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Clinical Research Article

Melatonin as a Possible Stimulus to Unmask an Oxytocin-Deficient State in Hypopituitarism and Hypothalamic Damage

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Abstract

Context: Increasing evidence supports the presence of oxytocin deficiency (OXT-D) in hypopituitarism and hypothalamic damage (HHD). Identifying an applicable and reliable test to diagnose OXT-D is an unmet need. Melatonin (MEL) might be a candidate for such a test as it regulates OXT release in animals.

Objective: This work aimed to examine the effects of melatonin on OXT release in HHD compared to healthy controls (HCs) and to describe the psychopathology, sexual function, and quality of life (QoL) and their associations with OXT.

Methods: This proof-of-concept study (NCT05319301) included 20 participants with HHD (11 women) and 20 HCs (11 women). Blood samples were collected over 120 minutes to assess plasma OXT. A linear mixed-effects regression model was used to evaluate the change in OXT in response to MEL in HHD compared to HCs.

Results: MEL significantly increased OXT at T90 vs T0 in HCs compared to the HHD group (difference 14.57 pg/mL 26% increase; 95% CI, 1.90-27.23; $P = .02$). The HHD group had more depression symptoms, alexithymia, impaired sexual function, and worse QoL compared to HCs. The mean percentage change in OXT from T0 to T90 was negatively associated with depressive and alexithymia symptoms in the HHD group and anxiety in both groups.

Conclusion: The reduced OXT response after MEL in HHD supports the existence of an impaired OXT response at least in a subset of patients with HHD. The associations between OXT changes and psychopathology suggest its role in mood and QoL. These findings support further investigation into MEL's role as a diagnostic tool to address OXT-D.

Key Words: hypopituitarism, melatonin, oxytocin, arginine-vasopressin deficiency, pineal gland, stimulation test

Abbreviations: ACTH, adrenocorticotropin; AUC, area under the curve; AVP, arginine-vasopressin; AVP-D, arginine-vasopressin deficiency; BIS, Barrat Impulsiveness Scale; BMI, body mass index; FSFI, Female Sexual Function Index; GH, growth hormone; HCs, healthy controls; HHD, hypopituitarism and hypothalamic damage; IIEF, International Index of Erectile Function; IIH, insulin-induced hypoglycemia; MDMA, 3,4-methylenedioxymethamphetamine; MEL, melatonin; OXT-D, oxytocin deficiency; QoL, quality of life; QoL-AGHDA, Quality of Life Assessment of Growth Hormone Deficiency in Adults; SF-36, Short-Form 36; STAI, State-Trait Anxiety Inventory; TAS-20, Toronto Alexithymia Score.

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Hypopituitarism and hypothalamic damage (HHD) can be associated with multiple comorbidities and sequelae that substantially reduce quality of life (QoL) compared to the general population (1, 2). Increased rates of psychopathology (ie, anxiety, depression), alexithymia (ie, difficulty discerning and explaining one's own emotions), impaired prosocial functioning, and sexual dysfunction persist despite receiving standard hormone replacement, driving the need for additional therapeutic strategies to address the unmet needs of individuals with HHD (3, 4).

Importantly, the role of clinically relevant oxytocin deficiency (OXT-D) in patients with HHD has experienced a growing interest over the last decade, since OXT is involved in several physiological processes including psychological and social behaviors in both sexes (5-14). OXT, like arginine-vasopressin (AVP), is a neuropeptide mainly synthetized in the supraoptic and paraventricular nuclei of the hypothalamus and secreted into the peripheral circulation from the posterior lobe of the pituitary gland, as well as released to the central nervous system (3, 4). Therefore, an impaired OXT system could be present in some patients with HHD and might explain—at least partly—the observed psychopathology.

Initial research evaluating OXT secretion in HHD was limited to a single measurement of OXT (15-18). A more reliable approach using a 1-hour pool of fasting plasma OXT (19) evidenced significantly lower OXT levels in patients with AVP deficiency (AVP-D) who also had greater psychopathology compared to healthy controls (HCs). These initial findings suggested that an OXT deficient system might exist at least in a subset of patients with HHD; however, the difference compared to HCs was too small to be considered a reliable test (15-19). Going a step further searching for a stimulus to diagnose OXT-D, a few stimuli have been investigated in humans so far, including insulin-induced hypoglycemia (IIH) (20-23), hypertonic saline infusion (24), arginine (24), macimorelin (24), angiotensin II (25), 3,4-methylenedioxymethamphetamine (MDMA) (26), glucagon (27), corticotropin-releasing hormone (28), and kisspeptin (29), among others. Nonetheless, most of them were not found to be suitable as a provocative test to diagnose OXT-D, except for IIH, which variably increased OXT in HCs (20-23) but not in patients with AVP-D (20); hypertonic saline infusion, which increased the OXT response in healthy volunteers but with a high variance (24); and MDMA, which induced a remarkable and sustained increase in OXT concentrations in the HC group with no increase in patients with AVP-D (26). In addition, the lack of OXT increase in the AVP-D group was associated with reduced subjective prosocial and anxiolytic effects of MDMA compared to HCs, further supporting the central lack of OXT (26). Nevertheless, a safer and simpler stimulus to reveal an OXT deficient state in patients with HHD is still required since MDMA is not exempt from risks (ie, tachycardia, diaphoresis) and it is contraindicated in some clinical conditions.

Melatonin (MEL) is a neurohormone mainly produced by the pineal gland (30). Most of the physiological functions of MEL are controlled by the hypothalamus and the pituitary gland and mediated by MEL receptors (MT1) widely distributed in the hypothalamus, and colocalized with the oxytocinergic neurons in the paraventricular and supraoptic nuclei (30, 31). Several in vitro and in vivo studies have suggested that MEL might regulate the synthesis and release of OXT, evidencing an anatomic and functional interrelationship between the pineal gland and the hypothalamic-neurohypophysial axis (32). Pinealectomy in animal models was associated with a decrease in the storage of OXT in the neurohypophysis (33-36) and some in vitro and animal studies have shown a stimulating effect of MEL on OXT release (34, 37, 38). Preliminary studies in healthy volunteers showed an increase of OXT secretion following a low dose of oral MEL vs placebo (39). Likewise, MEL increased OXT-dependent myometrial contractions (40). Altogether these findings suggest that MEL, currently used to mitigate jet lag and to treat sleep disorders, may be a good stimulating agent for endogenous OXT secretion and ultimately be applicable as a potential diagnostic test to unmask an OXT deficient state in humans.

Thus, this study aimed to examine plasma OXT dynamics in response to a low dose of oral MEL (1.95 mg) in patients with HHD compared to HCs. To improve our understanding of OXT-D, we also explored the relationships between OXT levels and clinically relevant features of psychopathology, sexual function, and QoL in both groups. Based on prior evidence, we hypothesized that OXT release would be blunted in patients with HHD compared to HCs in response to MEL and, a blunted OXT response to MEL would be associated with greater psychopathology, impaired sexual function, and worse QoL in patients with HHD.

Materials and Methods

Trial Design

This is a proof-of-concept study with a quasi-experimental design conducted in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice Guideline of the International Conference of Harmonisation (41, 42). The study protocol was approved by the institutional review board of the Hospital de la Santa Creu i Sant Pau (protocol code IIBSP-OXI-2021-112), and all participants provided written informed consent to a study physician before any study procedure. The study was registered at ClinicalTrials.gov (NCT05319301).

Study Participants

Twenty-one adult patients with HHD and 20 HCs were included. HCs were of similar age and sex as the patients with HHD. Participants with HHD were primarily recruited from the Research Center for Pituitary Diseases at the Hospital de la Santa Creu i Sant Pau and Hospital Universitari Vall d'Hebron (Barcelona, Spain). HCs were recruited from the surrounding community and from the volunteers' list of the Research Center for Pituitary Diseases that had previously consented to be informed of future research projects.

The pituitary diagnoses were established as per routine clinical practice based on the standard protocol and clinical practice guidelines (2). We included patients with hypopituitarism (>1 anterior pituitary deficit) and at least one sign of hypothalamic damage (AVP-D and/or severe-onset obesity immediately after hypothalamic and pituitary damage and/or hyperphagia and/or brain tumors involving the hypothalamus [ie, craniopharyngioma, germinoma] and/or radiotherapy of the hypothalamic-pituitary area and/or hypothalamic damage visualized by neuroimaging). Patients with HHD were on stable hormone replacement for at least 3 months prior to the study visit (Supplementary Appendix 1 provides the main exclusion criteria (43)).

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Procedures

This study comprised 2 visits: a screening visit to assess eligibility criteria and, if eligible, an outpatient visit.

The screening visit included personal medical history and, in those with HHD, a complete history of the hypothalamic and pituitary disease, a physical examination, and the assessment of baseline biochemical variables, including the hormone profile in patients with HHD to confirm appropriate hormone substitution. If a hormone imbalance was detected, dose adjustments were performed accordingly, and hormone levels were reassessed 6 to 8 weeks later. Before each study visit, urine pregnancy tests were performed on premenopausal female participants.

A 3-hour main visit was conducted at the Center for Drug Research of the Sant Pau's Biomedical Research Institute in a quiet room and was run by one investigator and a research nurse. The main visit started at 8 AM after an at least 8-hour fast, and ad libitum water intake was allowed in patients with AVP-D. We confirmed no alcohol intake nor vigorous physical activity 24 hours before each visit. Participants were asked to take their morning medication after finishing the main visit, except for desmopressin (in patients with AVP-D), as required. We scheduled the study visit of premenopausal female participants in the early to midfollicular phase of their menstrual cycle to minimize the effects of increasing estradiol on OXT levels (8). At the beginning of the visit, participants were asked about their current health status and changes in medication use, and a physical examination was performed (including body mass index [BMI], waist-to-hip ratio, blood pressure, heart rate, and temperature) to confirm eligibility and rule out any potential exclusion criteria not previously detected. Once eligibility was reconfirmed, an intravenous catheter was placed and participants were asked to complete validated questionnaires to assess mood (Beck Depression Inventory-2 [BDI-II] (44, 45) and State-Trait Anxiety Instrument [STAI] questionnaires (46-48)), alexithymia (Toronto Alexithymia Scale 20 [TAS-20] (49)), impulsivity (Barratt Impulsiveness Scale [BIS] (50)), sexual function (Female Sexual Function Index [FSFI] (51) in women and International Index of Erectile Function [IIEF] (52) in men), and QoL (with the Short Form 36 [SF-36] (53) and the QoL Assessment of Growth Hormone Deficiency when applicable [QoL-AGHDA] (54)). A more detailed description of the questionnaires used is provided in Supplementary Appendix 2 (43).

After completion of the questionnaires, a baseline blood sample was drawn (T0) for basic metabolic panel, lipid profile, complete blood count, anterior pituitary hormone assessment (thyrotropin, free thyroxine, luteinizing hormone, follicle-stimulating hormone, testosterone [men], estradiol [women], prolactin, adrenocorticotropin [ACTH], cortisol, growth hormone [GH], insulin-like growth factor-1), and OXT. Low-dose MEL, a compounded product considered a dietary supplement in Spain (1.95 mg), was administered sublingually. Blood samples for OXT measurements were collected after MEL administration over 120 minutes at the following time points: 30 (T30), 60 (T60), 90 (T90), and 120 (T120) minutes. Blood sampling and processing were performed by a research nurse and a study physician, with identical procedures used for the patients and the HCs. Participants were instructed to refrain from using cell phones, listening to the radio, watching TV, and engaging in conversations to avoid any potential increase in OXT concentrations due to social stimulation.

Safety Events

All participants were monitored by the investigator team for treatment-emergent adverse events for the entire duration of the visits. Vital signs (blood pressure, heart rate, and body temperature) were assessed at the beginning and the end of each main visit. All these data were collected in a specific case report form.

Biochemical Measurements

Biochemical and blood parameters were analyzed using routine laboratory methods, and all hormonal measurements were performed using immunoassay methods by the Hormones and Biochemistry laboratory in the Hospital de la Santa Creu i Sant Pau, except for OXT.

Equal aliquots of plasma from each time point for OXT measurement were immediately stored at −80 °C and were run blinded in a single batch at the end of the study by the Neurobiology Laboratory for Brain Aging and Mental Health at Basel University (Switzerland), experienced in measuring OXT (24, 26, 27). The OXT concentration was measured using the Oxytocin ELISA kit (ENZO Life Sciences) (Arbor Assays catalog No. K048-H, RRID:AB_2924717) according to the manufacturer's protocol (55). Intra-assay coefficient of variation was 2.25% and interassay coefficient of variation was 4.45%. In brief, the plasma was diluted at a ratio of 2:1 in 1.5% TFA-H_2O and centrifuged at 17 100 *x g* for 15 minutes at 4 °C. The supernatant was collected. In the next step, the supernatant was loaded onto an Oasis PRiME HLB 96-well plate, 30 mg sorbent (Waters Corporation) and washed with 0.10% TFA-H_2O. Afterwards, the sample was eluted with 95% acetonitrile + 5% of a 0.1% TFA-H_2O solution. Then, the elute was collected and dried in an Eppendorf centrifugal vacuum concentrator 5301. For the measurement, the residue was reconstituted in assay buffer. The reconstituted samples, standards, and controls were plated on the goat anti-rabbit immunoglobulin G microtiter plate and incubated with the OXT conjugate at 4 °C overnight. Thereafter the plate was washed, and the substrate was added. The reaction was stopped after 1 hour and the plate was read at 405 nm. OXT concentration was calculated with a standard curve determined from 4 parameter logistics curve fit.

Statistical Analysis

Statistical analysis was performed using STATA software, version 17.0 (StataCorp LLC). For descriptive analysis, quantitative data were expressed as mean and SEM (gaussian distribution) or as median and interquartile range (25th percentile-75th percentile) (nongaussian distribution); and categorical data as absolute frequencies and percentages. Distribution of continuous data was tested for normality using the Shapiro-Wilk test. Means across groups (HHD vs HCs) were compared using the *t* test or Mann-Whitney *U* test accordingly, and the Fisher exact test was used to compare categorical variables between 2 or more groups.

The primary outcomes measure was the change in OXT concentrations from baseline (T0) to each time point evaluated (T30, T60, T90, T120) over 120 minutes following MEL administration. To analyze OXT level change relative to baseline at each time point post MEL administration, we used a linear mixed-effects regression model (mixed command), including time (5 time points as categorical variable: baseline, T30, T60, T90, and T120), and between-subject

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factor diagnosis (patient with HHD vs HC), and the interactions (two-way) between both factors as fixed effects, and controlled for BMI. 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 OXT area under the curve (AUC) was also calculated using the trapezoidal formula (56). All *P* values were 2-sided, and statistical significance was set at *P* less than .05.

We used Spearman rank correlation coefficients to explore the associations between questionnaire scores and fasting OXT levels, AUC of OXT, and relative change of OXT levels, only when differences in OXT levels were statistically significant between HHD and HCs. All *P* values were adjusted for multiple comparisons using the Holm-Bonferroni method.

Results

Sample Characteristics

Between April 2022 and July 2023, a total of 41 participants (21 patients with HHD and 20 HCs) participated in this quasi-experimental study. One woman with HHD voluntarily abandoned the study after the screening visit. Finally, 40 participants (20 patients with HHD and 20 HCs) completed the study.

Baseline characteristics across groups are summarized in Table 1. HHD and HC groups did not differ in age and sex distribution. The median BMI was higher in the HHD group compared to the HC group, 30.20 (3.79) vs 22.91 (7.34) kg/m^2, respectively ($P = .02$). The remaining demographic and baseline characteristics did not differ between both groups, except for a higher prevalence of psychiatric disorders ($P = .02$) and lower bone mineral density ($P = .01$) in the HHD group in comparison to HCs. No statistically significant differences in the prevalence of psychiatric disorders among patients with HHD with or without GH deficiency were observed as well as in the prevalence of psychiatric treatment used between patients with HHD and HCs.

The clinical history of the hypothalamic and pituitary disease of patients with HHD are summarized in Table 2. The most frequent hypothalamic-pituitary disease was craniopharyngioma in 50% of the participants. Eighty-five percent of the patients with HHD (n = 17) presented with 3 or more anterior hormone pituitary deficits with a mean time since first anterior pituitary deficiency of 17.98 ± 2.37 years, ranging from 1.40 to 38.0 years. Eighty-five percent of participants (n = 17) had AVP-D at study entry for a median time of 14.52 (7.50) years, ranging from 0.52 to 38.0 years.

Ten (91%) women with HHD had central hypogonadism, whereas only 1 woman maintained gonadal axis function preserved but with irregular menses (see Tables 1 and 2). Among women with hypogonadism, 6 (60%) were menopausal and 4 (40%) had regular menses on estrogen/progestogen treatment (3 were treated with estrogen and progestogen at a substitutive dose and 1 was treated with oral contraceptive pills). Regarding healthy women, 4 (36.36%) were menopausal and the remaining had regular menses (of these, only 1 participant was treated with oral contraceptive pills). Mean days since the last menstrual period at the time of the study visit were similar between groups (HCs: 5.67 ± 1.28 days vs HHD: 3.60 ± 1.03 days; $P = .25$). Eight (89%) of the men with HHD presented with central hypogonadism; 4 (50%) were treated with daily transdermal testosterone and the other 4 (50%) received monthly to quarterly intramuscular testosterone. Median testosterone levels were similar between the groups (HCs: 18.30 [4.80] nmol/L vs HHD: 13.20 [12.70] nmol/L; $P = .38$).

Oxytocin Levels in Response to Melatonin

Table 3 shows the response of OXT concentrations over time (T0, T30, T60, T90, and T120) after MEL administration across groups (HHD vs HCs). Baseline OXT concentrations were similar between the groups (HHD 56.74 ± 4.13 vs HCs 57.05 ± 3.99 pg/mL; $P = .86$). In response to sublingual MEL administration, the change in plasma OXT concentrations at T90 vs T0 was greater in the HC group than the HHD group (OXT difference 14.57 pg/mL; 95% CI, 1.90-27.23; $P = .02$) (Fig. 1), with a significant increase in OXT levels at T90 (vs T0) only in the HC group ($P = .003$). Specifically, the mean percentage increase in OXT levels from T0 to T90 in HCs compared to the HHD group was

Table 1. Summary of baseline characteristics across groups (participants with hypopituitarism and hypothalamic damage and healthy controls)

	Participants with HHD (n = 20)	Healthy controls (n = 20)	*P*
Sex (male/female), n (%)	9 (45%)/ 11 (55%)	9 (45%)/ 11 (55%)	≥.99
Age at study entry, years	57.21 (18.46)	45.29 (28.43)	.12
Estrogen status in women, n (%)			.40
Menopausal	6 (54.55%)	4 (36.36%)	
Regular menses	4 (36.36%)	7 (63.64.%)	
Irregular menses	1 (9.09%)	0 (0%)	
Body mass index, kg/m^2	30.20 (3.79)	22.91 (7.34)	.02
Waist-to-hip ratio, iliac	0.91 (0.13)	0.82 (0.20)	.06
Hypertension, n (%)	5 (25%)	2 (10.53%)	.41
Diabetes mellitus, n (%)	2 (10.53%)	2 (10%)	≥.99
Dyslipidemia, n (%)	10 (52.63%)	6 (30%)	.15
Psychiatric disorder, n (%)	8 (40%)	1 (5%)	.02

Numerical data are reported as median and interquartile range (25th percentile-75th percentile).
Abbreviation: HHD, hypopituitarism and hypothalamic damage.

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Table 2. Summary of the clinical history of hypothalamic-pituitary disease in participants with hypopituitarism and hypothalamic damage

Hypothalamic-pituitary disease	Participants with HHD (n = 20)
Diagnosis	
Age at diagnosis, years	36.46 ± 4.10
Hypothalamic pituitary disease, n (%)	
Craniopharyngioma	10 (50%)
NFPA	5 (25%)
Granular cell tumor of pituitary stalk	2 (10%)
Prolactinoma	1 (5%)
Other	2 (10%)
Tumor size, mm	26.25 ± 4.44
Treatment	
Surgery, n (%)	20 (100%)
Type of surgery, n (%)	
Transsphenoidal	10 (50%)
Craniotomy	9 (45%)
Both	1 (5%)
Radiotherapy, n (%)	7 (35%)
Current clinical situation	
≥3 anterior pituitary deficiencies, n (%)	17 (85%)
TSH deficiency, n (%)	19 (95%)
FSH/LH deficiency, n (%)	18 (90%) (10 women and 8 men)
ACTH deficiency, n (%)	15 (75%)
GH deficiency, n (%)	13 (65%)
AVP deficiency, n (%)	17 (85%)
Signs of hypothalamic damage, n (%)	
Suprasellar lesion or involving hypothalamus	19 (95%)
Multiple surgeries at hypothalamic-pituitary level	3 (15%)
Radiotherapy at hypothalamic-pituitary level	7 (35%)
Hypothalamic obesity	4 (20%)

Numerical data are reported as mean ± SEM (gaussian distribution), median, and interquartile range (nongaussian distribution).
Abbreviations: ACTH, adrenocorticotropin; AVP, arginine-vasopressin; FSH, follicle-stimulating hormone; GH, growth hormone; HHD, hypopituitarism and hypothalamic damage; LH, luteinizing hormone; NFPA, nonfunctioning pituitary adenoma; TSH, thyrotropin.

25.85 ± 9.05 vs −1.39 ± 8.93%, respectively (95% CI, 1.30-53.18; $P = .04$). There were no changes in OXT levels in response to MEL at other time points. When analyzing the subgroup of participants with AVP-D (n = 17) in comparison to HCs, the overall results did not change and OXT concentrations at T90 vs T0 were higher in the HC group compared to the HHD group (OXT difference 13.29 pg/mL; 95% CI, 0.95-25.65; $P = .03$). Baseline sodium levels were within the normal range in all participants.

The median AUC of plasma OXT concentrations was lower in the HHD than in the HC group (7003.5 [1511.4] vs 7689.8 [1580.3] pg/mL, respectively; $P = .05$) (Fig. 2).

Adverse Events

MEL administration did not cause any adverse effects and did not affect vital signs.

Table 3. Adjusted mean plasma oxytocin concentrations (pg/mL) after melatonin administration across groups

Time points	Participants with HHD (n = 20) OXT concentrations, pg/mL	HCs (n = 20) OXT concentrations, pg/mL	HCs vs HHD Mean difference[a] (95% CI)
0	56.75 ± 4.13	57.05 ± 3.99	
30	57.62 ± 4.56	61.76 ± 4.66	3.8 (−7.2 to 14.9)
60	55.17 ± 4.56	62.91 ± 4.66	7.4 (−5.5 to 20.4)
90	54.07 ± 4.37	68.95 ± 4.37	14.6 (1.9 to 27.2)
120	60.50 ± 4.24	69.23 ± 4.13	8.4 (−5.6 to 22.5)

Abbreviations: HCs, healthy controls; HHD, hypopituitarism and hypothalamic damage; MEL, melatonin; OXT, oxytocin.
[a]Shows the mean adjusted difference in OXT concentrations (pg/mL) after MEL administration between HCs vs HHD across all postintervention time points (respect to baseline, T0) (two-way interaction between the 2 factors: participant and time point) and controlled for body mass index.

Psychopathology, Sexual Function, and Quality of Life Across Groups

Table 4 shows baseline scores of the questionnaires to assess psychopathology, sexual function, and QoL across groups.

In comparison to the HC group, patients with HHD scored higher on depression symptoms (BDI-II) (8.50 [11] vs 5 [7.50]; $P = .02$) (35% HHD vs 5% HC with mild-moderate depression and 5% HHD vs 0% HCs with severe depression). HHD individuals also had higher scores with regard to symptoms of alexithymia (TAS-20) in the subscales of difficulty identifying feelings (17.30 ± 1.59 vs 13 ± 1.02; $P = .03$) and externally oriented thinking (21.93 [7] vs 18 [4]; $P = .02$).

In addition, participants with HHD, when compared to HCs, had impaired sexual function (FSFI total score in women 15.10 [27.10] vs 28.10 [24.30]; $P = .05$; IIEF total score in men 25 ± 5.32 vs 47 ± 6.63; $P = .02$).

Finally, worse QoL was observed in the HHD group in comparison to the HC group (SF-36 physical functioning 85 [20] vs 97.50 [7.50]; $P < .01$; SF-36 physical health 90 [50] vs 100 [6.70]; $P = .01$; SF-36 bodily pain 66.70 [55.60] vs 88.90 [22.20]; $P = .01$; and SF-36 general health 45 [50] vs 82.5 [20]; $P < .001$).

Psychopathology, Sexual Function, and Quality of Life and Their Associations With Oxytocin

In both groups, the mean percentage change in OXT levels from T0 to T90 was associated with lower anxiety symptoms (HHD: $r = -0.58$; $P = .02$ and HCs: $r = -0.59$; $P = .01$). In the HHD group only, the mean percentage change in OXT levels from T0 to T90 was associated with lower depressive ($r = -0.59$; $P = .01$) and alexithymia total scale ($r = -0.59$; $P = .01$) symptoms. These relationships remained statistically significant after controlling for multiple comparisons. No significant associations were found between the mean percentage change in OXT levels from T0 to T90 and sexual function or QoL in either the HHD or HC groups. Overall baseline OXT concentrations and the AUC of OXT were not significantly associated with psychopathology, sexual function, or QoL in either patients with HHD or in the HCs (Supplementary Table S1 (43)).

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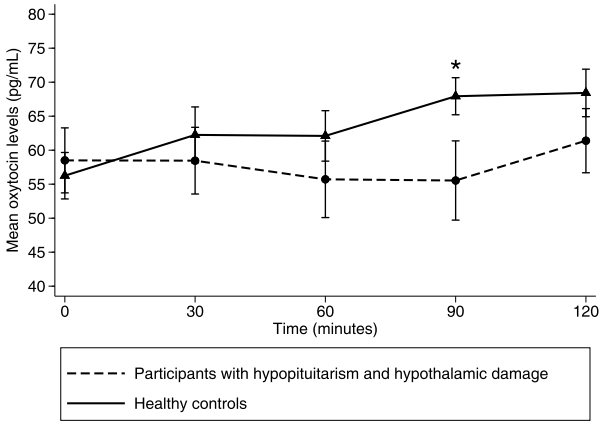

Figure 1. Response of OXT levels over time (from T0 to T120) after MEL across groups (HHD vs HC). Dot represents the mean value of OXT and whiskers represent the SEM range. *P less than .05 (statistically significant change from T0 to T90 between groups). HC, healthy controls; HHD, hypopituitarism and hypothalamic damage; MEL, melatonin; OXT, oxytocin; T; time point.

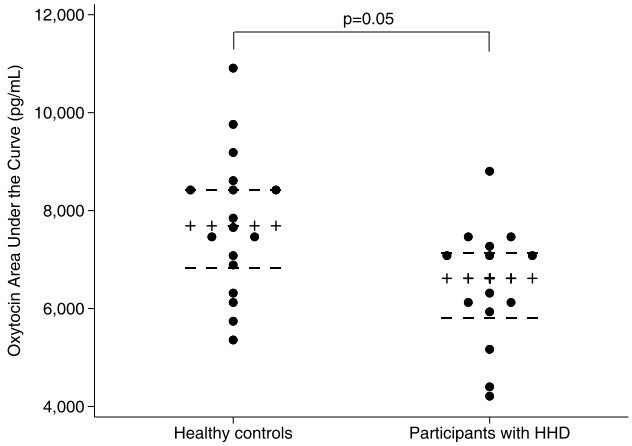

Figure 2. Dot plot comparing the AUC of plasma OXT concentrations after MEL across groups (HC and HHD). Dots represent the AUC of OXT after MEL for each participant, plus signs represent the median of AUC of OXT after MEL across groups (HC and HHD), and dashed lines represent the interquartile range for each median. HC, healthy controls; HHD, hypopituitarism and hypothalamic damage; MEL, melatonin; OXT, oxytocin.

Discussion

To the best of our knowledge, this is the first study that has investigated plasma OXT dynamics in response to low doses of sublingual MEL by comparing patients with HHD to healthy individuals, aimed at identifying a provocative test to unmask OXT-D and clinically characterize an OXT deficient state. We demonstrated lower plasma OXT concentrations after MEL administration in the HHD group in comparison to the control group, supporting the evidence of an OXT deficient state in HHD. However, further studies are required to identify the MEL dose regimen (eg, dose, time, route of administration) to more efficiently magnify the OXT differences from baseline to peak between HHD and HCs before suggesting MEL as a possible test to unmask OXT-D in HHD. The HHD group suffered more psychopathology, impaired sexual function, and worse QoL compared to HCs; notwithstanding, most of them were not in the clinically relevant range. Associations between greater percentage change in OXT levels from T0 to T90 and lower depressive and alexithymia symptoms in the HHD group and lower anxiety symptoms in both groups provide additional evidence for a clinically significant OXT deficient state.

Similar to our clinical observation, some but not all experimental studies found a stimulating effect of MEL on OXT release (34, 37, 38), while others showed either no effects (34, 57) or reduced OXT concentrations following MEL administration (33, 38, 58-63). Such variations could be explained by differences in study species (rodents, mammals vs humans and in vitro or in vivo), dose and regimen employed (pharmacological or supraphysiological vs physiological) (59), time of day when the research was performed (62), as well as in the route of administration (intravenous, oral vs sublingual) (34, 59, 64). Few human studies, mostly in healthy men, have evaluated circulating OXT release following MEL administration, evidencing a dose-dependent secretion of OXT, with high doses of MEL causing a decrease in OXT release, and low doses increasing OXT levels. In an initial study, 10 healthy men received 5 mg of MEL orally for 4 days in the late afternoon vs placebo, and a mild decrease of OXT concentrations after MEL was observed in comparison to the placebo group (63). Similarly, the administration of higher doses (6 and 12 mg) of oral MEL vs placebo in basal conditions did not modify OXT release over 3 hours in healthy men (65). Thereafter, Forsling et al (39) explored the effect of oral MEL given in the afternoon at different doses (0.05, 0.5, and 5 mg) on OXT release over 150 minutes, showing dose-dependent changes in plasma OXT levels. While the lowest dose did not show a change in OXT levels, the dose of 0.5 mg showed a stimulatory effect and 5 mg an inhibitory effect on OXT levels. In particular, the 0.5 mg dose produced a peak of OXT of around 30% after 60 minutes compared to baseline.

According to the aforementioned studies, we chose a low dose of sublingual MEL (1.95 mg) to examine peripheral OXT secretion in HCs and in participants with HHD. In line with Forsling et al (39), we observed an increase of the AUC of plasma OXT concentrations in healthy individuals that peaked at 90 minutes, with a 26% increase of OXT compared to baseline, whereas, as expected, we did not observe any increase in OXT in participants with HHD. The difference in the time point when the peak was achieved −60 minutes in Forsling's vs 90 minutes in our study might be attributed to dose differences, pharmacokinetics (oral vs sublingual), the time of day when the study started (14:30 in Forsling's study vs 8:00 in the present study), as well as variability in OXT levels. It could be possible that MEL at doses above 2 mg as approved by drug agencies for sleep disorders would have had a greater effect on circulating OXT release. Nevertheless, a better understanding of the mechanisms involved (eg, receptor downregulation or desensitization, neurochemical interactions, feedback inhibition) in dose-dependent effects of MEL on OXT release is crucial to select the optimal dose regimen to be used as a provocative test for OXT-D.

The detailed mechanisms by which the pineal gland and MEL interact with the OXT system and increase OXT release remain unclear, although different mechanisms have been proposed: (i) OXT-containing fibers extend into the pineal gland, facilitating anterograde and retrograde axonal

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Table 4. Baseline scores of questionnaires of study participants across groups

Questionnaires	Participants with HHD (n = 20)	HCs (n = 20)	*P*
Beck Depression Inventory-2	8.50 (11.0)	5 (7.50)	.02
STAI-State subscale[a]	12.50 (11.50)	9 (7)	.13
STAI-Trait subscale	17 (23.50)	14 (10.50)	.40
TAS-20	49.22 ± 3.81	41.40 ± 2.33	.09
TAS-20 Difficulty describing feelings	13.20 ± 1.02	10.95 ± 0.88	.11
TAS-20 Difficulty identifying feelings	17.30 ± 1.59	13.0 ± 1.02	.03
TAS-20 Externally oriented thinking	21.93 (7)	18 (4)	.02
BIS	36.48 ± 3.07	33.25 ± 2.60	.43
BIS Cognitive impulsivity	12 ± 1.01	11.85 ± 1.06	.92
BIS Motor impulsivity	11.01 ± 1.44	11.50 ± 1.10	.79
BIS Nonplanning impulsivity	11 (10.50)	12 (7)	.71
FSFI[b]	15.10 (27.10)	28.10 (24.30)	.05
FSFI Desire	2.84 ± 0.44	3.27 ± 0.32	.43
FSFI Arousal	2.40 (4.50)	4.50 (4.50)	.09
FSFI Lubrication	2.48 ± 0.75	3.71 ± 0.77	.27
FSFI Orgasm	2 (4.80)	4.80 (6)	.07
FSFI Satisfaction	2.69 ± 0.72	4.44 ± 0.42	.05
FSFI Pain	3.20 (4.80)	5.20 (6)	.16
IIEF[c]	25 ± 5.32	47 ± 6.63	.02
IIEF Erectile function	8.89 ± 2.60	18.11 ± 3.70	.06
IIEF Intercourse satisfaction	0 (5)	9 (9)	.03
IIEF Orgasmic function	0 (6)	10 (3)	<.01
IIEF Sexual desire	5.33 ± 0.87	6.22 ± 0.87	.40
IIEF Overall satisfaction	6 (2)	8 (2)	.17
SF-36 score			
SF-36 Physical functioning	85 (20)	97.50 (7.50)	.003
SF-36 Role limitations due to physical health	90 (50)	100 (6.70)	.01
SF-36 Bodily pain	66.70 (55.60)	88.90 (22.20)	.01
SF-36 General health	45 (50)	82.50 (20)	<.01
SF-36 Vitality	59.40 (25)	68.80 (25)	.13
SF-36 Social	87.50 (43.75)	100 (12.50)	.06
SF-36 Emotional	95.85 (50)	100 (12.50)	.13
SF-36 Mental health	77.50 (32.50)	82.50 (15)	.70
QoL-AGHDA (n = 13)	8.77 ± 2.19	—	—

Data are reported as mean ± SEM (gaussian distribution) and as median (25th percentile-75th percentile) (nongaussian distribution).
Abbreviations: BIS, Barrat Impulsiveness Scale; FSFI, Female Sexual Function Index; HCs, healthy controls; HHD, hypopituitarism and hypothalamic damage; IIEF, International Index of Erectile Function; QoL-AGHDA, Quality of Life Assessment of Growth Hormone Deficiency in Adults; SF-36, Short-Form 36; STAI, State-Trait Anxiety Inventory; TAS-20, Toronto Alexithymia Score.
[a]Available in 19 HCs.
[b]Only in women (11 HHD and 11 HCs).
[c]Only in men (9 HHD and 9 HCs).

transport between the hypothalamus and the pineal gland that may promote interaction between both neurohormones (34, 37, 66). Further, MEL receptors are found in the median eminence and hypothalamic nuclei (67). (ii) The pineal gland has been shown to have effects on the 24-hour rhythmic variations of the neurohypophysial hormones (68, 69). Indeed, pinealectomy and the exposure to constant light (that inhibits MEL) change the daily rhythm of posterior pituitary hormone secretion (65, 70, 71). (iii) MEL could interfere with the metabolism of some intermediate neurotransmitters (serotonin, glutamate, noradrenaline, dopamine, and prostaglandins) in the hypothalamus that are also involved in the release of neurohypophysial hormones (33). (iv) MEL can cross the brain-blood barrier and, due to its lipophilicity, could also act on cells of the neurohypophysial system through a non–receptor-mediated manner independent of the effect on its receptors (60, 72).

In clinical practice, the evaluation of an endocrine deficiency (ie, GH or ACTH) often requires a provocative test since a single hormone measurement may overlap with physiological states and does not always rule out or confirm a hormone deficiency. Currently, despite the increasing evidence of a possible OXT deficient state in patients with HHD, a validated, safe, and feasible provocative test to rule out OXT-D does not exist. Although we observed a significant increase of OXT concentrations of 26% from T0 to T90 in HCs compared to no change (−1%) in HHD, this increment was mild compared to the reported 650% of OXT increase (at 180 minutes) after MDMA administration or 200% (at 45 minutes) after an IIH test (22, 26) or 50% after hypertonic saline (at 150 minutes) (24). In addition, high interindividual variability in OXT response was observed, indicating that MEL at this dose regimen is not a suitable candidate for a provocative test to unmask OXT-D. Therefore, further research is needed to determine whether different doses or time of MEL administration could induce more powerful increments in OXT release. Importantly, the MEL test is inexpensive, easy to administrate, well tolerated, and accepted by patients and with no risks compared to MDMA or IIH.

Worse psychopathology, sexual function, and QoL have been widely observed in patients with HHD in comparison to healthy individuals (18, 19, 26). Growing evidence suggests that an OXT deficient state could be involved in this poorer mental health and QoL in patients with hypopituitarism and AVP-D (16, 17, 26, 73). Although most of the questionnaires' scores observed in this study were not in the clinical range, we detected some significant negative associations between the OXT dynamics (mean percentage change in OXT levels from T0 to T90) and anxiety symptoms in both groups and depressive symptoms and alexithymia only in the HHD group. One explanation for this lack of association between the mean percentage change in OXT levels from T0 to T90 and depressive symptoms and alexithymia in the HC group could be the lower variability in the questionnaires' scores in comparison to the HHD group. We did not detect any statistically significant association between the OXT dynamics and some psychological, sexual function, and QoL tests in both groups.

Our study had some limitations, but also strengths. This is a proof-of-concept study with a strict protocol testing a potential novel and safe stimulus (MEL) to unmask an OXT deficient state in patients with HHD. While the results confirm prior evidence for an OXT deficient state in HHD and suggest that MEL might be a tool to diagnose OXT-D, the overall effects of MEL on OXT secretion with the current protocol are modest. In addition, the lack of a placebo group does not allow us to state with certitude that MEL was the single driver

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of OXT increase. It is possible that different MEL doses may exert a stronger effect on OXT secretion. Therefore, additional doses and regimens of MEL administration should be evaluated to test the efficacy of MEL as an OXT stimulus to warrant its applicability in clinical practice. On the other hand, due to the low molecular weight of OXT and low plasma concentrations in nonpregnant humans, measurement and interpretation of OXT levels are still a major challenge and there is no consensus about the most appropriate assay and sample preparation to use (74). For these reasons, OXT samples were collected following a rigorous and identical protocol for each participant and were measured in a single batch to reduce variability in an experienced laboratory. The sample size, although sufficient to detect relevant differences in OXT release after MEL between HHD and HCs, did not allow us to perform subgroup analysis (sex or pituitary diseases). Finally, some human studies but not all have shown low OXT levels in patients with some psychiatric disorders (ie, posttraumatic stress disorder, depression, and autism spectrum disorders) (75-77). Nevertheless, in our study, OXT levels did not differ at any time point among patients with HHD with or without a psychiatric disorder.

In summary, patients with HHD have a diminished response of plasma OXT concentrations after a low dose of sublingual MEL compared to HCs, supporting the existence of an impaired OXT response at least in a subset of patients with HHD. The associations between OXT changes and psychopathology suggests its role in mood and QoL. These findings support further investigation into MEL's role as a diagnostic tool to address OXT-D.

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Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

Clinical Trial Information

Clinical trial registration number NCT05319301 (registered March 17, 2022).

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