–52.

19 Dziobek I, Rogers K, Fleck S, et al. Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). *J Autism Dev Disord* 2008; **38:** 464–73.

20 Hurlemann R, Patin A, Onur OA, et al. Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J Neurosci* 2010; **30:** 4999–5007.

21 Brouns F, Bjorck I, Frayn KN, et al. Glycaemic index methodology. *Nutr Res Rev* 2005; **18:** 145–71.

22 Valstad M, Alvares GA, Egknud M, et al. The correlation between central and peripheral oxytocin concentrations: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2017; **78:** 117–24.

23 Brandi ML, Gebert D, Kopczak A, Auer MK, Schilbach L. Oxytocin release deficit and social cognition in craniopharyngioma patients. *J Neuroendocrinol* 2020; **32:** e12842.

24 Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf)* 2005; **62:** 397–409.

25 Pereira AM, Schmid EM, Schutte PJ, et al. High prevalence of long-term cardiovascular, neurological and psychosocial morbidity after treatment for craniopharyngioma. *Clin Endocrinol (Oxf)* 2005; **62:** 197–204.

26 Mantella RC, Vollmer RR, Li X, Amico JA. Female oxytocin-deficient mice display enhanced anxiety-related behavior. *Endocrinology* 2003; **144:** 2291–96.

27 Ferguson JN, Young LJ, Hearn EF, Matzuk MM, Insel TR, Winslow JT. Social amnesia in mice lacking the oxytocin gene. *Nat Genet* 2000; **25:** 284–88.

28 Kiani Z, Farkhondeh T, Aramjoo H, et al. Oxytocin effect in adult patients with autism: an updated systematic review and meta-analysis of randomized controlled trials. *CNS Neurol Disord Drug Targets* 2023; **22:** 906–15.

29 Huang Y, Huang X, Ebstein RP, Yu R. Intranasal oxytocin in the treatment of autism spectrum disorders: a multilevel meta-analysis. *Neurosci Biobehav Rev* 2021; **122:** 18–27.

30 Kranz TM, Kopp M, Waltes R, et al. Meta-analysis and association of two common polymorphisms of the human oxytocin receptor gene in autism spectrum disorder. *Autism Res* 2016; **9:** 1036–45.

31 Cook N, Miller J, Hart J. Parent observed neuro-behavioral and pro-social improvements with oxytocin following surgical resection of craniopharyngioma. *J Pediatr Endocrinol Metab* 2016; **29:** 995–1000.

32 Hoffmann A, Özyurt J, Lohle K, Reichel J, Thiel CM, Müller HL. First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. *Endocrine* 2017; **56:** 175–85.

33 Kirkpatrick MG, Francis SM, Lee R, de Wit H, Jacob S. Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans. *Psychoneuroendocrinology* 2014; **46:** 23–31.

34 Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT_{1A} receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). *Neuroscience* 2007; **146:** 509–14.

35 Kuypers KPC, Dolder PC, Ramaekers JG, Liechti ME. Multifaceted empathy of healthy volunteers after single doses of MDMA: a pooled sample of placebo-controlled studies. *J Psychopharmacol* 2017; **31:** 589–98.