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The Neuropeptide Hormone Oxytocin in Eating Disorders

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Abstract

Purpose of review—The neurohormone oxytocin (OXT) impacts food intake as well as cognitive, emotional, and social functioning – all of which are central to eating disorder (ED) pathology across the weight spectrum. Here, we review findings on endogenous OXT levels and their relationship to ED pathology, the impact of exogenous OXT on mechanisms that drive ED presentation and chronicity, and the potential role of genetic predispositions in the OXT-ED link.

Recent findings—Current findings suggest a role of the OXT system in the pathophysiology of anorexia nervosa. In individuals with bulimia nervosa, endogenous OXT levels were comparable to those of healthy controls, and exogenous OXT reduced food intake. Studies in other ED are lacking. However, genetic studies suggest a broad role of the OXT system in influencing ED pathology.

Summary—Highlighting findings on why OXT represents a potential biomarker of and treatment target for ED, we advocate for a systematic research approach spanning the entire ED spectrum.

Keywords

Anorexia nervosa; Binge eating; Bulimia nervosa; Eating disorders; Food intake; Oxytocin

Introduction

The neuropeptide hormone oxytocin (OXT) is primarily produced in the supraoptic and paraventricular nuclei of the hypothalamus. Magnocellular OXT neurons have axonal connections to the posterior pituitary gland, which secretes OXT into the periphery, where it plays a key role in parturition and lactation. OXT is also produced in and secreted by peripheral tissues (e.g., in the uterus, gastrointestinal tract, and bone), exerting autocrine (on the same cell) and paracrine (on nearby cells) effects [1, 2]. In addition, there is vagal relay

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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of peripheral OXT signals to the brain [3]. OXT also exerts central effects through dendritic release with diffusion to adjacent brain regions, widespread axonal projections of parvocellular OXT neurons, and binding to widely distributed OXT receptors – a member of the G protein-coupled receptor family that activates intracellular signal transduction when detecting specific extracellular molecules [1, 4–7]. Through its central pathways, OXT affects cognitive, emotional, and behavioral processes, including dietary choices and food intake, emotional reactivity and regulation, and social cognition.

While eating disorders (ED) are heterogeneous illnesses, they share core defining characteristics of aberrant eating behaviors, which include under- or overeating, binge eating, and/or purging and unhealthy attitudes and perceptions regarding food, weight, and body shape. ED frequently co-occur with emotional and social dysfunction, which further promote illness manifestation and chronicity [8–10]. Herein, we review the literature on endogenous OXT levels and response to exogenous OXT administration in ED and the link between OXT and eating behaviors, negative affect, and social cognition, complemented by a brief summary of the relationship between OXT and bone health. We highlight key areas of future research and the potential of OXT pathways as a transdiagnostic treatment.

Interpretation of Human OXT Studies

When interpreting studies measuring OXT levels in humans, several considerations are warranted. First, commercially available enzyme-linked immunosorbent and radioimmunoassays to determine OXT levels in human specimens measure not only OXT but also likely OXT fragments, degradation products, and other substances due to cross-reactivity [11]. Second, how well peripheral OXT levels reflect central OXT availability affecting cognitive processes, emotions, and behavior is debatable [12]. Third, cerebrospinal fluid (CSF) levels might not reflect activity in specific neurocircuitries. Fourth, OXT levels measured peripherally in different body fluids do not correlate highly in individuals with AN [13] or in other populations [14], and a history of self-induced vomiting further reduces the association between salivary and plasma OXT levels [13]. Fifth, OXT measurement in saliva and urine is not well-validated [11]. Improved methodology and validation for OXT measurement in human specimens is critical and under development. In the meantime, findings across studies should be integrated qualitatively rather than quantitatively. Meta-analytical approaches should be applied only after careful consideration of methodological overlap and differences. To maximize transparency and allow for accurate interpretation of the available findings, careful reporting of context information (e.g., sample type and analysis method used for determining OXT levels, participants' characteristics) is mandatory. However, despite the outlined shortcomings, current OXT measurements represent valuable tools in establishing differences between investigated groups and correlations with relevant endpoints and are thus reviewed here.

In addition to investigations of endogenous OXT levels, exogenous OXT is a useful tool for studying the OXT system in humans. When interpreting these studies, it is important to remember that the doses used are supraphysiologic. Thus, observed effects do not necessarily reflect the impact of endogenous OXT on the outcomes. Further, OXT at these doses may also act at vasopressin receptors [1]. Despite these limitations, studies

administering OXT can be useful in understanding OXT functioning and provide proof-of-concept evidence for considerations of OXT as a neurohormonal treatment for ED.

OXT and Food Intake

Preclinical and clinical studies have provided accumulating evidence that OXT is closely linked to food intake and weight. In rats and primates, repeated OXT administration induced clinically relevant, sustained weight loss [15, 16]. A first human study of obese adults demonstrated weight loss of almost 20 lbs with 8 weeks of intranasal OXT [17]. In animal models, the beneficial effects of OXT on weight are driven by multiple processes, including increased energy expenditure and lipolysis as well as reduced food intake [15]. Central and peripheral OXT administration in fasting rats resulted in a dose-dependent reduction in caloric intake and delayed eating [18, 19], which was reversed by giving an OXT antagonist prior to OXT treatment [18]. In men, single-dose administration of OXT reduced caloric consumption, particularly of palatable foods, without affecting subjective appetite [20–23], establishing its potential to reduce food intake in humans [24, 25].

OXT effects on homeostatic and hedonic food motivation and cognitive control pathways may, in part, drive the impact of OXT on food intake.[22, 24, 26] The ventral tegmental area (VTA) at the core of the mesolimbic dopaminergic reward system is rich in OXT receptors [27] and receives projections from OXT neurons from the paraventricular and supraoptic nuclei of the hypothalamus [28]. Rodent studies show that OXT administration into the VTA and nucleus accumbens reduced sucrose intake; and these effects were attenuated when an OXT receptor blocker was given prior to OXT exposure [29, 30]. In a study of overweight and obese men, a single dose of 24 IU intranasal OXT (the same dose that reduced food intake [20]) versus placebo decreased functional magnetic resonance imaging (fMRI) activation in the VTA and other key brain areas processing reward and homeostatic food motivation in response to images of high-calorie foods versus non-foods [26]. This study also found increased activity in the dorsal anterior cingulate cortex and frontopolar prefrontal cortex (PFC) regions involved in cognitive control. In normal-weight men, 24 IU intranasal OXT increased neural activity in the anterior cingulate cortex, supplementary motor cortex, and ventrolateral PFC (all linked to cognitive control) together with increasing neural activity in the ventromedial PFC (involved in processing food reward) in response to high-calorie vs. low-calorie food images, resulting in reduced food intake ad libitum [22].

Taken together, OXT modulates food intake; and in humans, these effects are likely driven, in part, by OXT effects on homeostatic pathways, reward processing, and cognitive control. In addition to aberrant eating behavior, altered processing of food (and non-food) rewards and differences in cognitive control are well-documented in ED across the weight spectrum [31–38], where they facilitate and consolidate extreme dietary patterns. Further, due to its widespread central reach [39], OXT can reduce negative affect and stress [40–43] and promote social cognition and social behavior [44, 45]; problems in these areas have been implicated in the development, maintenance, and outcome of ED across the weight spectrum [8, 10, 46, 47].

Endogenous OXT Levels in ED

To date, research on the functioning of the OXT system in individuals with ED has primarily focused on anorexia nervosa (AN) and bulimia nervosa (BN). Compared to healthy controls (HC), CSF OXT concentrations were lower in five females with restricting AN, but not in 12 with binge/purge AN or 35 with BN [48]. Fasting plasma OXT levels were lower in females with AN than those with BN or HC, with no differences between AN subtypes [49]. Using pooled serum OXT from frequent overnight sampling, AN patients showed more than two-fold lower OXT levels than HC [50]. Other studies found no differences in fasting serum OXT levels between individuals with AN and HC [51] or in basal plasma OXT levels between AN, BN, and HC [52]. With regard to stimulated OXT levels, individuals with AN but not BN demonstrated a blunted plasma OXT response to stimulation by estrogen and insulin compared to HC [52]. Finally, serum OXT levels following a 400-kcal standardized mixed meal were higher in women with AN compared to women with weight-restored AN and HC [53].

In summary, extant work found no evidence for alterations of endogenous OXT levels in BN, whereas AN seems to be associated with reduced basal CSF and circulating levels of OXT. OXT levels may be suppressed as an adaptive response to chronic starvation, sending the signal to eat and reduce energy expenditure. In addition, since food intake stimulates the release of OXT in rats [54], persistent dietary restriction could also cause lower basal OXT levels due to a lack of stimulation, which may explain lower OXT levels found in restricting AN compared to binge/purge AN [48]. Regardless of the cause of low OXT levels, women with AN fail to respond by increasing food intake, likely due to top-down control of behavior to maintain dietary restriction despite self-starvation.

Regarding the observed higher postprandial OXT levels in AN [53], α -melanocyte-stimulating hormone (an inhibitor of appetite stimulated by leptin) increases central but inhibits peripheral OXT release [55]. Thus, higher peripheral OXT levels following a meal could indicate a decrease in the anorexigenic OXT signaling in central appetite-regulating centers as an adaptive response to self-starvation [56]. Alternatively, higher postprandial OXT levels in AN may reflect the anxiolytic properties of OXT in response to the stress of eating [57] (see below). Studies investigating the OXT system in other types of ED, including avoidant/restrictive food intake disorder (ARFID), binge eating disorder (BED), and other specified feeding and eating disorder (OSFED) types are lacking and will be key to understanding the role of the OXT system in ED pathology.

Endogenous OXT Levels Following Partial or Full Recovery From an ED

Studies of OXT levels in individuals with weight-recovered AN show mixed results with evidence for normal or low endogenous OXT levels. One year following recovery, CSF OXT levels were comparable in 10 women with binge/purge AN, 23 with BN, and 17 HC [58]. In line with these data, low CSF OXT levels in acutely ill females with restricting AN normalized after re-feeding and maintenance of target weight for three weeks [48]. OXT responsiveness to both estrogen and insulin also normalized in individuals with AN following full weight recovery [52]. These results suggest that altered OXT levels and

responses characterize the acute low-weight state of AN and reverse with recovery. However, investigations of fasting serum OXT levels in partly and fully weight-recovered women with AN showed lower OXT levels compared to HC [51, 53]. Likewise, postprandial serum OXT levels remained suppressed in weight-recovered AN individuals [53]. A study investigating the effects of 4–6 weeks of sustained intranasal OXT administration during an in-patient re-feeding program for AN found no changes in plasma OXT levels following weight restoration in AN in either treatment or placebo group [59]. These data suggest alterations in OXT pathway functioning in individuals with a history of AN that persist even following weight recovery and raise the question of whether alterations of the OXT system represent a scar of illness or a pre-existing trait that increases vulnerability to developing a low-weight ED.

Characteristics of the OXT System as a Determinant of the Vulnerability for Developing an ED

Genetic studies provide critical insights into the question of whether neurobiological alterations observed in acute, chronic, or post-disease states represent causes or consequences of pathology. Genetic predispositions in the function of the OXT system are investigated by analyzing the relationship between variations in single nucleotides (single nucleotide polymorphisms, SNPs) that have been linked to the gene encoding the oxytocin receptor (*OXTR*). It has been hypothesized that the minor *OXTR* alleles might be more frequently evident among those with an ED. In women with active AN but not in those recovered from AN, A carriers for the *OXTR* SNPs rs53576 and rs2254298 showed more pronounced symptoms than GG carriers [60]. AN individuals with an A allele at either location versus GG carriers for both locations had more pronounced ED psychopathology, preoccupation with food, and body shape concerns, leading the authors to speculate that the GG/GG haplotype might serve a protective function [60]. In line with these findings, Micali et al. [61] found that the rs2254298 A allele was associated with more restrictive eating over the lifetime in a community sample of women.

Studying six *OXTR* SNPs in 69 women with AN, 90 with BN, and 103 HC, Kim et al. [62] found the rs53576 GG genotype was more common in individuals with BN than HC, while there were no differences between individuals with AN and HC. Among women with BN, the GG genotype was not associated with severity of ED pathology, but G carriers reported a stronger tendency to move away from unpleasant stimuli. In a mixed sample of 7,723 women, those with the rs53576 GG genotype endorsed life-time experiences of purging behavior more frequently than A carriers [63]. Similarly, Micali and colleagues [61] found that individuals with the rs53576 GG genotype had a higher likelihood of life-time binge eating and purging. *OXTR* variation (SNPs rs2268493, rs2268494, rs2268498, and rs237885) has also been associated with overeating and unhealthy dietary choices, predominantly through increased preference for sweet and fatty foods, as well as greater sensitivity to reward and punishment [64]. In contrast, a genome-wide association study in a large accumulated patient sample did not support the hypothesis of more frequent minor *OXTR* alleles in AN [65], and a study of women with active or weight-recovered AN and

current BN found that five candidate SNPs of the *OXTR* were not predictive of the development of either AN or BN [60].

Exploring the role of gene-environment interactions, namely, the interaction of the *OXTR* SNPs rs53576 and rs2254298 and quality of maternal care, women with an rs2254298 A allele coupled with experienced poor maternal care reported a four-fold higher frequency of life-time binge eating and purging [61], which is in line with accumulating evidence suggesting a close relationship between those *OXTR* SNPs and early paternal care in determining the occurrence of psychopathology across the lifespan [66]. Cytosine bases within deoxyribonucleic acid (DNA) can be methylated, which can affect gene expression and therefore contribute to phenotypes or disease. Only one study has investigated methylation status of the *OXTR* gene in individuals with ED. Contrasting individuals with AN versus HC with regard to methylation in the *OXTR* M2 region in buccal samples, the authors found a total of six CpG sites with differences in methylation levels between groups (i.e., five instances of increased and one of decreased methylation). In addition, for the five sites with increased methylation, methylation levels were explained by body mass index and, to a lesser extent, ED psychopathology and anxiety [67].

Genetic studies indicate that the physiology of the OXT system might confer vulnerability to aberrant eating behaviors across the lifespan, and environmental risk factors interact to modulate risk for developing an ED. While these data suggest a genetic vulnerability to a lifetime occurrence of ED pathology through the OXT system, the observed altered methylation in AN could be cause and/or consequence (through low weight and nutritional deficiencies altering methylation) of ED pathology and thus warrants further investigation into its origin. As genetic studies point to an inherited vulnerability for both AN and BN with regard to *OXTR*, endocrine investigations provide converging evidence for alterations of endogenous oxytocin levels in AN but not BN. As *OXTR* and OXT levels represent different foci of investigation, it will be important to conduct studies that assess genetic encoding of the OXT receptor together with current endogenous OXT levels as well as careful assessment of environmental influences throughout the lifespan and ED and other pathology within the same individuals. This approach will allow researchers in the field to develop a model that integrates genetic predisposition, environmental factors, endocrine status, and clinical presentation. Going beyond AN and BN, more research in other ED is needed.

OXT and Food Intake in ED

Little research has investigated the direct link between OXT and food intake in those with ED; and there are no data using an experimental test meal, which offers a range of caloric and macronutrient options and has been employed in studies of OXT effects in psychiatrically healthy populations [20, 22, 23]. In a randomized, double-blind, placebo-controlled crossover trial of 34 young women with BN compared to 33 HC, a single dose of 40 IU intranasal OXT did not impact apple juice consumption 90 min after administration, but decreased total reported calorie consumption over 24 h [68]. The reduced food intake following OXT administration in BN is consistent with the anorexigenic effects of OXT reported in healthy normal-weight, overweight, and obese animals and humans [18–23]. In

the same study, no differences in apple juice consumption or reported 24-h total caloric intake were observed between 35 women with active AN and HC [68]. Two other studies found no evidence for altered caloric intake in women with AN versus HC in a juice or smoothie challenge following administration of a single dose of 40 IU intranasal OXT, while OXT showed significant effects on other outcome measures related to ED pathology (i.e., salivary cortisol and selective attention to food and eating-related stimuli) in the same individuals [69, 70]. In AN, exogenous OXT administration may be ineffective in countering physiological signals (e.g., changes in other appetite-regulating hormone levels) that increase the drive to eat in the setting of chronic dietary restriction.

OXT and Cognitive Processes Driving Aberrant Eating Behaviors in ED

Other studies have focused on the relationship between OXT and cognitive processes guiding eating patterns, negative affect, and social cognition in ED. Fasting plasma OXT levels in women with weight-recovered AN were related to more pronounced total ED pathology and weight concerns; this relationship was absent in women with active AN, where nutritional and endocrine consequences of self-starvation might prevail over OXT deficiency [51]. In active and weight-recovered women with AN, postprandial OXT levels were associated with severity of eating pathology, including dietary restriction, eating, weight, and shape concern [53]. Using an fMRI visual food stimuli paradigm, patients with active and weight-recovered AN showed reduced activation in key brain regions processing homeostatic and reward-related food motivation (including hypothalamus, amygdala, and anterior insula) while fasting and, in women with active AN, hypoactivation in the anterior insula after a meal [32]. The between-group differences in OXT levels explained a significant proportion of these differences in brain activation [53].

Several studies have investigated the effects of exogenous OXT on selective attention (frequently biased toward illness-related stimuli) in individuals with AN and BN. In a randomized, double-blind, placebo-controlled crossover study of a single-dose of 40 IU intranasal OXT in women with active AN, OXT decreased selective attention toward images of eating and fat body parts in a visual probe detection task [69]. The authors speculated that the impact of OXT on selective attention might reflect reduced eating and shape concerns. The same dose reduced the selective attention to images of palatable food following (but not preceding) a smoothie challenge in women with AN, further supporting the notion that OXT can affect attentional control in the presence of illness-related stimuli [70]. Studies have also investigated its impact on selective attention to images of faces with emotional expressions. Employing a version of the visual probe detection task with happy and angry faces, 40 IU intranasal OXT reduced selective attention to angry faces in women with BN and HC with similar impact [71]. In contrast, individuals with AN showed an avoidance of angry faces in the placebo condition; and the same dose of intranasal OXT increased vigilance to this image category [72]. These data show that OXT affects emotional attentional bias in AN, further supporting the concept that exogenous OXT exerts illness-specific effects in individuals with AN. Regarding effects of sustained OXT administration on cognitive processes driving aberrant eating behaviors, following administration of 36 IU intranasal OXT or placebo daily for 4–6 weeks during inpatient treatment, individuals with AN in the treatment arm showed reduced eating concern despite similar weight gain [59]. In the same

study, cognitive rigidity, known to contribute to maintaining ED pathology, also improved with OXT treatment.

Thus, in individuals with active or past AN, alterations in OXT levels are linked to ED pathology by means of cognitive processes governing food intake, including eating attitudes, attention and perception, cognitive flexibility, and reward processing. Moreover, studies using intranasal OXT suggest that the lower basal OXT levels reported in the active and recovered state might be causally involved in clinical sequelae. Studies of OXT and cognitive processes in other ED are lacking.

OXT, Negative Affect, and Stress in ED

Negative affect plays a key role in the development, maintenance, and poor outcome of ED [9, 10, 46]. Lower fasting OXT levels in women partially recovered from AN were not only related to total ED pathology and weight concerns, but were also associated with higher state and trait anxiety levels [51]. For individuals with current and past AN, higher postprandial OXT levels were associated with more pronounced depressive and anxiety symptoms, including higher anxiety surrounding a study meal [57]. These relationships between OXT and negative affect in AN are in line with the reported link between OXT pathways, neurocircuitries processing and regulating emotions, and the hypothalamic-pituitary-adrenal (HPA) axis. First, OXT has been shown to exert anxiolytic effects in human and animal studies [41, 43]. The positive impact of OXT on anxiety is likely due to a combination of (1) reduced activity and functional connectivity within the limbic system processing fear and anxiety; (2) an increase in activation of PFC areas involved in emotion regulation; and (3) increased functional connectivity between PFC and limbic system [73–76]. In AN, where unstimulated OXT levels are markedly low, the reduced availability of OXT could contribute to increased emotional reactivity and lack of successful top-down emotion regulation and thus to increased anxiety levels. Increased anxiety, in turn, is known to precede and promote ED pathology [9, 77] and hinder successful recovery [10]. Accordingly, low OXT levels in AN could negatively impact illness severity and trajectory by increasing anxiety.

Importantly, OXT impacts HPA axis functioning via direct and indirect routes [42]. In humans, central OXT administration reduces basal and stress-induced HPA axis activation and cortisol release [40, 78–83]. Individuals with active AN also show marked hypercortisolism (believed to result from a defect at the pituitary level or above) [84, 85], and cortisol levels in this population are positively linked to symptom severity, even when controlling for body mass index [86]. Again, lower OXT availability could contribute to promoting hypercortisolism and associated psychopathology. While cortisol levels normalize after weight recovery [85, 87], subtle HPA axis abnormalities persist [88]. Similarly, basal peripheral OXT levels were still low after weight gain [51], and cognitive features of ED also frequently persist with weight gain [89, 90]. Interestingly, in BN, for which no evidence of alterations in OXT levels has been reported, hypercortisolism was not found [85]. Support for a potential impact of OXT on HPA axis activation in ED comes from Leppanen et al. [70], who showed that a single dose of 40 IU intranasal OXT in young women with AN reduced salivary cortisol levels assessed 55 and 80 min after administration. In individuals with AN, daily intranasal OXT administration (36 IU) in addition to inpatient treatment for

4–6 weeks not only decreased eating concern but also led to reduced salivary cortisol levels in anticipation of an afternoon snack compared to placebo [59]. Proof-of-concept studies with single-dose or sustained OXT administration are important to further explore the link between OXT and negative affect and stress.

OXT and Social Cognition in ED

Similar to negative affect, alexithymia and associated social difficulties are part of ED across the weight spectrum [8, 47, 91], preceding and contributing to their development and maintenance [92–94]. Relatively few studies have investigated the link between OXT and social-cognitive features in individuals with ED. In a mixed sample of women with active AN, weight-recovered AN, and HC, serum OXT levels were inversely related to severity of alexithymia [95]. In a study of 40 IU single-dose intranasal OXT versus placebo, OXT increased emotion recognition sensitivity in a dynamic facial morphing task in BN and HC, but not in AN [68]. In line with this finding, the same dose of OXT did not change interpretation of emotional states in females with AN [96]. Four weeks of intranasal OXT, while promoting cognitive flexibility and reducing salivary cortisol in anticipation of food intake, did not alter social cognition in women with AN [59]. Further research is required to understand the relationship between OXT and social cognition across ED. Future investigations should include studies of the relationships between endogenous OXT levels and social cognition as well as causal tests of the involvement of OXT pathways in social cognition with exogenous OXT administration.

OXT and Bone Health

In addition to its effects on food intake and weight as well as cognitive, emotional, and social functioning, OXT is anabolic to bone [97, 98]. AN is associated with severe bone loss and increased fracture risk due to malnutrition and endocrine alterations [99], and low serum OXT levels in AN are associated with lower bone mineral density and reduced estimated bone strength [50, 100]. Taken together, this indicates that low basal OXT levels may play a role in the multifactorial bone loss in AN. Although OXT could be studied as a potential treatment for AN-induced bone loss, safety of OXT in this population must first be demonstrated.

OXT Pathways as a Treatment Target in ED?

The use of OXT administration to treat ED has been suggested [101, 102]. Administration of supraphysiologic exogenous OXT via the intranasal route increases central and peripheral OXT levels [103, 104]. Moreover, exogenous OXT administration can induce endogenous OXT secretion, thus altering OXT availability [105]. A meta-analysis has shown that single-dose or short-term OXT administration (up to 182 administrations) is well-tolerated in both healthy individuals and selected psychiatric populations [106]. As reviewed above, first proof-of-concept studies show that single-dose intranasal OXT alters illness-related cognitive, emotional, and social processes in AN. As OXT deficiency may contribute to bone loss in AN, exogenous OXT administration could additionally improve bone health. However, its weight-loss properties (including effects on food intake, energy expenditure,

and metabolism) raise concerns regarding its safety in individuals with low-weight ED. A first study showed evidence for safety and tolerability of repeated exposure to intranasal OXT at supraphysiologic doses [59]. This investigation took place within the well-controlled environment of an inpatient hospital setting, and extensions to outpatient settings will require careful additional considerations. In addition to close monitoring of safety parameters, investigators could consider stimulation of endogenous OXT release or use of OXT replacement rather than supraphysiologic doses. The study by Russell et al. (2018) did not require participants to discontinue their psychotropic medication, and thus it is unclear whether OXT directly caused the observed positive effects or whether it promoted improvement by augmenting the positive impact of medication [107].

In individuals with BN, there is first evidence for exogenous OXT reducing food intake, which suggests that OXT may impact overeating – but not necessarily loss of control of eating, namely, bingeing – in this population. OXT pathways may represent a promising target for BED where with the available treatments, up to 50% of patients continue to binge, and sustained weight loss is difficult to achieve [108, 109]. In BED, disordered eating often drives obesity, and elevated reward responsiveness and impaired cognitive control are more severe than in obese individuals without BED [35, 110, 111]. Given the evidence that OXT may reduce consumption of palatable foods by decreasing reward responsiveness and increasing cognitive control [22, 26], OXT effects on eating behavior and weight in BED (as well as other ED associated with bingeing) will be particularly relevant to study. For all ED, studies establishing endogenous OXT levels and the response to exogenous OXT will be important. Within AN, more research on the subtypes or differences between AN and atypical AN would be valuable. Safety of chronic OXT use in these specific populations will be critical to investigate before advancing clinical use.

Conclusions

The neurohormone OXT may play a role in the pathophysiology of AN, and first evidence indicates that OXT administration impacts core aspects of AN pathology. Further research is needed to clarify OXT effects on dietary choices and food intake as well as cognitive, emotional, and social difficulties driving AN. Furthermore, investigations of the potential role of OXT in other ED across the weight spectrum (ARFID, BED, and OSFED) are required to fully understand OXT functioning in relation to ED pathology. Genetic studies implicate the OXT system in restrictive, binge eating, and purging behaviors. Going forward, studies combining genetic assessments with measurements of OXT levels along with assessments of environmental influences and careful characterization of ED pathology are required to understand the role of genetic vulnerability for an altered OXT system in the development and maintenance of ED pathology. Transdiagnostic approaches may prove useful in linking endogenous OXT levels and OXT administration to the different types of aberrant eating behavior. Before advancing OXT administration as a treatment, safety and efficacy in these ED populations need to be established. Given the high burden of illness associated with ED and the challenges inherent in their treatment, the emerging literature highlighting OXT as a candidate novel intervention holds great promise. It is our hope that the literature reviewed herein coupled with the outlined plans for future studies will guide the field in the next wave of investigations of this neurohormone.

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Conflict of Interest

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EAL is on the scientific advisory board and has a financial interest in OXT Therapeutics, a company developing an intranasal oxytocin and long-acting analogs of oxytocin to treat obesity and metabolic disease. EAL's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. This company was not involved in any way in this research.

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