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Review

The Oxytocin System and Implications for Oxytocin Deficiency in Hypothalamic-Pituitary Disease

Anna Aulinas[1,2] **and Elizabeth A. Lawson**[3,4]

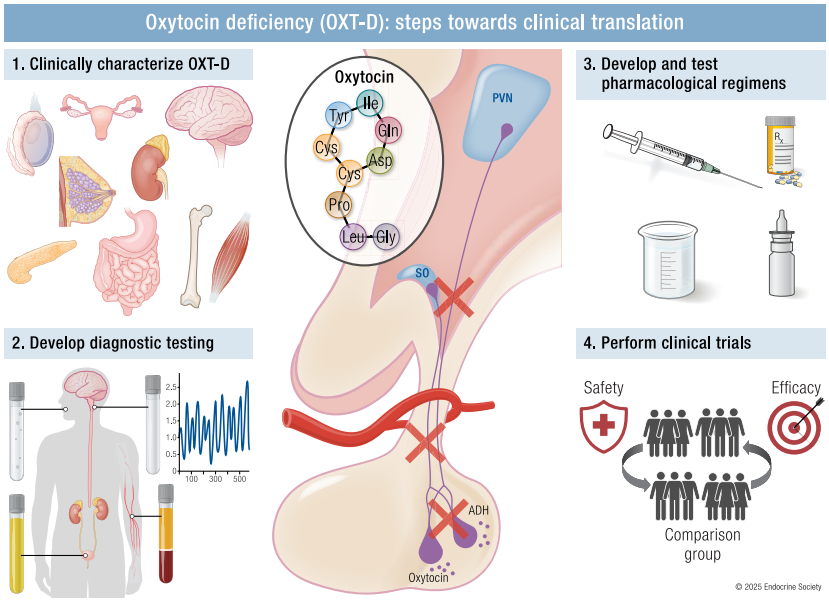
[1]Endocrinology Department, Hospital de la Santa Creu i Sant Pau, IR-Sant Pau, CIBERER U747 (ISCIII), EndoERN, 08041, Barcelona, Spain
[2]Faculty of Medicine, University of Vic-University Central of Catalonia (UVic-UCC), 08500, Vic/Manresa, Catalonia, Spain
[3]Neuroendocrine Unit, Division of Endocrinology, Department of Medicine, Massachusetts General Hospital, 02114, Boston, USA
[4]Department of Medicine, Harvard Medical School, 02115, Boston, USA

Correspondence: Anna Aulinas, MD, PhD, Endocrinology Department, Hospital de la Santa Creu i Sant Pau, IR-Sant Pau, CIBERER U747 (ISCIII), EndoERN, C Mas Casanovas, 90, 08041 Barcelona, Spain. Email: aaulinas@santpau.cat; or Elizabeth A. Lawson, MD, MMSc, Neuroendocrine Unit, Division of Endocrinology, Department of Medicine, Massachusetts General Hospital, 50 Staniford St, Ste 750B, Boston, MA 02114, USA. Email: ealawson@mgh.harvard.edu.

Abstract

Oxytocin (OXT) is a hypothalamic-posterior pituitary hormone with multiple effects, ranging from regulation of energy homeostasis to bone health and psychological well-being, in addition to its well-known effects on labor and lactation. Patients with hypothalamic and pituitary damage have a higher risk for medical and psychiatric comorbidities despite standard-of-care hormone replacement, and a clinically relevant OXT-deficient state has been identified in patients with arginine vasopressin deficiency (formerly known as central diabetes insipidus) in the last decade. Therefore, OXT deficiency in patients with hypothalamic and pituitary damage is an emerging field. While intranasal oxytocin is readily available to patients, it is not Food and Drug Administration approved in the United States and the quality of compounded formulations is unclear. In addition, more research is needed to establish the safety and efficacy of OXT-based therapeutics in patients with hypothalamic and pituitary damage before recommending treatment. This review summarizes the current knowledge of the OXT system, OXT deficiency in other clinical conditions, and relevance to patients with hypothalamic and pituitary damage. We highlight emerging data supporting OXT deficiency in hypothalamic-pituitary disease, diagnostic challenges, development of therapeutic strategies, and future research directions to advance the field.

Graphical Abstract



Key Words: oxytocin, hypopituitarism, hypothalamic damage, arginine-vasopressin deficiency

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Abbreviations: ACTH, adrenocorticotropin; AN, anorexia nervosa; APDs, anterior pituitary deficiencies; ASD, autism spectrum disorder; AVP-D, arginine-vasopressin deficiency; AVPRs, AVP receptors; BBB, blood-brain barrier; BMD, bone mineral density; BMI, body mass index; CCK, cholecystokinin; CNS, central nervous system; CP, craniopharyngioma; CRH, corticotropin-releasing hormone; CSF, cerebrospinal fluid; DDAVP, desmopressin; EIA, enzyme immunoassay; FDA, US Food and Drug Administration; FERT, facial expression recognition task; GLP-1, glucagon-like peptide 1; HCs, healthy controls; HI, hypothalamic involvement; HPDs, hypothalamic and pituitary diseases; HSA, hip structural analysis; IM, intramuscular; IV, intravenous; LC-MS, liquid chromatography–mass spectrometry; MDMA, 3,4-methylenedioxymethamphetamine; mRNA, messenger RNA; NTS, nucleus tractus solitarius; OXT, oxytocin; OXT-D, oxytocin deficiency; PTSD, posttraumatic stress disorder; PVN, paraventricular nuclei; PWS, Prader-Willi syndrome; QoL, quality of life; RAGE, receptor for advance glycation end products; RCT, randomized clinical trial; RIA, radioimmunoassay; RMET, reading the mind in the eyes task; SON, supraoptic nuclei.

ESSENTIAL POINTS

- Hypothalamic and pituitary diseases (HPDs) are complex disorders associated with hormonal deficiencies and multisystemic comorbidity despite standard-of-care hormone replacement
- OXT is a neurohormone that mediates a range of physiologic processes in both sexes, and recent early-stage clinical research has focused on the potential value of OXT-based therapies for clinical conditions including neuropsychiatric and metabolic disorders
- In the last decade, emerging research provided evidence for a clinically significant OXT deficiency (OXT-D) in patients with HPDs
- Ongoing research is focused on clinical characterization of OXT-D, methods for diagnosis, and therapeutic value of OXT administration
- Optimal translation of early findings to improved clinical care will require improved understanding of OXT secretory dynamics and functions in humans, development and validation of measurement and diagnostic methods, novel formulations and OXT receptor agonists, and well-designed clinical trials

Hypothalamic-pituitary diseases (HPDs) are rare, complex disorders that require multidisciplinary and lifelong care due to chronic hormonal dysfunction and multisystemic comorbidities. Pituitary hormone dysfunction (excessive or deficient secretion) is most frequently a complication of benign pituitary or nonpituitary tumors located in the hypothalamic-pituitary region (1, 2). Other causes of pituitary deficiencies include infiltrative and/or malignant disease, neurosurgery, radiotherapy, head trauma, and/or congenital abnormalities (2). Anterior pituitary hormone deficiencies, including central hypothyroidism, hypoadrenalism, growth hormone deficiency, and hypogonadism, are well established with known clinical complications and guidelines regarding standard-of-care hormone replacement and monitoring. Similarly, deficiency of posterior pituitary hormone arginine-vasopressin (AVP-D; formerly known as central diabetes insipidus) is clinically characterized and treated with hormone replacement. However, whether there is a clinically relevant deficiency of oxytocin (OXT-D), which like AVP is produced in the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus and released centrally as well as to the periphery via the posterior pituitary, with widespread physiologic effects, has been until recently unexplored.

OXT-D in patients with HPDs is of clinical importance as these individuals are at increased risk for medical and psychiatric comorbidities despite standard-of-care hormone replacement. Patients with HPDs have increased cardiovascular risk, poor bone health, greater psychopathology, social isolation, and impaired quality of life (QoL), leading to more sick days at work and premature mortality (3-6). Although OXT is well known for its role in inducing labor and lactation in women, recent research has demonstrated that OXT exerts a wide spectrum of central and peripheral effects in both sexes, ranging from regulation of energy homeostasis and cardioprotection to bone health and psychological well-being (7, 8). Emerging evidence in the last decade supports the presence of a clinically significant OXT-D state in HPDs, particularly in those with AVP-D. Efforts to develop diagnostic testing are under way and will facilitate further characterization of OXT-D and identification of individuals who could potentially benefit from OXT replacement. The aim of this review is to summarize current knowledge of the OXT system, OXT-D in other clinical conditions and relevance to patients with HPDs, and emerging data supporting OXT-D in HPD. The review will focus on what is known about clinical features of this new disorder, diagnostic challenges, therapeutic avenues, and future research directions to advance the field.

Oxytocin: A Pleiotropic Hypothalamic-Pituitary Hormone

Overview of the Oxytocin System

An understanding of the physiology of the OXT system is essential to elucidate the clinical relevance of OXT-D, as well as potential strategies for diagnosis and treatment. OXT, like AVP, is a highly conserved 9-amino acid neuropeptide, and the two hormones differ only by 2 amino acids. OXT and AVP are produced in overlapping regions of the SON and PVN of the hypothalamus and secreted by parvocellular neurons directly into multiple brain regions and the spinal cord, and via magnocellular neurons that simultaneously project both to forebrain regions and to the posterior pituitary gland, where they are stored until release to the peripheral circulation (9, 10). Based on this anatomy, patients with HPDs presenting with AVP-D, most commonly due to suprasellar lesions like craniopharyngiomas and germinomas or surgery in the hypothalamic-pituitary region, are presumably at highest risk for OXT-D (Fig. 1).

OXT, AVP, and their respective carrier proteins (neurophysin I and neurophysin II) evolved from genes located on chromosome 20p13 and are separated by 12 kilobases of intergenic sequences (11, 12). Both are stored with their neurophysin carrier protein in secretory granules in the posterior pituitary gland, outside of the blood-brain barrier (BBB) and are independently and episodically released into the bloodstream in response to specific stimuli, where they separate from neurophysins and circulate to target organs (11, 13). In addition to neurophysin II, copeptin, the C-terminal

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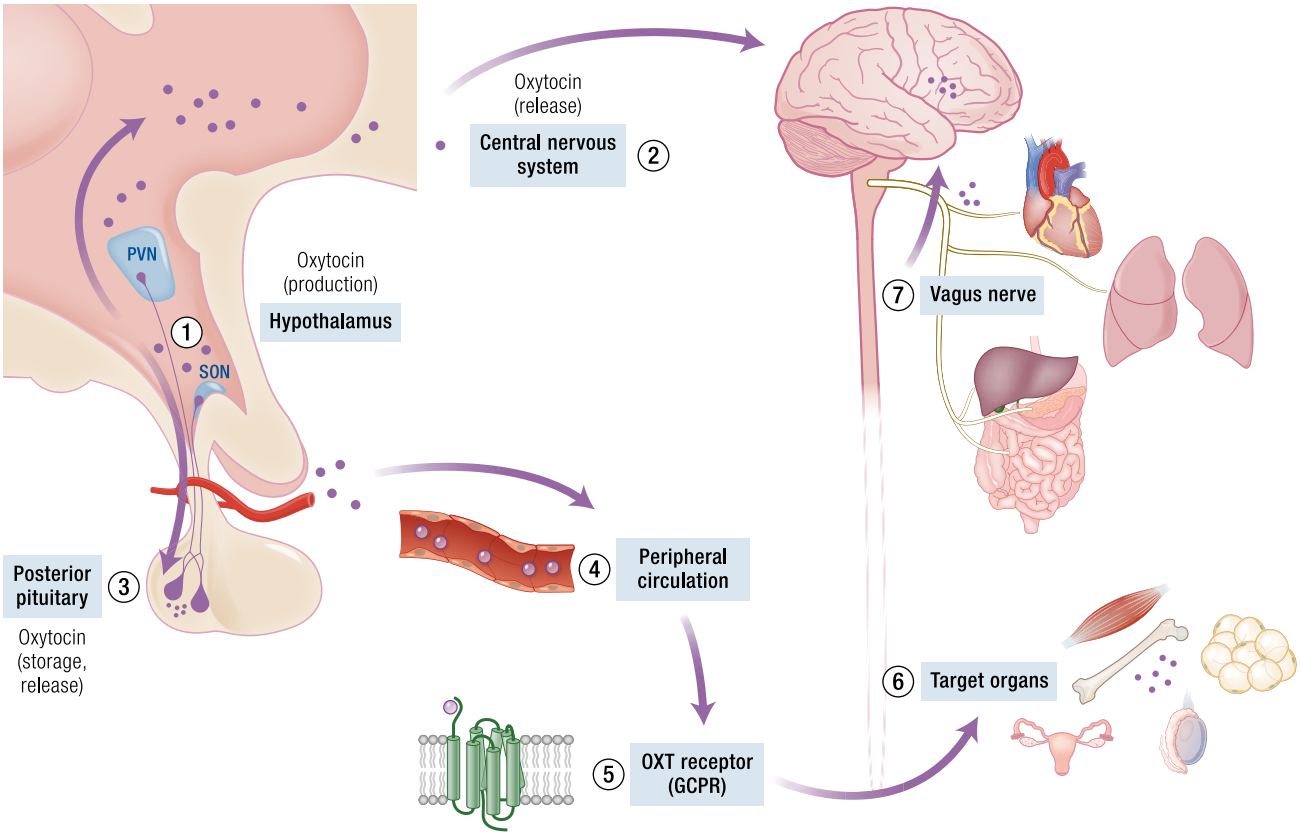

Figure 1. Schematic diagram of the oxytocin (OXT) system. (1) OXT is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and (2) secreted into brain regions via parvocellular neurons and (3) to posterior pituitary gland via magnocellular neurons. OXT is stored in the posterior pituitary gland until (4) release to the peripheral circulation. (5) OXT binds to OXT receptors (OXTR; class-I G protein–coupled receptor superfamily, GCPR) (6) on target organs where OXTR is distributed (eg, reproductive system, gastrointestinal tract, adipose tissue, skeletal muscle, bone, myocardium, vascular endothelium, vagus nerve). (7) The vagus nerve functions as a point of entry for circulating OXT signals to reach the brain.

segment of the precursor protein of AVP, is released to peripheral circulation in equimolar concentrations to AVP and serves as a good surrogate marker of AVP secretion (14). The neurophysin I-OXT concentration ratio in the posterior pituitary gland is 1:1, similar to the copeptin-AVP ratio (15). Once OXT is released into the peripheral circulation, it is bound to carrier proteins, primarily immunoglobulin G and albumin (9, 16-18). Endogenous soluble receptor for advance glycation end products (esRAGE) also binds OXT in circulation (19).

Plasma OXT has a short half-life, around 3 to 5 minutes, and is quickly degraded by endothelial and circulating aminopeptidases (oxytocinase) (20), whereas OXT half-life in cerebrospinal fluid (CSF) is about 28 minutes (21, 22). OXT concentrations in extracellular fluid of the hypothalamic SON and CSF are around 100- to 1000-fold higher than in plasma (23). Furthermore, synthesis of OXT has been documented in peripheral sites such as bone, kidney, adipose tissue, gastrointestinal tract, and myocardium, where OXT acts in an autocrine and/or paracrine manner (24-27).

A single human OXT receptor (OXTR) has been identified (11). It has recently been shown that the OXTR can heterodimerize with other G protein–coupled receptors, such as ghrelin (GHS-R1a) or serotonin (5-HT2AR, 5-HT2CR) receptors, though the downstream effects have not yet been uncovered (28, 29). OXTR is encoded on the human chromosome 3p26.2 and is a member of the class-I G protein–coupled receptor superfamily (11, 30, 31). OXTR and AVP receptors (AVPRs) have structurally common features, and both neuropeptides can bind to both receptors, especially in the extracellular binding domain (32). Nevertheless, OXT in comparison with AVP has about 10-fold higher affinity for the OXTR, while the AVP concentration required to act as a partial agonist at the OXTR is up to 100-fold higher than that of OXT (33, 34). Regulation of *OXTR* gene expression and signaling is complex. Epigenetic changes, environmental factors, hormones, inflammatory signals, and other molecules and cofactors can regulate gene expression levels and/or functionality of the OXTR (35-37). For example, estrogen and interleukin-6 are key modulators of *OXTR* gene expression (38, 39), whereas cholesterol and magnesium affect OXTR functionality, by increasing the OXT binding capacity and affinity state of OXTR (11, 40-43). The mechanisms of such regulation, especially in vivo, are not well understood. Most of the studies examining the physiology and functions of the OXT system have been performed in animal models, mainly rodents, and the clinical translation of these findings to humans is not clear. Determining OXTR distribution across tissues has been challenging due to lack of reliable OXTR antibody to perform immunohistochemistry, given cross-reactivity with AVPRs (44, 45). Overall, investigations have reported that distribution of OXTR expression differs across species, suggesting that some OXT functions might be species specific (11). For example, OXTR and detectable levels of OXT messenger RNA (mRNA) are present in testes of mammalian species, but not in mice (46, 47). In humans, wide distribution of

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OXTR in many tissues and organs, including the female reproductive system (myometrium, endometrium, corpus luteum, ovaries), male reproductive system (testis, prostate gland), breasts, adrenal glands, bone, myocardium, vascular endothelium, kidneys, thymus, gastrointestinal tract, muscle, adipose tissue, and brain (eg, ventromedial hypothalamus, nucleus basalis of Meynert, ventral tegmental area, spinal trigeminal nucleus in brainstem) have been reported (11, 48, 49). Using an optimized OXTR autoradiography technique with higher selectivity of radioligands in postmortem human and primate central nervous system (CNS), a recent study showed dense OXTR expression in the spinal trigeminal nucleus, consistent with the vagus nerve functioning as a point of entry for peripheral OXT signals to reach the brain (45, 50). While there is evidence that OXT regulates release of prolactin, gonadotrophins, and adrenocorticotropin (ACTH) via portal vessels connecting posterior and anterior lobes (51-53), there are no published reports of OXTR in the human adenohypophysis other than a conference abstract showing OXTR mRNA across cell types in a single postmortem adult pituitary (54). Application of novel techniques for the identification of OXTR in humans will be useful in advancing our knowledge of the OXT system in health and disease.

Oxytocin Measurement: Utility and Limitations

The measurement and interpretation of OXT levels in human biological samples are major challenges in OXT research and translation to clinical care. Even though endogenous OXT concentrations have been assayed for more than 50 years, accurate measurement of OXT is difficult due to its low molecular weight and low plasma concentrations in nonpregnant humans. The appropriate methodology to use is still a matter of debate (55-57), and it is not yet clear exactly what the OXT assays are measuring (58). Most human studies measure circulating plasma, serum, or salivary OXT concentrations, and measurement in other biological samples, such as urine, hair, and CSF, has also been reported (59-62). The relationships between OXT concentrations across biological specimens are not yet understood (17, 57, 63-65). Similar to cortisol, salivary OXT has been widely used in research studies in humans; however, correlations between salivary and plasma OXT concentrations are weaker than for cortisol (<0.6 vs >0.9) (56, 66).

The most commonly used assays for OXT measurement are enzyme immunoassays (EIA) and radioimmunoassays (RIA), although liquid chromatography–mass spectrometry (LC-MS) and less conventional approaches have been tested (67-73). Antibodies used to perform immunoassays can also bind to other peptides in plasma, which may result in artificially elevated levels of OXT (57). LC-MS methods are under development and could provide better specificity. However, current LC-MS methods may not be sensitive enough to detect low circulating OXT levels found in nonpregnant humans, and this may be particularly problematic when measuring OXT in deficient states (74, 75). A reduction/alkylation step to free protein-bound OXT has recently been recommended to improve analyte detection sensitivity in LC-MS (72). Substantially different OXT concentrations with mean levels ranging from less than 1 pg/mL (extracted RIA) to greater than 1000 pg/mL (EIA) have been reported in human/serum samples depending on the assay and whether an extraction procedure was performed to remove interferences (57, 67-69, 76-80).

Preanalytic steps may influence peptide measurement, yet there is no consensus on how to collect and process blood samples for OXT. Physiologic considerations (eg, time of day, social stimuli) should be taken into account and standardized in research studies. Serum and plasma have both been used to measure OXT with a lack of evidence favoring either approach, and there are very limited data on whether a preservative (eg, protease inhibitor) could be useful. A recent review recommended the use of aprotinin to prevent OXT degradation, as well as an extraction step prior to analysis to remove unrelated interferences that could otherwise lead to falsely high measured OXT levels (55, 56). A recent study showed that EIAs without extraction measured similar levels of urinary OXT between wild-type and OXT null mice, supporting that peptides other than OXT are measured (58). The authors employed a new method (mixed-mode cation-exchange solid-phase extraction) to minimize interference in null mice, raising the question whether prior conclusions based on urinary OXT measurements need to be reassessed (58).

In addition to removing interferences, extraction also likely discards alternative OXT forms and degradation products, which may be biologically active and/or represent biomarkers of OXT levels (81). Moreover, sample extraction may remove protein-bound OXT, resulting in artificially low OXT levels (55, 58, 81). Levels of OXT are often undetectable following extraction in blood samples of humans, which may be a challenge when studying individuals with OXT-D (58, 67, 82, 83). While some studies have found no correlation between extracted and unextracted OXT levels, a positive correlation has been reported (67, 84).

In populations with low OXT levels, various studies assessing OXT in response to stimuli or using an integrated measure have used different methods (RIA, EIA; extracted, unextracted) and shown lower OXT levels in clinical groups and correlations with relevant clinical end points (84-89). While currently available methods are used to understand the OXT system in healthy and disease states, there is a critical need to determine optimal preanalytic methods and develop and validate assays to measure OXT. Research is also needed to identify which proteins other than OXT (eg, metabolized products of OXT) are measured by current assays and to determine their biological relevance and clinical utility.

Neurophysin I, the carrier protein of OXT from the hypothalamus to the posterior pituitary gland, could be a surrogate marker for OXT (56, 90). Neurophysin I is secreted in equimolar concentrations to OXT but has a longer half-life (11). Therefore, neurophysin I levels, which reflect OXT release over time, are higher than OXT levels. A recent study reported that the two measures are highly correlated (90). Although neurophysin I measurement offers advantages relative to measuring OXT itself (eg, higher stability in plasma, longer half-life, requirement of less time-intensive extraction protocols), the longer half-life may not capture acute fluctuations in OXT levels (90, 91). Further research will be important to validate neurophysin I assays and determine whether neurophysin I could be used as a clinical biomarker for OXT, similar to copeptin for AVP.

Effects Beyond Childbirth: What We Have Learned From Oxytocin-Deficient Genetic Models and Pharmacologic Studies

In addition to its classic role in regulating parturition, maternal caregiving behaviors and lactation (52, 92, 93), OXT

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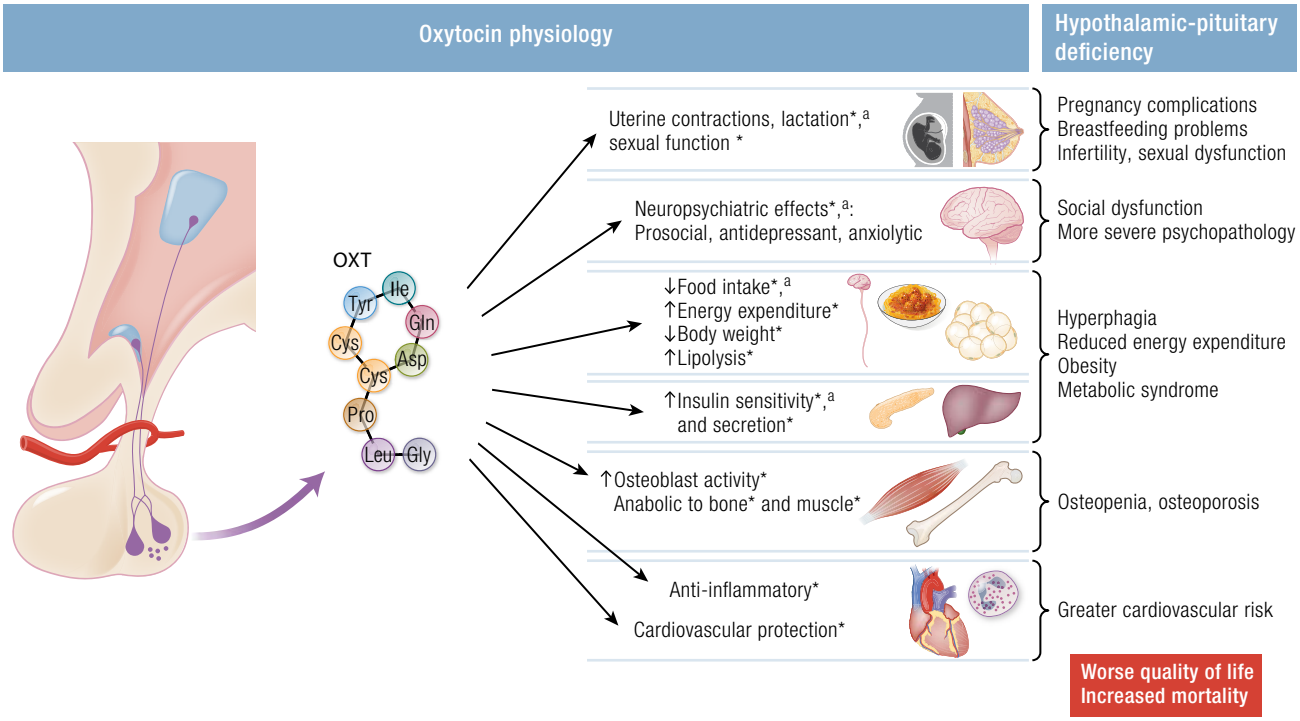

Figure 2. Physiologic effects of oxytocin and relevant features of hypopituitarism. *There is evidence in animal models. [a]There is some evidence in humans.

Table 1. Phenotype of oxytocin knockout ($OXT^{-/-}$ and $OXTR^{-/-}$) mice models

$OXT^{-/-}$ and $OXTR^{-/-}$ mouse phenotype	
Lactation effects	Difficulties in breastfeeding
Psychological effects	Greater anxiety-related behavior Social recognition deficits Heightened aggressive behavior Repetitive behaviors
Metabolic effects	Obesity Reduced energy expenditure Impaired thermoregulation
Bone and muscle effects	Reduced bone formation Severe osteoporosis Defects in muscle regeneration

Abbreviations: OXT, oxytocin; OXTR, oxytocin receptor.

mediates a range of physiologic processes and exerts a wide spectrum of central and peripheral effects in both sexes (Fig. 2). Recent early-stage clinical research has focused on the potential value of OXT-based therapies in numerous clinical conditions, including neuropsychiatric (eg, autism spectrum and anxiety disorders), metabolic (eg, obesity and diabetes mellitus) and bone (eg, osteopenia/osteoporosis) diseases in children and adults (94-99).

Genetic knockout mice lacking OXT or the *OXTR* gene, models of OXT-D, have helped to elucidate physiological functions of the oxytocinergic system (100, 101) (Table 1). $OXT^{-/-}$ mice develop abnormal parturition, sexual dysfunction, greater social-related anxiety and abnormal social behaviors, late-onset obesity, impaired thermoregulation, metabolic derangements, sarcopenia, and osteoporosis, among others (100, 102-115). These findings have set the foundation for human research studies aimed at determining whether the OXT-D phenotype in mice translates to humans. Some of the signs and symptoms of knockout models of OXT resemble the clinical phenotype of patients with HPDs, and it is plausible that OXT-D might partially contribute to the comorbidities observed in HPDs.

Reproduction and sexual functioning

OXT induces parturition in females and is commonly administered to induce labor in women. An early study reported that $OXT^{-/-}$ mice underwent normal parturition and showed maternal caregiving behaviors, suggesting redundant pathways for these critical functions (116). For example, OXT-like peptides could bind to OXTR, or other endogenous uterotonic hormones (eg, prostaglandins or placental corticotropin-releasing hormone [CRH]) might be upregulated in the context of OXT-D (117). However, a recent experiment suggests that OXT is essential to maternal and neonate survival in childbirth. In this study, nearly all singly housed $OXTR^{-/-}$ mice and their offspring died in childbirth, while cohousing prevented mortality due to extraction and cleaning of offspring by the nonpregnant female mouse (115). $OXT^{-/-}$ mice also experienced severe difficulties with lactation, supporting an essential role for OXT in successful nursing (116, 118). Along these lines, intranasal (IN) OXT has been shown to be effective at producing milk ejection (119). $OXT^{-/-}$ mouse models did not show deficits in sexual behaviors (120, 121), but ablation of PVN OXT neurons abolished penile erection (103), consistent with data demonstrating oxytocinergic neuron projections to spinal cord facilitating penile erection and sexual activity (122). OXT injected in some brain areas (eg, amygdala, hippocampus, ventral tegmental area) induced penile erection in rats (123). In humans, circulating OXT levels increased during orgasm in both sexes (124),

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and postintercourse OXT levels were lower in anorgasmic compared to orgasmic women (125); a single dose of IN OXT (24 IU) did not have any effects on the facilitation of sexual behavior in women (126). Similarly, a single dose of 24 IU of IN OXT vs placebo in men did not affect sexual arousal or orgasm induced by an erotic film and had no effects on sexual drive, arousal, and penile erection (122, 127). Whether exogenous OXT facilitates sexual behavior in humans is not still clear and warrants further investigation with different OXT doses, formulations, and/or OXTR agonists.

Psychological and social behaviors

Preclinical studies have demonstrated a key role for OXT in the regulation of anxiety, mood, and social behaviors (128, 129). Transgenic $OXT^{-/-}$ and $OXTR^{-/-}$ mice showed greater anxiety-related behavior in response to psychogenic provocation than their wild-type counterparts that were reversed after intracerebroventricular administration of OXT, providing evidence for anxiolytic effects of OXT (100, 104). Moreover, $OXT^{-/-}$ and $OXTR^{-/-}$ mice showed impaired social memory, increased resistance to change of learned behavioral patterns, and heightened aggressive behaviors compared to $OXT^{+/+}$ mice that could be rescued by administration of intracerebroventricular OXT (105, 107, 108, 130, 131).

Pharmacological studies in animal models have shown that anxiogenic and stressful stimuli activate the OXT system, leading to OXT release into the brain and decreased activation of the hypothalamic-pituitary-adrenal axis, reduced anxiety and depressive symptoms, as well as prosocial behaviors (132-134). In humans, some but not all studies have shown low OXT levels in patients with posttraumatic stress disorder (PTSD), depression, and autism spectrum disorders (ASDs), and relationships between plasma OXT levels as well as OXTR polymorphisms with anxiety symptoms have been demonstrated (129, 135-144). Several studies have examined effects of IN OXT in social anxiety disorder, with some but not all reporting improvements in anxiety symptoms (145-148). IN OXT administration also attenuated hypothalamic-pituitary-adrenal axis reactivity in response to stress, with more pronounced effects in stressful situations and in clinical populations (ie, with depression, substance abuse, neurodevelopmental disorders), according to a meta-analytic review (149). IN OXT improved depressive symptoms in mice and in preliminary studies of humans with major depressive disorder (150-152). IN OXT has also been evaluated to promote social behaviors in autism with mixed results, which might be due to differences in methodology (eg, drug formulation and regimen, end points assessed) or OXTR sensitivity (153-155). A recent randomized controlled trial (RCT) of 8 weeks IN OXT in adults with obesity reported an improvement in mental health-related QoL; however, the study was not powered for this specific end point and this finding requires further investigation before suggesting OXT as a beneficial therapy for psychiatric indications (99).

Energy metabolism

OXT is also involved in the regulation of energy homeostasis and metabolism (156). Adult-onset obesity has been reported in $OXT^{-/-}$, $OXTR^{-/-}$, and $Sim1^{+/-}$ (transcription factor essential for PVN formation, resulting in an 80% reduction of OXT mRNA expression) mice, characterized by greater fat mass and, in some cases, type 2 diabetes (106, 157, 158). The primary mechanisms of weight gain appear to be decreased sympathetic tone to adipose tissue, impaired thermoregulation, and decreased energy expenditure, rather than changes in food intake (106, 157, 159, 160), though an increase in sucrose consumption has also been reported (102, 106, 109, 110, 158, 161, 162). In studies of rodents and rhesus monkeys, activation of PVN OXT neurons increased resting energy expenditure and stimulated brown adipose tissue thermogenesis (112, 163, 164). Studies have consistently shown that central or peripheral OXT administration in obese rodents and nonhuman primates reduces food intake, increases energy expenditure, and decreases body weight (97-99, 165-169).

Exogenous OXT reduces caloric intake in animal models and humans through several mechanisms (97-99, 165-169). OXT neurons project to mesolimbic reward pathways, and OXT has been shown to preferentially reduce reward-driven caloric consumption, for example, of sucrose solution and high-carbohydrate/high-fat chow in rodents, and chocolate cookies in humans (109, 170-173). OXT neurons also extend to the arcuate nucleus, a key hypothalamic brain region in appetite regulation, that expresses OXTR and stimulates the melanocortin-leptin pathway inducing satiation (174, 175). OXT additionally participates in the control of gut-brain signaling (176, 177). Gut-released peptides, such as satiety hormones cholecystokinin (CCK) and secretin, activate central and peripheral OXT release by mechanisms involving several pathways (eg, direct activation of Fos expression in OXT neurons; indirect stimulation through afferent vagus nerve, which signals to the hypothalamus via noradrenergic pathways), resulting in increased satiety and smaller meal size (178-181). Similar to studies in animal models, human investigations of IN OXT demonstrated that OXT modulates functional magnetic resonance imaging activation of reward and homeostatic neural circuitry (176, 182, 183). In addition, IN OXT in men with overweight/obesity increased activation of cognitive control brain regions in response to images of high-calorie foods, and improved impulse control in a behavioral task (176, 184), identifying another potential mechanism for OXT effects on eating behavior in humans.

A postmortem hypothalamic tissue study of patients with type 2 diabetes observed a reduction in OXT neuron density in the PVN compared to nondiabetic controls, suggesting that OXT has a role in glucose metabolism (185). In vitro studies showed that OXT stimulates release of insulin and glucagon from the pancreas (186). There is also evidence that OXT increases insulin sensitivity in animal models by inhibiting dipeptidyl peptidase-4 and increasing glucose transporter type 4 expression (187, 188). Studies in diet-induced obese rodents showed that central or peripheral OXT administration improved insulin sensitivity and glucose tolerance (97, 189, 190). However, OXT administration for 2 weeks to leptin-deficient *ob/ob* mice worsened fasting glucose and glucose tolerance (191). Some interventional studies in nondiabetic humans found that OXT administration increased β cell-responsiveness to glucose administration and modestly decreased glucose peak in adults, while another study using a similar design did not demonstrate any effect of OXT on glucose metabolism in men with obesity or type 2 diabetes (97, 192-195). Well-designed studies are needed to better understand the role of endogenous OXT and effects of exogenous OXT on glucose homeostasis in humans, including in patients with diabetes.

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Few studies have examined chronic IN OXT effects on energy homeostasis and metabolism in humans. While a pilot RCT of 8 weeks IN OXT (24 IU 4 times daily before meals and bedtime) in adults with obesity (9 of whom received OXT) showed a mean of 8.9 ± 5.4 kg weight loss (97), a larger RCT in 61 adults with obesity showed no effect of the same regimen of IN OXT on body weight (primary end point), resting energy expenditure, or body composition. Compared to placebo, OXT reduced caloric intake at an experimental breakfast test meal, but not in self-reported food diaries (99). There were no effects on markers of glucose homeostasis. The fact that the metabolic effects of OXT in animal models do not consistently translate to humans may be due to differences across species or experimental design. The optimal way to increase OXT signaling (eg, formulation with allosteric modulators or selective OXTR agonist; short-acting burst vs longer-acting exposure; dosing regimen) is not clear. More research is needed using different dosing regimens and/or OXT-based therapeutics to determine whether increasing OXT signaling could be useful in treating metabolic disorders (196).

Body composition and musculoskeletal health

OXT null mice also support a role for OXT in modulating body composition, as these animals displayed increased adipocyte number, defects in muscle regeneration, and premature sarcopenia that improved with systemic OXT administration (197). $OXT^{-/-}$ and $OXTR^{-/-}$ mice also had reduced bone formation and consequently severe osteoporosis with marked reductions in vertebral and femoral trabecular bone that were improved by direct intraperitoneal injection of OXT, indicating a key role for OXT in skeletal homeostasis (111, 113, 161). Moreover, OXT administration restored bone loss in ovariectomized mice (113), indicating effects that are independent of estrogen, consistent with preclinical data showing direct effects of OXT on bone cells (26, 84, 198).

In vitro studies have shown that OXT shunts human multipotent adipose-derived stem cells toward osteoblast vs adipocyte lineage (161, 199). OXT also acts on OXTR expressed on osteoblast cells, resulting in osteoblast differentiation and increased bone formation (113). OXTR is additionally expressed in osteoclasts, where OXT has opposing effects to (i) stimulate osteoclastogenesis, and (ii) inhibit osteoclast resorptive function (111, 113, 114, 161). Studies in animal models have demonstrated that OXT administration increases lipolysis and lipid utilization and reduces lipogenesis, while promoting myogenesis and osteogenesis (113, 114, 161, 164, 168, 169, 191, 197, 199-205).

There are few data regarding OXT effects on body composition in humans. One small RCT of 8 weeks IN OXT (24 IU 4 times per day) in older adults with sarcopenic obesity showed an improvement in lean muscle mass (169). A larger RCT of adults with obesity receiving IN OXT (24 IU 4 times per day) showed no effects on body composition (99). Human studies have shown positive weak to moderate correlations between circulating OXT levels and bone mineral density (BMD) and microarchitecture (87, 206-208). Some of these studies included only females, raising the question of whether OXT is simply a marker of bone anabolic estradiol (84, 206). However, correlations between circulating OXT and bone health were also shown in men (209) and women independent of estradiol levels (85). There are no published trials to date that have investigated the effects of OXT administration on bone health in humans. A study of IN OXT to promote bone health in children with autism is underway (NCT05754073).

Other effects of oxytocin

OXT has anti-inflammatory properties, acting to suppress the production of inflammatory cytokines such as interleukin-6, reduce the production of reactive oxygen species by neutrophils, and decrease oxidative stress (210-212). These properties may translate to improved tissue repair and healing. For example, in rats OXT administration improved diabetic polyneuropathy as well as burn-induced gastric inflammation (213, 214). Strong evidence in animal models suggests that OXT modulates nociception and pain response promoting analgesic actions via central and peripheral actions (215, 216). Preliminary data on the effects of OXT on pain in humans are less consistent but suggest that OXT decreases pain sensitivity (215, 217, 218). Further research is needed to determine whether OXT has analgesic properties in humans.

OXT may also exert cardioprotective effects through multiple complementary mechanisms, including inhibition of atherosclerosis, reduction in inflammatory cytokines, and stimulation of endothelial and smooth muscle cell regeneration, as well as through improved glucose metabolism (193, 219-223). In vitro, OXT improved viability and function of ischemic cardiomyocytes (223). OXT administration also reduced the size of myocardial infarction induced in rabbits (224, 225). More studies are warranted to determine the role of OXT as a potential anti-inflammatory and/or cardiovascular therapeutic.

In summary, beyond the classic role of OXT inducing parturition and lactation, OXT has a wide range of physiological functions that have primarily been demonstrated in preclinical studies. A deficiency of this multifunctional neurohormone might therefore be expected to contribute to clinical morbidity. While there is great interest in the potential of OXT-based therapeutics for human disease, clinical research is still nascent. Most studies have used IN OXT, with variable response likely due to factors discussed in Therapeutic Challenges and Potential.

Oxytocin Deficiency in Humans Without Hypopituitarism

Oxytocin Deficiency in Human States of Energy Deficit

Given the role of OXT in the regulation of energy balance, OXT levels and dynamics have been extensively evaluated in human states of energy deficit, such as anorexia nervosa (AN) and oligomenorrheic athletes with low body fat. Recent research has focused on the hypothesis that in the context of an energy deficit, OXT levels may be suppressed to signal the need for resources but with negative clinical consequences of OXT-D. AN is a complex psychiatric disorder associated with endocrine alterations, such as central hypogonadism, growth hormone resistance, hypercortisolemia, and euthyroid sick syndrome (226). Several small studies showed low OXT levels in CSF (N = 5) and failure of peripheral OXT response to known stimuli (estradiol and insulin-induced hypoglycemia, n = 7) compared to controls (89, 227, 228). Both in AN and separately, in female athletes

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with oligomenorrhea and low body fat, overnight OXT (integrated measure of repeated overnight samples) levels were low compared to controls, even when controlling for estradiol levels (84, 85). Moreover, lower OXT levels in these energy-deficit states were associated with lower markers of energy stores (eg, body mass index [BMI], leptin), lower resting energy expenditure, lower BMD, structural integrity and estimated strength, and more severe anxiety and depressive symptoms as well as more severe social emotional functioning difficulties (79, 85, 88, 229, 230). Some studies suggested recovery of the OXT system with weight recovery in AN, supporting the notion that OXT suppression is an adaptive mechanism to counterbalance energy deficiency in AN (85, 228, 231). However, one study showed low OXT levels in women with past AN at normal weight or overweight compared to controls with no eating disorder history (79). This may be explained by persistently aberrant eating behaviors, energy deficit due to higher personal weight set point, scarring from undernutrition, or a trait characteristic that preceded development of AN (228). It is also possible that characteristics of AN, for example, comorbid disorders of anxiety, mood, and/or social emotional functioning, could result in low OXT levels (232).

Evidence for an OXT deficient state in AN characterized by worse mental health and bone health, along with trials showing that IN OXT might modulate anxiety, social behaviors, and functioning, have led to research studies examining the effects of IN OXT in AN and its potential as a therapeutic. Results of these studies provided inconclusive results (233-236). While some single-dose IN OXT studies (dose range, 24-40 IU) reported potential benefit, for example, in attenuating attentional vigilance to pictures of food, excessive body fat, and expressions of disgust compared to placebo, others did not show effects of IN OXT on recognition or expression of emotions in AN (233-235, 237). A meta-analysis of studies examining the effects of single-dose IN OXT vs placebo on attentional bias, emotion recognition, and threat processing in AN showed no significant effects of IN OXT in AN compared to healthy controls (HCs) (238, 239). IN OXT administration reduced salivary cortisol in response to food compared to placebo in AN, but no effects on subjective anxiety were observed (236, 240). An initial RCT evaluated the effects of 18 IU twice-daily IN OXT vs placebo for 4 to 6 weeks in 33 patients with AN during a hospital-based nutritional refeeding program. This study demonstrated that IN OXT compared to placebo reduced eating concern and cognitive rigidity and consequently improved nutritional rehabilitation in AN (236). However, a follow-up RCT by the same group including 61 female inpatients with AN during refeeding for 4 weeks did not observe any differential effect of 18 IU twice-daily IN OXT vs placebo. Moreover, and contrary to single-dose studies, no reductions in salivary cortisol and anxiety in response to a high-calorie snack were observed (241).

Several reasons might explain differences across studies, such as variance in disease severity (psychopathology scores, BMI differences), associated comorbidities (psychiatry, endocrine), dose regimens, and treatment duration. Differences in response could also be explained by variability in OXTR sensitivity, either due to undernutrition or genetic variation, as OXTR polymorphisms have been linked to eating disorder pathology and the effects of IN OXT (232, 242, 243). Therapeutic Challenges and Potential discusses other reasons for inconsistent results of studies using IN OXT.

While AN is a disorder associated with a relative OXT deficient state, the suppression of OXT may be a protective physiologic adaptation to undernutrition. Therefore, any investigations of therapeutics aimed at increasing OXT signaling in AN must be cautious and monitor participants closely given the potential harmful effects of decreasing caloric intake or weight in this population. The clinical characteristics associated with OXT deficient state in AN, for example, greater severity of anxiety and depressive symptoms, impaired social cognition, and worse bone health, are informative for other disorders of OXT-D, such as those with HPDs.

Autism

Based on extensive evidence that OXT is involved in social functioning, research on ASDs has focused on the OXT system. ASD is a neurodevelopmental disorder characterized by mild to severe social impairments that affect functioning and QoL (244). It has been hypothesized that deficient OXT signaling might contribute to core features of ASD, and there is evidence linking the OXT system to ASD pathophysiology (244). In addition, individuals with ASD are at higher risk for low BMD and bone quality, leading to higher fracture risk (245). While this is likely multifactorial, low OXT levels could contribute.

A recent meta-analysis found lower plasma OXT levels in children, but not adults, with ASDs compared to healthy individuals (139). Variations in OXTR expression, OXTR polymorphisms, and increased OXTR methylation (associated with decreased OXTR expression) have been identified in ASDs (246-249). Based on these findings, OXT has been considered as a promising potential therapy to improve social difficulties in ASD, with studies of IN OXT showing mixed results. A study of IN OXT to promote bone health in children with ASDs is under way (NCT05754073).

Single-dose studies of 24 IU IN OXT have in general shown improvements in social behaviors, such as emotion recognition, in ASDs (250-252). Neuroimaging studies suggest that IN OXT activates frontal, temporal, and limbic regions involved in decision-making, emotional experience, and reward, which could potentially improve core symptoms in ASDs (251, 253, 254). While these studies suggest a potential benefit of IN OXT in ASDs, the results of longer (5-24 weeks) RCTs using different dosing regimens (8-80 IU twice daily in most studies) have been inconclusive (153-155, 255). Several RCTs in young adults with ASDs showed therapeutic potential of IN OXT vs placebo. One RCT in 106 adults with ASDs using 48 IU OXT daily vs placebo for 6 weeks showed that IN OXT reduced repetitive behavior (using the Autism Diagnostic Observation Schedule) (256). Another study including 19 patients with ASDs using the same dose regimen reported that IN OXT improved social cognition and QoL (257). Recent meta-analyses of RCTs evaluating the effects of IN OXT vs placebo in children with ASDs showed a significant effect of OXT in improving the core symptoms of narrow interest and repetitive behaviors compared to placebo (96). Another multilevel meta-analysis including RCTs of both single-dose or longer-term trials (8-48 IU daily) in children and adults with ASDs found that overall IN OXT compared to placebo had beneficial effects on social functioning (258). The largest RCT in children with ASDs (290 participants; 8-80 IU IN OXT daily in divided dose twice daily) showed

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no significant effects on social or cognitive functioning over 24 weeks (154). There are a number of potential reasons for discrepant results in studies of IN OXT in autism. Some studies used compounded IN OXT, which is not well regulated and does not require the rigorous testing that Food and Drug Administration (FDA)-approved medications undergo. The optimal dose and frequency of IN OXT has not been established. ASD is genetically heterogeneous, and it is possible that some types of ASD involving abnormalities in OXT pathways may have greater benefit from OXT. Recent studies have examined predictors of response. OXTR single-nucleotide variations in individuals with ASDs predicted neural and behavioral response to IN OXT (259). Further, higher circulating OXT levels were associated with larger treatment effects of IN OXT in ASD (260).

Preliminary evidence showing benefit of IN OXT in some individuals with autism are encouraging, and future research should focus on selecting the optimal drug and dosing regimen and identifying predictors of response. Patients with HPDs, like those with autism, are at risk for social isolation and impairments in social functioning. Whether those with HPDs and OXT-D have more autism traits is not yet known.

Oxytocin-Deficient State in Patients With Hypothalamic and/or Pituitary Damage

Relevance of Oxytocin-Deficient State in the Context of Hypothalamic and/or Pituitary Damage

Hypopituitarism is a rare disease, with an estimated prevalence of 21 to 42 cases per million individuals, that is associated with high health and cost burden despite standard-of-care hormone replacement (2, 5, 261-264). HPD often results in pituitary hormone deficiencies, as well as multiple sequelae such as sexual dysfunction, neuropsychological symptoms (higher rates of anxiety, depression, impaired social functioning), altered patterns of eating behavior, obesity, metabolic disorders, and osteoporosis, among others, leading to lower QoL (6, 265-270). As mentioned earlier, these comorbidities are also observed in OXT-D states in animal models, and several of these (eg, neuropsychological symptoms, altered patterns of eating behavior, osteoporosis) have been identified in OXT-D states (eg, energy deficit) in humans (see Fig. 2).

Men and women with hypopituitarism have higher rates of infertility requiring assisted reproductive techniques (271-274). The reason for higher infertility rates in HPDs is multifactorial (ie, anterior and/or posterior pituitary hormone deficiencies and hyperprolactinemia). While some reports showed a high risk of pregnancy complications, such as postpartum hemorrhage, miscarriage, cesarean delivery, and newborns small for gestational age, in women with hypopituitarism (275, 276), recent studies reported successful pregnancies without major complications under appropriate hormone replacement therapy (273, 277). However, there are few data on pregnancies in women with AVP-D. Case reports suggest that labor can proceed normally in these women without requiring administration of OXT for induction, but there was a failure to lactate, consistent with the OXT-D mouse phenotype (116, 273, 278-280). In women with AVP-D, deficiency of prolactin or OXT-D could explain the inability to breastfeed. In some cases, OXT administration or cesarean delivery were required for delivery, and/or postpartum hemorrhage occurred, suggesting the possibility that endogenous OXT secretion was insufficient (273, 276, 278). In addition, patients with HPDs, in particular those with concomitant hypogonadotropic hypogonadism, commonly report decreased libido and sexual dysfunction (281, 282). Replacement of gonadal steroids improve sexual function; however, hypogonadal symptoms often do not return to baseline (2).

Patients with HPDs suffer from social and emotional dysfunction that can lead to relationship difficulties and social isolation. The reason for this is not fully understood, but likely involves multiple mechanisms including hypothalamic damage, hypopituitarism, as well as obesity (267). Greater psychopathology, including increased severity of anxiety, depression, and alexithymia (difficulty in identifying and expressing one's emotions) has been consistently reported in patients with HPDs (267, 268, 270, 283-287). HPDs may also result in disrupted impulse control and impulsive behaviors, leading to hyperphagia and aggressiveness (267, 288). Deficient OXT signaling might be expected to contribute to these symptoms in HPDs given the effects of OXT in improving mental health, impulse control, and social behaviors, and reducing food intake (176, 289).

More than half of individuals who undergo conventional therapies for sellar tumors (located in the hypothalamic-pituitary region) develop hyperphagic obesity (290). Hypothalamic obesity is associated with lower functional capacity and QoL, and increased risk for metabolic syndrome, cardiovascular disease, and increased mortality (4, 286, 291-293). The cause of hypothalamic obesity is multifactorial, attributed to damage to brain regions involved in control of energy homeostasis, including the PVN, where OXT—a key modulator of eating behavior and body weight—is produced. This can result in hyperphagia and reduced energy expenditure. Among those with HPDs, the extent of hypothalamic damage and presence of AVP-D were predictors of risk for developing hypothalamic obesity. AVP-D has also been linked to increased mortality risk among patients with pituitary deficiencies (286, 287, 294).

Hypopituitarism is also associated with less favorable body composition and poor bone quality (osteopenia and osteoporosis) linked with skeletal fragility and fracture risk (293, 295, 296). Anterior pituitary hormone deficiencies (eg, growth hormone deficiency, hypogonadism) or excess (eg, acromegaly, Cushing), hyponatremia secondary to desmopressin (DDAVP) therapy, and/or supraphysiologic glucocorticoid use, are important contributing factors (295, 297). Given the role of OXT in promoting musculoskeletal health over body fat, OXT-D would also be expected to contribute to this phenotype.

The pathophysiology underlying the development of comorbidities in patients with HPDs is clearly multifactorial, and although available treatments provide clinical benefits, sequelae do not completely resolve and persist lifelong (2, 298-300). Several factors might affect the extent and severity of comorbidities observed in HPDs, such as age of onset, etiology, surgical results, therapies received, and number and type of pituitary hormone deficiencies, among others (301, 302). Whether OXT-D contributes to sequelae in HPDs is under investigation. An OXT-D state seems plausible in individuals with HPDs, and OXT-D could contribute to the development of comorbidities and lower QoL.

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Evidence for Low Oxytocin Levels in Patients With Hypothalamic and/or Pituitary Damage and its Clinical Relevance

Based on the emerging data highlighting the important functions of OXT in both sexes and related long-term comorbidities occurring in hypopituitarism, research in the last decade has focused on OXT in patients with HPDs. Many studies have included patients with craniopharyngioma, an intracranial tumor located in the hypothalamic-suprasellar region often resulting in hypothalamic damage, pituitary deficiencies including AVP-D, and other clinical features of hypothalamic syndrome, including hyperphagia and hypothalamic obesity even before surgical intervention (3, 270, 288, 290-292, 301, 303-305). Hypothalamic damage is also associated with difficulties with emotion regulation, social functioning, and cognition (288). It is possible that damage to OXT neurons or downstream OXTR-expressing neurons from mass effect or treatment contributes to clinical features (288). Several studies of patients with craniopharyngiomas and/or hypopituitarism have provided preliminary evidence for a clinically relevant OXT-D state in HPD (86, 283, 306-309). Moreover, a handful of studies in patients with hypopituitarism due to brain tumors located in the hypothalamic and pituitary regions (mainly craniopharyngiomas) or hypothalamic diseases such as Prader-Willi syndrome (PWS) have provided early evidence for clinical improvement after exogenous OXT or carbetocin (longer-acting OXTR agonist) administration (310-313).

Table 2 summarizes studies evaluating endogenous OXT secretion in HPDs. Some studies have provided evidence for diminished peripheral OXT release in patients with HPDs, including lower baseline salivary OXT levels, lower 1-hour pool of plasma OXT levels, or a blunted salivary or plasma OXT response to a stimulus (eg, physical activity, 3,4-methylenedioxy-methamphetamine [MDMA]) (283, 306-308, 314-316).

In most studies, fasting plasma or salivary OXT levels were similar in patients with HPDs and control groups (283, 306, 309), which is not surprising, since there is often overlap in single time point hormone levels assessed in patients with pituitary deficiencies, for example, adrenal insufficiency or growth hormone deficiency, and HCs (2, 262). Residual function of hypothalamic structures and/or synthesis of OXT in other neuronal regions (ie, medial preoptic area, lateral amygdala) could in some cases explain similar baseline OXT levels in HPDs and healthy individuals (30). In one study, a subgroup of patients with postoperative damage exclusively to the anterior hypothalamus, where OXT-producing SON and PVN are located, had lower salivary fasting OXT levels than patients with damage both to the anterior and posterior hypothalamus or without hypothalamic involvement (309).

Early investigations measuring salivary OXT levels compared patients with craniopharyngioma or hypopituitarism to HCs. While studies showed lower basal or stimulated salivary OXT levels in patients with HPDs compared to HCs, subgroup analyses of AVP-D individuals, who would be most likely to have OXT-D, did not show differences from patients with anterior pituitary deficiencies (APDs) only. However, small sample sizes may have limited the ability to detect differences (306, 309). Several of these studies demonstrated a link between OXT levels and clinically relevant end points. Lower salivary OXT levels predicted deficits in the ability to identify facial expressions (307), and a blunted salivary OXT response

Table 2. Studies evaluating oxytocin levels and clinical outcomes in patients with hypothalamic and/or pituitary diseases

References	Study design and population	Intervention and measures	OXT levels	Clinical outcomes and relationship to OXT	OXT sample (assay)
Daubenbüchel 2016 (309)	Cross-sectional case-control study in adults • 34 with CP with or without HI • 73 HC	• OXT levels before and after standardized breakfast	• Baseline OXT levels were similar in CP with or without preoperative HI • Postsurgical anterior HI had lower fasting OXT levels compared to patients with posterior HI or without HI	• CP with anterior HI showed less variability in OXT levels in response to feeding • Changes in OXT levels in response to meal correlated negatively with BMI	Saliva (extracted EIA)
Daughters 2017 (307)	Cross-sectional case-control study in adults • 20 with hypopituitarism and AVP-D • 15 adults with hypopituitarism without AVP-D • 20 HC	• OXT levels before 2 empathy tasks: RMET and FERT	• Hypopituitary patients with or without AVP-D had lower BL OXT than HCs	• Hypopituitary patients with or without AVP-D performed worse on RMET and FERT compared to HC • OXT levels predicted performance on easy items of RMET only in AVP-D group	Saliva (EIA)
Gebert 2018 (306)	Cross-sectional case-control study in adults • 26 with CP • 26 sex- and age-matched HCs	• Fasting OXT levels before and after physical exercise	• No differences in OXT levels before physical exercise between CP vs HCs • Patients with HI only had lower BL OXT levels • After exercise: blunted OXT-release in CP compared to HCs	• Higher BL OXT related to higher trait anxiety • Blunted OXT-release linked with higher state anxiety • OXT measures not associated with depression, empathy	Saliva (extracted RIA)

(*continued*)

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Table 2. Continued

References	Study design and population	Intervention and measures	OXT levels	Clinical outcomes and relationship to OXT	OXT sample (assay)
Eisenberg 2019 (316)	Cross-sectional case-control study in adults • 18 with hypopituitarism (9 with AVP-D) • 20 HCs	• Single time point OXT levels • Questionnaires to evaluate depression, QoL, stress, emotion recognition tasks	• OXT levels highest in patients with AVP-D compared to controls • Longer duration of hypopituitarism associated with higher OXT	• No significant differences in questionnaire scores between groups • Plasma OXT did not predict any questionnaire score	Plasma (extracted EIA)
Aulinas 2019 (283)	Cross-sectional case-control study in adults • 20 with hypopituitarism and AVP-D • 20 with APD only • 22 HCs	• Frequent sampling of blood every 5 min for OXT over 1 h fasting • Questionnaires to assess psychopathology and QoL	• Single time point OXT similar among groups • 1-h pool of OXT lower in AVP-D group compared to APD and HCs	• Greater psychopathology (depression, anxiety, and alexithymia) and worse mental health QoL in AVP-D than in HCs	Plasma (extracted RIA)
Daubenbüchel 2019 (314)	Cross-sectional case-control study in adults • 34 with CP with or without HI • 73 HCs	• OXT levels before and 60 min after standardized breakfast	• Results reported in (309)	• Decrease in postprandial compared with fasting OXT associated with: ◦ adverse eating behavior in whole sample ◦ higher BMI in CP only	Saliva (extracted EIA)
Brandi 2020 (315)	Cross-sectional case-control study in adults • 13 with CP • 23 HCs	• OXT levels before and after exercise • Self-report questionnaires and a FERT	• Results reported in (306)	• Blunted OXT release in response to exercise in CP associated with higher autistic traits and reduced levels of hedonia for social encounters • CP had more difficulties in FERT • Gaze behavior positively associated with OXT increase in response to exercise across all participants	Saliva (extracted RIA)
Aulinas 2021 (86)	Cross-sectional case-control study in adults • 17 with hypopituitarism and AVP-D • 20 with hypopituitarism without AVP-D	• Fasting single timepoint and 1-h pooled blood samples for OXT • BMD and HSA using dual-energy x-ray absorptiometry	• Results reported in (283)	• Mean BMD *Z* scores were lower in participants who had lower single time point OXT levels (below median rather than above) • Lower single timepoint OXT in AVP-D correlated with lower BMD *Z* scores and worse hip geometry and strength variables	Plasma (extracted RIA)
Atila 2023 (308)	Randomized, double-blind, placebo-controlled crossover study in adults • 15 with AVP-D • 15 HCs matched by age, sex, BMI	• OXT levels at several time points time 0-300 min after oral MDMA (100 mg) vs placebo	• OXT AUC 82% higher in HCs than in patients with AVP-D	• Increase in OXT in HCs was associated with subjective prosocial, empathic, and anxiolytic effects, whereas only minimal effects were observed in patients with AVP-D	Plasma (extracted EIA)

Abbreviations: APD, anterior pituitary deficiencies; AUC, area under the curve; AVP-D, arginine-vasopressin deficiency; BL, baseline; BMD; bone mineral density, BMI, body mass index; CP, craniopharyngioma; EIA, enzyme immunoassay; FERT, facial expression recognition task; HCs, healthy controls; HI, hypothalamic involvement; HSA; hip structural analysis; IT, intertrochanteric; MDMA, 3,4-methylenedioxymethamphetamine; OXT, oxytocin; QoL, quality of life; RCT, randomized clinical trial; RIA, radioimmunoassay; RMET, reading the mind in the eyes task.

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to exercise was associated with higher anxiety and autistic traits and reduced levels of hedonia for social encounters in patients with HPDs (306, 315). Lower salivary OXT levels after a standardized breakfast were associated with higher BMI and adverse eating behavior in patients with craniopharyngioma (309, 314).

Later studies measured circulating OXT in blood samples. One study showed paradoxically higher fasting plasma OXT levels in patients with AVP-D compared to controls (316). Possible explanations for this finding includes increased production of OXT by peripheral sources (eg, gonads) to compensate for the reduced delivery of centrally produced OXT to the periphery or assay cross-reactivity with desmopressin, though the assay kit manufacturer reported low cross-reactivity with vasopressin (316). Another study sampled blood every 5 minutes for an hour and pooled each individual's samples to obtain an integrated measure of basal and pulsatile OXT secretion. This study demonstrated that men with AVP-D, considered most likely to have OXT-D, had approximately 20% lower OXT levels than men with similar APDs but no AVP-D, as well as HCs of similar age and BMI. The patients with AVP-D (but not those with similar APDs and no AVP-D) also had greater symptoms of anxiety, depression, and alexithymia, and worse mental health-related QoL, than HCs (283), though mean scores were within the normal range. In addition, lower OXT levels were associated with lower BMD *z* scores at the lumbar spine, femoral neck, total hip, and subtotal body, as well as unfavorable hip geometry and estimated strength at the intertrochanteric region in men with AVP-D (86). These findings were consistent with a potentially clinically relevant OXT-D state in men with AVP-D. Most recently, MDMA, a known stimulus both for peripheral and central OXT release in animal models, was administered to evaluate the OXT system in patients with AVP-D (308, 317). The study included 15 adults with AVP-D compared to 15 controls, and it showed that MDMA administration resulted in a robust (peak 8-fold) and sustained (over 5 hours) increase in plasma OXT levels in healthy individuals but not those with AVP-D. Additionally, while healthy individuals experienced clinical effects of MDMA, such as euphoria, increased empathy, and reduced anxiety, patients with AVP-D did not, suggesting a deficiency in the central release of OXT in AVP-D (308). This landmark study provided further strong evidence for OXT-D in patients with AVP-D, supporting recognition of OXT-D as a "new" clinical condition (318).

These early studies have identified a new clinical syndrome of OXT-D in patients with HPDs. There is preliminary evidence that lower OXT levels in these patients may be related to clinical features of HPDs, in particular worse mental and bone health. Larger studies are needed to further define and clinically characterize OXT-D. Clinical features of OXT-D may be dependent on the site and extent of hypothalamic and/or pituitary damage and resulting reduction in central and/or peripheral OXT release. It will be critical to study both sexes as OXT-D may present differently in males and females given sexually dimorphic effects of OXT (319).

Diagnostic Challenges

While patients with AVP-D are presumably most at risk for OXT-D, it is possible that some individuals with AVP-D, particularly if mild, may not have OXT-D, either due to sparing or regeneration of OXT-producing neurons (320, 321). In rats, OXT neurons were more likely to survive and regenerate after stalk transection compared to AVP neurons (322). At the same time, the clinical diagnosis of AVP-D is currently prompted by polyuria and polydipsia due to deficient circulating AVP acting at renal AVP (V2) receptors, and there may be other consequences of AVP-D that are not understood or captured by our present evaluation (302). Therefore, assuming that only patients with diagnosed AVP-D have OXT-D may result in missed identification of OXT-D in patients with HPDs. Development of diagnostic testing for OXT-D is needed, and there are challenges to overcome to achieve a clinically useful test.

In addition to the previously discussed difficulties in measuring OXT and the need to develop an optimal and standardized assay, there is a lack of knowledge regarding the "normal" range of OXT in any biological specimen in humans. Moreover, like other hormone axes, evidence to date indicates that a single hormone measurement is likely to miss individuals with deficient hormone secretion. While serial sampling of blood every 5 minutes for an integrated measure of basal and pulsatile OXT for an hour showed lower mean levels of OXT in those with AVP-D who are likely OXT-D, this type of sampling is resource intensive and not practical in clinical practice (283). Provocative tests, for example, the ACTH stimulation test for diagnosis of adrenal insufficiency and glucagon test for growth hormone deficiency, are commonly used in clinical practice to unmask hormone deficiencies. Preliminary studies in suspected OXT-D states (AN and HPDs) have demonstrated a blunted OXT response to stimulation, but no validated diagnostic test is yet available (283, 306, 309).

Physiologic (eg, childbirth, lactation) and pathological (eg, pain, hemorrhage, dehydration) conditions, endocrine signals, and pharmacological stimuli can promote OXT synthesis and release (Fig. 3) (92, 323, 324). Numerous neuromodulators (eg, serotonin, noradrenaline) are involved in the release of OXT from dendrites, somata, and axons of neurosecretory neurons. Mechanisms of OXT release include altered interaction between transcription factors and gene promoters, change in strength of synaptic input, and activation of intracellular Ca^{2+} stores to trigger dendritic OXT release, among others (325, 326). Both direct and indirect stimuli of oxytocinergic neurons leading to increased OXT mRNA expression, hypothalamic OXT content, immunoreactivity for excitatory firing OXT neurons, and/or higher peripheral OXT levels, have been reported in the literature. Most of these effects have been shown in animal models or in vitro studies, but there are also limited data in humans (179, 327-331).

Importantly, as previously mentioned, central OXT release does not necessarily coincide with peripheral OXT secretion. In fact, there is evidence for positive, inverse, and no relationship between central and peripheral OXT release, depending on the context (179, 331, 332). Central and peripheral OXT release also likely follow distinct timelines, as OXT levels in the brain typically peak later and remain elevated longer than in blood (23, 326). Therefore, when evaluating potential provocative stimuli for diagnosis of OXT-D, context and specimen sampled must be considered.

Several potential provocative stimuli for OXT release have been examined in patients with HPDs (283, 306, 308, 309) and are summarized in Table 2. The insulin tolerance test increased plasma OXT levels following 30 minutes of severe

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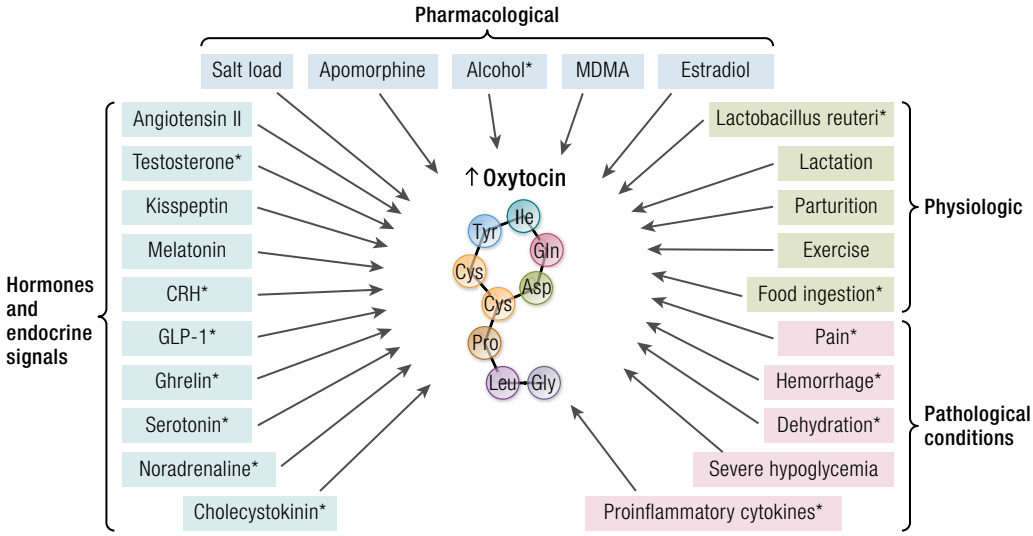

Figure 3. Potential oxytocin (OXT) stimuli that increased central or peripheral OXT levels in preclinical studies, animal models, and/or humans. *There is evidence in animal studies only. CRH, corticotropin-releasing hormone; GLP-1, glucagon-like peptide 1; MDMA, 3,4-methylenedioxy-methamphetamine.

hypoglycemia in healthy individuals, but response was variable (333, 334). One study showed that the insulin tolerance test failed to increase OXT levels in 5 patients with AVP-D; however, increased OXT levels were also not consistently observed in the 10 HCs evaluated (335). Furthermore, severe hypoglycemia can result in serious complications and is contraindicated in patients with epilepsy or cardiac disease. In response to physical exercise, patients with craniopharyngioma did not increase OXT levels in saliva compared to HCs, whose OXT levels increased by 25% (306). While exercise could be pursued as a provocative candidate stimulus for OXT release, a standardized exercise test would be difficult to implement and individual responses could vary.

Moreover, due to difficulties obtaining OXT in the CSF, there is a need to identify a provocation test that activates OXT secretion both in central and peripheral compartments. The use of psychoactive substances like MDMA might be a promising approach, since MDMA showed an increase in peripheral OXT levels and modulation of centrally mediated effects like anxiolysis in healthy individuals, in contrast to individuals with AVP-D (317, 336). Recently, a randomized, double-blind, placebo-controlled crossover trial of single-dose MDMA (100 mg) showed an 8-fold increase in plasma OXT levels in healthy adults, with no increase in individuals with AVP-D (317). This resulted in an OXT area under the curve that was 82% higher in controls over 300 minutes (308). While MDMA could be pursued as a provocative test to identify OXT-D, it is a recreational drug that can alter mood and perception, with potential adverse effects. Half of participants in this study experienced fatigue, impaired concentration, low appetite, and dry mouth, and 27% of patients with AVP-D developed transient mild hypokalemia. MDMA is under investigation for the treatment of PTSD and substance use disorders, with several studies showing improvement in symptoms and providing reassuring safety data (336, 337). However, the FDA recently rejected MDMA in combination with psychotherapy for PTSD, requesting additional efficacy and safety data. Whether lower doses of MDMA minimizing the risks could also distinguish individuals with OXT-D is unknown and warrants further investigation. A secondary analysis of an RCT with a crossover design using glucagon (1 mg) vs placebo in 10 patients with AVP-D and 10 healthy participants did not find any effect of glucagon on plasma OXT levels, with similar OXT levels between groups (338).

Several recent and ongoing RCTs in patients with HPDs and healthy volunteers focus on identifying a suitable provocative test to diagnose OXT-D. Based on preclinical data showing that CRH receptors are present on oxytocinergic neurons, and intravenous (IV) administration of CRH increased plasma OXT (339, 340), a recently completed RCT examined CRH (1 µg/kg) but found no difference in OXT levels between those with HPDs and HCs (341). Another study is examining exenatide (NCT05319301), a glucagon-like peptide-1 (GLP-1) receptor agonist, as a potential OXT stimulus. GLP-1 receptors are present in rodent hypothalamus and posterior pituitary gland, and administration of a GLP-1 receptor agonist (exendin-4) increased central OXT release from the isolated rat hypothalamo-neurohypophyseal system (342). Melatonin, a hormone mainly produced in the pineal gland with receptors widely distributed in the hypothalamus, is also under investigation (NCT04897802). Pinealectomy resulted in decreased OXT concentrations in the neurohypophysis of rodents, and high doses of melatonin stimulated OXT release from hypothalamo-neurohypophyseal explants in rats, suggesting that melatonin may activate the OXT system (343, 344). A preliminary study in humans showed that oral melatonin produced dose-dependent changes in OXT levels, with low doses (0.5 mg) increasing peripheral OXT levels in healthy men compared to placebo, and higher doses (5 mg) decreasing OXT levels (345). The current study investigates effects of melatonin (1.9 mg) over 120 minutes on plasma OXT levels in adults with HPD and controls.

Finally, a study of ethinylestradiol-norethindrone acetate (70 µg and 0.5 mg, respectively) will investigate circulating OXT response in blood and salivary samples of adults with AVP-D and HCs (NCT06460948). Sex steroids are one of the most potent regulators of OXT and *OXTR* gene expression, with differential effects depending on the tissue. Plasma OXT levels fluctuate throughout the menstrual cycle in fertile women, resulting in peak circulating OXT levels at

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ovulation, when estradiol levels are highest, and lowest levels during the follicular phase, when estradiol levels are lowest (78, 346-349). Most studies showed that women taking low-dose (30-50 µg) oral contraceptives have higher plasma OXT levels than those not taking contraceptives (350-352). A single dose (1 mg) of oral ethinylestradiol induced significant elevations in plasma OXT with a peak between 24 and 36 hours in healthy females, whereas there was no increase in OXT in females with AN, who are OXT-D (89). OXT also increased 24 hours after one dose of mestranol/ethynediol diacetate (100 µg/1 mg) in 5 healthy adults of both sexes (353). These studies highlight the potential of oral estrogen to stimulate OXT levels and unmask OXT-D. The results of these trials are anticipated in the next few years and will shed light on whether these stimuli could serve as the basis for development of diagnostic testing for OXT-D.

Peripheral OXT release in response to different stimuli used for other purposes in endocrinology, like arginine infusion and hypertonic saline (for the differential diagnoses of polyuria and polydipsia syndromes) or oral macimorelin (used to diagnose growth hormone deficiency), have also been examined in healthy individuals in a secondary analysis of prospective studies (354). Neither the arginine nor the macimorelin test stimulated plasma OXT levels, whereas there was an increase in OXT using hypertonic saline infusion with high variance in response. Nevertheless, these studies were not specifically designed to evaluate OXT secretion and only baseline and a single post-drug time point were measured; thus, it is possible that evaluation of other doses or time points could have provided different results.

Other potential stimuli for OXT release based on preclinical data have also been studied in healthy individuals, with mixed results, which could be due to experimental design (eg, dosing regimen) or differences in OXT physiology across species. While hypertonic solutions resulted in robust central and peripheral OXT release independent of route of administration (355, 356) in rodents, an oral salt load (200 nmol sodium daily over 5 days) did not affect serum OXT levels and hypertonic saline only mildly increased OXT levels in humans (355, 357). Central angiotensin II administration increased plasma OXT levels in rats (358, 359). In humans, higher pressor doses of angiotensin II infusion increased (334, 360), but lower doses decreased circulating OXT levels (361). Cholecystokinin octapeptide (CCK8), a peptide released after food ingestion that induces satiety, robustly increased central and circulating OXT levels in rodents (362, 363). However, studies of IV CCK8 administration in women were inconclusive with one study showing no effects and another showing an increase in circulating OXT concentrations (364, 365).

Whether kisspeptin, a hypothalamic neuropeptide known for its role in the control of gonadotropin-releasing hormone and fertility, stimulates OXT release has also been studied. Kisspeptin neurons have connections to and around the SON and PVN, and kisspeptin receptors have been found in oxytocinergic neurons of PVN in rodents (366, 367). Kisspeptin stimulated OXT secretion from isolated rat hypothalamo-neurohypophyseal tissue and transiently increased plasma OXT levels in nonpregnant rats (368-370). In a recent study of 12 healthy adults, IV kisspeptin (0.24 nmol/kg bolus) increased plasma OXT levels, driven by a 31.9% increase in men and 5.7% in women (371). Further research in a larger sample could determine whether kisspeptin could be used diagnostically for OXT-D in males.

In sum, while preclinical studies have uncovered stimuli for central and/or peripheral OXT release, there are limited data in humans. In some cases, effects in animals were not confirmed in humans, possibly due to dose or differences across species. Ongoing research focuses on the identification of OXT stimuli in humans, and investigation of potential stimuli to unmask OXT-D. Some stimuli may not increase OXT enough to separate OXT-D from healthy individuals at the doses studied. Estradiol, shown to double OXT levels in healthy individuals, shows promise as the basis of diagnostic testing for OXT-D. There is also evidence for the utility of kisspeptin to provoke OXT release in men (371). Other substances, like MDMA, may be useful at different doses than studied thus far. While data suggest that MDMA may unmask central and peripheral OXT-D, the relationship between peripheral OXT levels that are assessed in other tests under investigation and CNS OXT-D is not known. Research is active with the goal of developing a diagnostic test for OXT-D that could be used in clinical practice. Better methods for OXT measurement (see Oxytocin Measurement: Utility and Limitations) will be critical for translation to patient care.

Therapeutic Challenges and Potential

Limited Data on Normal Secretory Patterns in Humans to Guide Replacement Strategies

The next step in optimizing care of patients with OXT-D will be to develop therapeutic strategies for OXT replacement. Ideally, replacement of OXT would mirror secretory patterns in healthy individuals. However, secretory dynamics and circadian rhythms of OXT in physiological conditions are unknown. OXT release patterns differ within and across species, and have scarcely been evaluated in humans (372). Some stimuli for OXT release in animal models did not increase OXT in humans (357, 362, 363, 365). While no circadian rhythm has been found in CSF OXT of mice, goats, and rats (373, 374), monkeys have a clear circadian pattern with higher OXT levels in CSF during the light period that was not observed in plasma (375). Different patterns of OXT concentrations in plasma vs CSF in primates suggest that mechanisms controlling the release of OXT into the CNS differ from those involved in the release of OXT into plasma (332, 375-377).

Data describing OXT changes over time in physiological conditions in humans are limited to a few studies with mixed results. Similar to monkeys, time-dependent variation in CSF OXT (highest levels at 12:00 and lowest at 18:00 and 24:00) was found in human CSF samples (6 individuals, 4 females) obtained every 6 hours (378). In contrast, peak OXT plasma levels occurred overnight, from 24:00 to 6:00, with considerable variation between participants (372, 378-381). Pulsatile peripheral release of OXT has been demonstrated in women during labor (varying across labor stage from 4 pulses over 30 minutes at the first stage to 7 pulses over 30 minutes at the third stage of labor) and lactation (average of 5 pulses over 10 minutes during breastfeeding), but there are few data describing OXT secretory patterns outside these states or in men (382, 383).

Several studies using more sophisticated approaches, such as "Detect program" or "Pulsar," to determine circulating OXT secretory patterns in adults did not show pulsatility over 8 hours (351, 384). However, the relatively low frequency of blood sampling (every 10 minutes), may have

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reduced the ability to detect pulses, since plasma OXT half-life is about 3 to 5 minutes (385). A recent study sampled serum OXT every 5 minutes overnight over a period of 10 hours in 5 healthy men and used a "gold-standard" approach of deconvolutional analysis to determine secretory patterns (386). This study demonstrated a pulsatile secretory pattern in men with a mean of 2.2 pulses per hour, and interpulse interval of 27 minutes (386). Although the physiological interpretation of the pulsatile vs basal OXT levels and their clinical effect remain to be established, lower OXT pulse height and mass were associated with worse social-emotional functioning in this study (386).

In summary, there are cross-species differences in OXT physiology, and little is known about OXT secretory dynamics in healthy individuals to guide replacement strategies in OXT-D. Studies indicate between-individual variability in OXT levels. There is evidence for pulsatile OXT secretion in both sexes, but the short half-life and difficulty in measuring OXT have limited investigation in this area. Furthermore, the relationship between central and peripheral OXT release is context dependent and not well understood.

Knowledge of secretory patterns of OXT and its circadian rhythm in humans will be useful in developing treatment strategies to mimic physiology, and to establish reference ranges for monitoring OXT replacement in patients with OXT-D. Development and validation of accurate and reliable methods for measurement of OXT are critical next steps.

Oxytocin-based Therapeutics

Few OXT-based therapeutics are currently available for clinical practice. Oxytocin delivered IV or intramuscularly (IM) is FDA approved for labor induction (only IV) and prevention of postpartum hemorrhage (387). A more practical approach for outpatient use, OXT nasal spray is the most frequent route of administration used in clinical research. IN OXT is clinically available in many countries to promote lactation, though FDA approval was withdrawn in the United States for business reasons.

Compounded formulations with less rigorous testing requirements are accessible through pharmacies and the internet. This may result in inconsistent formulations and effects. Substantially higher, lower, or absent active ingredient along with additional active ingredients have been well documented in studies of other compounded drugs (388). Compounded formulations and quality-controlled IN OXT manufactured in countries where IN OXT is approved for clinical use have both been used in research.

Strong evidence for positive effects of IN OXT administration is lacking (389, 390), and most of the interventional studies using IN OXT have demonstrated only mild treatment effects (391, 392). Recently, several large and well-designed clinical trials using IN OXT vs placebo did not show beneficial effects on primary study end points in patients with obesity and ASDs (99, 154, 311). Several reasons could explain the negative findings, such as drug regimen (dose/frequency), duration of OXT administration, OXT-based drug/formulation, OXTR polymorphisms, or insufficient OXT reaching target brain regions (390, 393). While certain OXT functions have been highly conserved across evolution, for example, in sexual reproduction, it is important to consider that there may be differences in OXT physiology in humans compared to other species. Therefore, some effects of OXT administration in animal models may not translate to humans.

Acute and chronic IN OXT administration appear to be safe and well tolerated regardless of clinical condition studied with no serious events and no differences in adverse events compared to placebo (311, 394-397), other than increased nasal irritation in one study (99). While preclinical studies showed that OXT could increase QT interval, limited data from human studies showed no effects of IN OXT on QT interval or risk for arrhythmias (99, 311). Research studies of chronic OXT administration should exclude individuals with prolonged QT syndrome and monitor electrocardiograms, particularly when OXT is used in combination with other QT-prolonging drugs. Relevant to patients with HPDs, supraphysiologic IN OXT could theoretically cross over to the AVPRs, though studies have not reported an increased risk for hyponatremia (34). The one small pilot study evaluating the effects of chronic IN OXT for 8 weeks in patients with hypothalamic obesity and AVP-D reported no difference in hyponatremia or DDAVP dose adjustments in OXT vs placebo conditions (311). Nonetheless, monitoring effects of OXT administration on AVPR-mediated end points, such as sodium levels, as well as DDAVP doses, will be important when studying patients with HPDs (34). In animal models, OXT modulates hypothalamic-pituitary hormone axes, for example, decreasing cortisol levels (398). There are few data of OXT effects on pituitary hormone levels in humans (399). In single-dose studies of IN OXT, decreased ACTH and cortisol levels have been reported (149, 240, 400). Hypoadrenalism has not been described as a consequence of chronic IN OXT administration. More data on OXT crosstalk with other hypothalamic-pituitary hormone axes are needed.

IN OXT administration may affect physiology through direct action both on central and peripheral OXTRs. However, mechanisms of IN OXT effects are not yet well understood. Studies in humans showed that plasma levels of OXT are elevated 15 to 60 minutes after IN administration (389, 401, 402). Circulating OXT can act on OXTRs that are widely distributed (see Overview of the Oxytocin System), including in reproductive, cardiovascular, and gastrointestinal tissues, and the vagus nerve, which transmits peripheral OXT signals to the brain (403-405). There is a lack of evidence for IN OXT reaching target brain regions in quantities sufficient to result in a therapeutic response (318, 390). Nonetheless, there is compelling evidence supporting the use of IN OXT for central effects. For instance, IN OXT administration delivered into the cribriform plate in macaques allowed for a rapid uptake through olfactory and trigeminal nerves into the CSF within 40 minutes post administration (406-408). Peripheral OXT may also reach the brain via olfactory and trigeminal nerves (407), nasal epithelium, gaps in the BBB (eg, area postrema), or by binding to the receptor for advance glycation end products (RAGE) in endothelial cells to cross the BBB (19, 409, 410). Exogenous OXT may increase endogenous OXT release in the brain (411). Studies in rodents, including $OXT^{-/-}$ mice, showed that IN OXT increased OXT levels in brain extracellular fluid (410-412). In addition, IN OXT increased CSF OXT levels and modulated amygdala activity in macaques and humans (401, 406, 413). Further, radiolabeled IN OXT given to rats and macaques reached the brain (75, 414, 415). The availability of OXTRs is dynamically modulated by exogenous OXT administration, with higher expression in brain areas modulated by IN OXT suggestive of direct actions of IN OXT on the brain (416). Moreover, transport to

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the brain may not be necessary for IN OXT to have central effects, as peripheral OXT signals can be transmitted to the CNS by the vagus nerve (403, 405). For example, peripheral administration of an OXTR antagonist that does not penetrate the brain stimulated caloric intake and weight gain in rats (417), lending support to the concept that circulating OXT can modulate energy homeostasis. In obese rodents, peripheral OXT administration at doses that suppress caloric intake and body weight activated neurons in brain regions that receive peripheral satiety signals from the vagus nerve (dorsal motor nucleus of the vagus, nucleus tractus solitarius [NTS] and area postrema), process satiety signals to control energy homeostasis (arcuate and PVN hypothalamic nuclei), and contain OXT-producing neurons (PVN) (166, 167, 190). In mice, vagotomy reversed effects of peripherally administered OXT to activate the NTS and reduce food intake (404). Further, suppression of caloric intake in response to peripherally administered OXT required activation of preproglucagon neurons in the NTS that receive inputs from afferent OXT receptor-expressing vagal neurons.

IN OXT is one of few available tools to probe the OXT system and is currently under investigation for a wide range of indications, including for neuropsychiatric disease, metabolic disease, and OXT-D (99, 154, 311, 388). One drawback is that nasal cavity congestion or disease can dramatically reduce the efficacy of IN OXT, and absorption is variable. Given variability in interindividual response to IN OXT and failure to replicate study results, standardization of methodology, including design of nasal applicator, spray administration techniques, and formulation is needed, as well as identification of markers of response to evaluate the effect of the dose administered (418, 419). There is no consensus regarding a strategy for selection of a dosing regimen, and optimal dosing may depend on the indication studied. The optimal dose frequency and/or need for a "drug holiday" given OXTR internalization within hours of continuous exposure have not been established (420, 421). Few dose-ranging studies of IN OXT in humans have been reported, with several suggesting that lower doses may be more effective than higher doses (415, 422-425). Recent studies evaluating the dose-response in targeting effective brain reactivity employed different dose ranges from 8 IU to 48 IU. The maximal effects of OXT were observed at the lowest dose in 2 studies (8 and 9 IU) and intermediate dose (24 IU) in another study (422-424). Dose-response effects may differ depending on the experimental task and target brain region evaluated. It still unclear whether the doses used are within the range to induce therapeutic effects. The investigation of optimal dose regimens is a crucial area for future research, since it is vital for clinical efficacy and application in clinical practice.

The addition of magnesium, which increases OXT binding and efficacy at the OXTR, may result in greater effects of IN OXT at higher doses (42). Recently, a potentiated formulation with magnesium, which increases OXT binding to its receptor and efficacy, was developed (TNX-1900; Tonix Pharmaceuticals) and is in phase 2 trials for binge eating disorder (NCT05664516), obesity (NCT04551482), and bone health in children with ASDs (NCT05754073). It is unclear whether IN OXT doses should differ based on sex, age, BMI, or clinical condition. There is some evidence that IN OXT may be more effective in males than females (426). Endogenous OXT levels and/or OXTR sensitivity could affect response to IN OXT; however, there are few related data. Preclinical studies suggest that OXT may be more effective in the setting of inflammation, which results in upregulation of OXTR (427). Cholesterol is a known cofactor for high-affinity binding of OXT to OXTR, but it is not known whether higher endogenous cholesterol levels improve drug efficacy (11, 42, 200, 421, 423, 424, 427, 428).

Most studies of IN OXT in humans have used supraphysiologic doses, and the optimal physiological dosing replacement strategy for OXT-D is unclear. A better knowledge of OXT circadian rhythm could guide development of replacement protocols aimed at mirroring physiological secretion. Future studies applying different OXT formulations (eg, magnesium to increase efficacy, nanoparticle-encapsulated to increase duration (429)), dosing regimens, routes of administration, and OXTR agonists will be useful.

Oral formulations of OXT have recently been developed. Oral OXT (0.25 mg of powdered OXT; Peptide Institute) in a gelatine-coated capsule (TORPAC Inc) in mice pretreated with proton pump inhibitor (to prevent OXT degradation due to low gastric pH), resulted in increased OXT levels in blood and gastrointestinal tract and decreased food intake (430), consistent with known anorexigenic effects of OXT. Moreover, increased expression of neural activation marker c-Fos protein was observed in PVN and suprachiasmatic nuclei in response to oral OXT. Central effects of oral OXT were attributed to likely transport across the BBB by RAGE or indirect signaling via OXTR on the vagus nerve (430). Behavioral effects following oral OXT administration were also observed in rodents (430, 431). In humans, an oral OXT spray was effective in the treatment of social dysfunction in patients with ASDs, with similar therapeutic effects as IN OXT in disorders associated with social attention deficits (432). A recent study found that oral OXT modulated neural responses to emotional scenes in different ways in males and females, suggestive of sex-specific effects (433). A preliminary study in men showed that medicated lollipops with 24 IU of OXT increased blood OXT concentrations and improved social attention and anxiety behaviors, with similar effects as in IN and sublingual routes (434). Further research and development of OXT-medicated lollipops could have potential therapeutic application, particularly for use in children.

A sublingual fast-dissolving OXT tablet, similar to the sublingual desmopressin formulation used in patients with AVP-D, was recently developed (435). The sublingual route has advantages of direct delivery to the systemic circulation, bypassing the stomach where aminopeptidases can degrade OXT, and a rapid onset of action (436). A pilot study evaluated the pharmacokinetics of sublingual OXT in rabbits, demonstrating absorption in plasma within 5 minutes, although OXT levels in plasma were 5 times lower than when using IM OXT (437). While both oral and sublingual OXT routes seem promising and well tolerated, research in humans is needed to confirm safety, appropriate dose regimen, efficacy, mechanisms of action, and any route-dependent functional effects (432).

Inhaled OXT that does not need to be refrigerated has been recently developed for use in inducing labor and preventing postpartum hemorrhage. Phase 1 randomized trials showed a safety profile similar to intramuscular administration of OXT in healthy individuals and women in the third stage of labor (438, 439). However, more research is needed to determine the efficacy of inhaled OXT.

Carbetocin (IV or IM), a longer-acting OXT receptor agonist, is used worldwide for obstetric applications. Carbetocin is

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less potent than native OXT, but has a longer half-life (~40 minutes in blood), and is more selective to the OXTR with minimal binding to vasopressin receptors. An IN carbetocin formulation under development for PWS demonstrated efficacy for reducing anxiety and hyperphagia at 3.2 mg but not 9.6 mg 3 times daily (312, 440). Whether carbetocin crosses the BBB is not known; thus, these effects may be indirect through action at OXTRs on the vagus nerve, but more research is needed to understand the mechanisms of action.

Lastly, several other peptide and nonpeptide OXTR agonists, with longer duration of action than OXT, have been developed. These drugs are in the preclinical stages of development, and fundamental questions of safety, efficacy, and feasibility in humans remain unanswered (429, 441). For all therapeutic options, understanding drug distribution and mechanisms of action will be important. Establishing biomarkers for central vs peripheral OXT-D will also be useful in guiding therapeutic strategy. For instance, a patient with extensive hypothalamic damage to the PVN and SON, the key sites of OXT production, may be more likely to have clinically central OXT-D requiring brain-penetrant therapeutic replacement than someone with AVP-D and no obvious hypothalamic involvement.

Pilot Data of Oxytocin-based Therapies in Patients With Hypothalamic and Pituitary Diseases

Few studies have evaluated the effects of IN OXT in patients with HPD. Table 3 summarizes case reports and studies evaluating the effects of IN OXT or carbetocin in patients with HPD.

A pilot study examined neuropsychological effects of a single dose of 24 IU daily IN OXT administration in patients with childhood-onset craniopharyngioma, a population with known deficits in social and emotional health (310). In patients with postsurgical lesions limited to the anterior hypothalamus, but not those with more severe damage involving both anterior and posterior hypothalamus, IN OXT resulted in improvement in ability to correctly perceive and identify emotions of vocal expressions.

OXT treatment has also been reported in patients with hypothalamic obesity, who present with difficult-to-treat hyperphagia, reduced energy expenditure, and rapid-onset obesity due to hypothalamic damage, for example, in the setting of tumor or surgery. Hypothalamic damage may result in the disruption of magnocellular OXT neurons or upstream pro-opiomelanocortin neurons, resulting in the reduced release of OXT acting on neurocircuits involved in energy homeostasis (442). There is also evidence that OXT may reduce hypothalamic dysfunction in craniopharyngioma mouse models, in which OXT treatment prior to surgery reduced lipotoxicity in neural stem cells by attenuating stress response signaling and reducing inflammation (443). A clinical case report of a 13-year-old boy with panhypopituitarism, AVP-D, and severe hypothalamic obesity post surgery for craniopharyngioma indicated that 6 IU daily IN OXT for 10 weeks was accompanied by a decrease in BMI *z* score from 1.77 to 1.49 SDS, as well as reduced hyperphagia and food preoccupation (165). The addition of naltrexone to IN OXT for 38 additional weeks was associated with a further decrease in BMI *z* score from 1.49 to 0.82 SDS despite giving the patient access to a fully unlocked kitchen. No adverse events were observed, and DDAVP dose was not affected by treatment. In contrast, another clinical case of a 6-year-old girl with hypothalamic

Table 3. Studies evaluating the effects of intranasal oxytocin on clinical endpoints in patients with hypothalamic and/or pituitary diseases

Reference	Study design and population	Intervention or manipulation	Outcomes
Studies in patients with hypothalamic and/or pituitary damage			
Cook 2016 (313)	• Case-report of girl aged 6 y with hypothalamic/pituitary dysfunction after CP removal	• IN OXT (5 IU twice daily), reduced to 2 IU twice daily due to increased thirst	• Increased desire for socialization and improvement in affection toward family • No effect on food focus or hypothalamic obesity
Hoffman 2017 (310)	• Interventional trial • 10 adults with CP	• IN OXT (single dose of 24 IU) • Evaluation of emotion recognition abilities and OXT levels before and after IN OXT	• IN OXT increased OXT levels in saliva and urine • IN OXT improved recognition of negative emotions • Patients with anterior hypothalamic lesions showed improvement in emotion identification
Hsu 2018 (165)	• Case report of boy aged 13 y with hypothalamic obesity and hyperphagia post-CP resection	• IN OXT (6 IU daily) for 10 wk, naltrexone added for 28 wk	• Significant and sustained reduction of BMI (from 96th percentile to 79th), reduction of hyperphagia
McCormack 2023 (311)	• Randomized, double-blind, placebo-controlled, crossover pilot trial • 13 children, adolescents and young adults aged 10-35 y with hypothalamic obesity from hypothalamic/pituitary tumors (10 completed study)	• IN OXT (16-24 IU 3× daily) at mealtimes vs excipient-matched placebo for 8 wk	• No difference in weight change in OXT vs placebo • Exploratory analyses showed benefits of OXT for anxiety and impulsivity

(*continued*)

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Table 3. Continued

Reference	Study design and population	Intervention or manipulation	Outcomes
Studies in patients with Prader-Willi syndrome			
Tauber 2011 (450)	• Randomized, double-blind, placebo-controlled study • 24 adult patients aged 18-44 y with PWS	• IN OXT (single dose 24 IU) vs placebo • Social skills and behaviors tested 45 min and 2 d after OXT administration	• 2 d after drug administration, OXT increased trust in others, decreased sadness tendencies with less disruptive behavior vs placebo • No differences in social skills (RMET) observed between groups
Einfeld 2014 (452)	• Randomized, double-blind, placebo-controlled crossover trial • 252 adolescents and young adults with PWS aged 12-30 y	• IN OXT (dose range 18-40 IU) twice daily for 8 wk vs placebo. (2-wk washout period) • Developmental behavior, obsessive compulsive symptoms, hyperphagia symptoms, RMET, ESS evaluated	• No differences observed between OXT and placebo conditions, except for increase in temper outbursts with higher-dose OXT
Kuppens 2016 (455)	• Randomized, double-blind, placebo-controlled crossover trial • 25 children with PWS aged 6-14 y	• IN OXT (dose range 24-48 IU/d) twice a day vs placebo for 4 wk (no washout period) • Social behavior and hyperphagia measured at baseline, after 4 wk, and after 8 wk	• Beneficial effects on social and food-related behaviors observed in patients aged <11 y, but not in those older than 11 y
Tauber 2017 (449)	• 18 children with PWS aged <6 mo	• Dose-escalation over 7 d: 4 IU/48 hours, 4 IU daily, 4 IU twice daily • Evaluation of effects on feeding and social skills, and changes in ghrelin and brain connectivity by functional MRI	• OXT induced improvements in feeding and social skills • OXT increased ghrelin and connectivity of right superior orbitofrontal network that correlated with changes in sucking and behavior • No dose effect observed
Miller 2017 (448)	• Double-blind, placebo-controlled crossover study • 24 children with PWS	• IN OXT (16 IU) vs placebo for 5 d (4-wk washout period) • Questionnaires administered: behavior checklist, social responsiveness and repetitive behavior scales, hyperphagia, clinical global impression scale • Blood Na+, K+, glucose on d 2, 4, 6	• All scales improved from d 3 to 6 on OXT treatment vs placebo • Low dose of OXT resulted in reduction in appetite, improvements in socialization, anxiety, and repetitive behaviors • No difference in safety between OXT and placebo
Dykens 2018 (441)	• Randomized, double-blinded, placebo-controlled study • 37 children with PWS aged 10-18 y	• IN carbetocin (9.6 mg 3× daily) vs placebo for 14 d • Change in hyperphagia, behavior, obsessive-compulsive scale, food domain, and clinical global impression-improvement scale	• Overall, IN carbetocin improved hyperphagia and behavioral symptoms compared to placebo
Damen 2020 (454)	• Randomized, double-blind, placebo-controlled, crossover study • 26 children with PWS aged 3-11 y	• IN OXT (dose ranged 16-40 IU/twice daily) vs placebo for 3 mo • Changes in behavior and hyperphagia	• OXT had positive effects on social and eating behavior in boys and in children with genetic deletion
Hollander 2021 (453)	• Randomized, double-blind, placebo-controlled trial • 35 children and adolescents aged 5-18 y with PWS	• IN OXT (16 IU daily) administration vs placebo for 8 wk • Changes in hyperphagia and repetitive behavior	• OXT did not have any effect on hyperphagia and repetitive behavior, while placebo showed modest improvements • OXT was well tolerated
Roof 2023 (312)	• Randomized, double-blind, placebo-controlled trial • 130 children with PWS (aged 7-18 y)	• IN carbetocin (9.6 mg or 3.2 mg) or placebo 3× daily for 8 wk • 56-week long-term follow-up, placebo participants randomly assigned to 9.6 or 3.2 mg carbetocin • Change in hyperphagia after intervention as well as assessments of anxiety and distress behaviors	• 3.2 mg carbetocin associated with improvements in hyperphagia, anxiousness, and distress behaviors compared to placebo that were sustained in long-term follow-up

Abbreviations: BMI, body mass index; CDI, central diabetes insipidus; CP, craniopharyngioma; ESS, Epworth Sleepiness Scale; HCs, healthy controls; HI, hypothalamic involvement; IN, intranasal; IU, International Units; MRI, magnetic resonance imaging; OXT, oxytocin; PWS, Prader-Willi syndrome; RMET, reading the mind in the eyes task.

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and pituitary dysfunction and AVP-D post resection of a craniopharyngioma reported that 14 months' IN OXT (2 IU twice daily) did not affect food focus nor hypothalamic obesity, but resulted in a dramatic improvement in socialization and affection toward family (313).

The only clinical trial evaluating the effects of sustained IN OXT vs placebo included 13 young patients (aged 10-35 years) with hypothalamic obesity from hypothalamic/pituitary tumors, of whom 9 had AVP-D and 10 completed the entire study. IN OXT (16-24 IU 3 times daily before mealtimes) vs placebo was administered in a crossover design for 8 weeks (311). Overall, OXT was well tolerated and adverse events were mild and similar between OXT and placebo. This pilot study did not detect any significant effect of IN OXT on body weight (−0.6 kg (95% CI, −2.7 to 1.5) but showed potential mild benefits of OXT to improve anxiety symptoms and impulsivity. However, psychological measures were not the primary end point of the study and larger studies should examine the potential psychosocial benefits in this unique population. There are several potential explanations for the lack of effects of IN OXT on body weight in this study. Hypothalamic syndrome is a heterogeneous disorder with varying causes and extent of hypothalamic damage. It is possible that some individuals, for example, those with intact downstream hypothalamic neurons mediating OXT effects, may respond better than others. Multiple hormone agonists (for example, GLP-1, gastric inhibitory polypeptide, glucagon agonists in combination with OXT) may be required to promote weight loss, given redundant energy homeostasis pathways designed to defend higher weight. The optimal dosing regimen for IN OXT is also not yet clear.

OXT-based therapeutics have also been investigated in PWS, a rare genetic neurodevelopmental disorder associated with hypothalamic dysfunction leading to behavioral and metabolic disturbances, including hyperphagia and obesity, with limited treatment options (444). Patients with PWS have reduced number (~40%), volume, and activity of OXT neurons in the PVN compared to controls that might partially contribute to clinical features (445). Plasma OXT levels in PWS have been variably reported from low to elevated in children with PWS compared to HCs (446, 447).

Trials evaluating the effects of IN OXT or OXT receptor agonists in patients with PWS primarily focused on symptoms of hyperphagia and socioemotional behaviors and are summarized in Table 3. Most of these studied children with mixed results. Some studies showed improvements in hyperphagia symptoms, emotion regulation, and/or social behavior overall or in subsets of participants (eg, boys but not girls) in response to IN OXT, but others did not observe any changes (312, 440, 448-455). However, these studies were small and used varied dosing regimens, study designs, and end points.

Two recent studies administered longer-acting IN carbetocin vs placebo. The first study demonstrated a reduction of compulsivity and improvement in overall functioning with IN carbetocin (9.6 mg 3 times daily) compared to placebo in children with PWS (440). The second and largest trial on PWS evaluating OXT-related therapies, with 130 children included, demonstrated clinically meaningful and sustained improvements in hyperphagia and distress behaviors with carbetocin at lower doses only (3.2 mg vs 9.6 mg 3 times daily) compared to placebo (312). In all studies, IN OXT and carbetocin were well tolerated in PWS with no severe adverse events reported.

In summary, there are limited data regarding effects of IN OXT in patients with HPDs, specifically in those with craniopharyngioma, tumor-induced hypothalamic obesity, and PWS. Most of these early studies are small, with the exception of an RCT of IN carbetocin in children with PWS demonstrating clinical improvement in hyperphagia and distress behaviors. While results of IN OXT are mixed, positive effects have been identified and warrant further investigation in larger, rigorously designed studies. There are currently 2 registered RCTs focused on patients with AVP-D. The first is a crossover study (NCT04789148) comparing effects of different doses of IN OXT (6 IU, 24 IU, placebo) on behavioral markers of anxiety, depression, and social emotional functioning, as well as bone turnover markers in 30 adults with AVP-D. The second RCT (NCT06036004), also in adults with AVP-D, is investigating the effects of 4 weeks of IN OXT (24 IU) twice daily vs placebo for 28 days on psychological symptoms and socioemotional functioning and is expected to be completed in 2026.

Conclusions

The recent identification of a clinically relevant OXT-D state is a breakthrough that provides a novel avenue to optimize the care of patients with HPD through OXT replacement. This is particularly important given the increased morbidity and mortality and lower QoL reported in individuals with HPDs despite standard hormone replacement. Early studies of IN OXT–based therapeutics suggest potential benefit for socioemotional health and eating behavior. However, there are considerable gaps in our knowledge that need to be addressed. Improving our understanding of the OXT system in health (eg, physiologic secretory dynamics and functions; central and peripheral mechanisms) as well as its role in disease, could guide us in our replacement strategies and clinical end points. Research focused on developing provocative tests for the diagnosis of OXT-D is active, but better methods to accurately assess OXT levels and establish normative data will be crucial for clinical translation. More work is needed to clinically characterize OXT-D and determine whether there are sex-specific features. Research administering OXT-based therapeutics should use formulations that have undergone testing (eg, following US Pharmacopeia standards) to ensure consistency of the drug/placebo given and reliability of research results. Novel formulations of OXT-based therapeutics and OXTR agonists are under development. Studies aimed at determining optimal OXT-based therapeutic dosing regimens for specific outcomes will be important to lay the groundwork for rigorous RCTs to determine safety and efficacy.

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