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Oxytocin and Anxiety Disorders: Translational and Therapeutic Aspects

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Abstract
Purpose of Review This review aims to evaluate the most recent literature examining the oxytocin (OXT) system's role in human anxiety by surveying various fields of preclinical and clinical research supporting this role, and queries whether the OXT system might be a target for novel anxiolytics.
Recent Findings Evidence from the diverse body of literature presented here, from translational research, genetic and neuroimaging studies, to clinical trials of intranasal (IN) OXT reveals a positive association. In addition, some moderators (e.g., sex, specificities to cues) of OXT's anxiolytic effects can have an important influence on its outcomes, awaiting further research.
Summary Evidence for the role of OXT in regulating anxiety is undeniable. We expect that the diverse particularities of the OXT system will help broaden our understanding of anxiety and stress-related disorders. We conclude that OXT promises an enticing treatment option for human anxiety disorders especially those associated with socio-emotional dysfunctions.

Keywords Oxytocin · Anxiety · Social anxiety · PTSD · Human · Rodent

This article is part of the Topical Collection on *Anxiety Disorders*

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Introduction

Anxiety disorders are the most prevalent of all psychiatric conditions, with a combined lifetime prevalence of generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), and social anxiety disorder (SAD) estimated around 30% [1]. Alas, conventional anti-anxiety treatments fail to help patients reach full remission and do not properly prevent relapses hence asserting the need to broaden the therapeutic arsenal of such ailments [2].

There is a growing interest in the neuropeptide OXT for its role in social cognition and behavior. OXT is now considered a *social* hormone owing to the voluminous literature alluding to its capacity to moderate many social behaviors in various mammalian, primate species, and humans. It has been found to increase trust, pro-social behavior, and sensitivity to reward which can ultimately increase motivation to treatment and improve therapeutic alliance [3, 4••, 5]. In addition, OXT is involved in the regulation of stress and anxiety, a property that has been validated by numerous pharmacological and genetic studies. For instance, endogenous OXT has been shown to amply rise in response to psychological and psychosocial distressing situations counteracting anxiety [4••]. The literature on OXT in anxiety disorders indicates that it might be an alluring treatment option for human afflictions bearing a socio-emotional dimension like PTSD and SAD [4••, 6]. This growing evidence that OXT might have a potential therapeutic benefit in this unmet need is comforting.

The present review article examines the most recent literature addressing this line of research focusing on both preclinical and clinical studies highlighting the role of the OXT system in human anxiety. The body of literature herein encompasses translational research on OXT's relationship to animal fear and anxiety, studies of genetic variation in the OXT system, neuroimaging research, and clinical trials of IN OXT

including investigations of moderators of OXT's anxiolytic effects (e.g., gender, genetic factors, type and timing of stressor). Due to the space constraint, and rather than discussing specific methodological limitations of individual studies, we offer a synthesis of the more general and frequently encountered limitations on this subject in the "misconceptions and controversies" and conclusion sections.

Neurophysiology and Neurobiology of the OXT System

The major OXT neurosecretory system consists mainly of the paraventricular (PVN) and supraoptic (SON) nuclei in the hypothalamic-neurohypophysial system, along with the accessory magnocellular nucleus of the hypothalamus. This neurosecretory system projects centrally to the neurohypophysis in order to modulate the activity of several brain regions where OXT can bind to the extensively distributed OXT receptors (OXTR) [7].

Although OXTR have not been conclusively mapped in humans, there is considerable progress in the representation of circuits moderating its role in rodents: whether by facilitating social approach in the medial Prefrontal Cortex (mPFC) [8] or by its synergistic action with serotonin to modulate social reward in the nucleus accumbens [9]. In rats, OXTR were found in the spinal cord, brainstem, hypothalamus, amygdala, and nucleus accumbens [10]. In primates, the hippocampus, and the anterior cingulate cortex hold OXT binding sites as well [11].

In humans, a recent systematic review and meta-analysis by Wigton et al. strengthened the evidence that the amygdala is highly involved by reporting that the majority of studies reported a reduction in the amygdala activation following IN administration of OXT. Nevertheless, the latter does not preclude that other brain structures would turn out to be important sites of OXT action [12•].

Oxytocin, Anxiety and the Hypopituitary-Hypophysis-Adrenal Axis

Translational animal studies on the effects of OXT repeatedly demonstrated evidence of its regulatory function on the hypopituitary-hypophysis-adrenal (HPA) axis to the extent of being considered today an irrefutable sign of its anxiolytic activity [13]. In human models, however, data on the IN OXT effects on cortisol levels is not unanimous, generating mixed results [14–16]. A more recent study by Jurek et al. was more conclusive regarding the anti-stress effect of OXT by inhibiting the expression of the main activator of the HPA, the corticotrophin releasing factor within the PVN [17].

In healthy male and female individuals, it was demonstrated that the protective stress-reducing effects of OXT unravels only after an initial, early stage, co-activation of both the HPA axis and the OXT systems, and this in terms of accelerated recovery rather than an attenuated reactivity [18].

Genetic and Epigenetic Variation in the OXTR Gene

The OXTR gene is located on chromosome 20 in humans and contains three exons, each encoding for a specific portion of the neuropeptide [19].

For the last two decades, several studies have taken interest in the relationship between allelic variations in the OXT system and many parameters related to anxiety disorders, anxiety-related personality traits, structural and dynamic brain variants, and responses to stress. The unveiling of potential associations between the behavioral phenotypes and a genetic predisposition further bolsters the implication of OXT in the etiology of socio-emotional dysfunctions.

An association with empathic, optimistic, and trustful social traits and the G allele of the 6930G>A (rs53576) variant in intron 3 of the OXTR gene contrary to the A allele carriers is an illustration [20•]. One year later, Chang et al. found that A/A carriers of this same gene had an interactive effect of dopamine and OXT levels with high scores of negative affectivity and neuroticism [21]. Concomitantly, Myers et al. identified a single nucleotide polymorphism (SNP) (rs139832701) to be correlated with early life stressors and higher anxiety, depression, and stress scores [22].

Epigenetic regulation of the OXTR receptor gene through methylation of cytosine-phosphate-guanine appears to be linked to the SAD categorical phenotype, with increasing social anxiety, increased cortisol response to stress, and increased amygdala activation [23•]. Other variations in the OXT system genes are being linked to higher social sensitivity and increase risk of full-blown SAD [24], (for review, [25]).

Balance of the Brain OXT System in Anxiety Regulation

The balance of the brain OXT system and its consequences on emotional and social behaviors illustrated by Neumann et al. were found to span along the continuum from normal mental health to psychopathology [4••, 7].

A low brain OXT activity reflecting high anxiety levels may be due to one or more of the following: (1) low OXT gene expression, (2) low levels of central OXT release and availability in the extracellular fluid at rest and/or when stimulated, and/or (3) low OXTR expression and binding capacity. Several factors may be involved in regulating this balance by improving these parameters (e.g., physiological and

environmental stimuli, genetic and epigenetic factors, pharmacotherapy). An adaptive shift to the opposite side of the balance can sometimes be the case (e.g., in the case of chronic adverse life events when maintaining a low level of anxiety can be beneficial) [4••, 7].

Interactions of the OXT System With Other Neurotransmitters

It is presumed that OXT interacts with other neurotransmitters in different brain regions.

In the amygdala, OXT interacts with serotonin to produce part of its anxiolytic effect, allowing for new prospects to therapeutic strategies [26]. Moreover, an interaction with the dopaminergic system, mostly within the nucleus accumbens [27], and the amygdala [28], boosting the rewarding effects of social encounters is robustly substantiated. The anxiolytic effects of OXT is also thought to be mediated via the potentiation of γ aminobutyric acid (GABA) inhibitory properties on cortico-releasing hormone neuronal activity [29, 30•]. Lately, an evidence of the interaction with the glutamatergic system in the septum was outlined [31].

Translational Animal Research on OXT and Anxiety

We provide a non-exhaustive review of a large body of translational and preclinical work highlighting the role of the OXT system in anxiety.

Albeit the mixed results of acute and chronic anxiolytic effects of OXT reported in the review by Rotzinger et al. [32], a series of important animal research highlighting the role of OXT as an anxiolytic were conducted [7, 33, 34]. In fact, OXT was found to reverse the social fear in social fear-conditioned mice [4••]. Moreover, in a rodent model of PTSD, OXT administration was observed to increase recall of extinction learning [35•]. In contrast, IN OXT increased anxiety to unpredictable shocks [36].

Translational research pertinent to human anxiety disorders featured three key points. First, animal research on OXT allows a better understanding of the dynamics potentially confirming the effects on distinct neuropeptide receptors and the possibility for their manipulation [37, 38], for example, the use of specific knockout strains of animals [37, 39, 40] and the implementation of other novel techniques unavailable in humans (e.g., optogenetics [34], or gene deletion [9]). A second feature worth discussing is the access to a wider interspecies variations in OXT-related parameters like aspects of sociality [41] and OXTR density [42, 43]. The third point is the information that translational research can amass when assessing the difference between short-term and long-term OXT treatment.

The acute anxiolytic effects of OXT in preclinical studies have been consistently demonstrated in male and female rodents when using intracerebroventricular (ICV) or local (PVN, central amygdala, PFC) administration of an OXTR agonist or antagonist [37, 44, 45]. On the other hand, the chronic effects of synthetic OXT in rodents strongly depend on the dose and duration of application, as well as on the baseline level of anxiety, with a significant difference in effect between gender [13, 46, 47•, 48•]. Actually, a chronic 2-week ICV infusion of OXT in male mice proved to be highly anxiogenic at a regular 10 ng/h dose whereas a tenfold lower dose prevented the hyper-anxiety and decreased in vitro adrenal sensitivity [48•].

Moreover, the differential effects between single, repeated (e.g., four administrations over 7 days) and chronic subcutaneous OXT administrations on memory consolidation and fear-related behavior were recently studied in a rat model of PTSD.

The reduction in generalized fear behavior was only obtained with the repeated and chronic subcutaneous OXT administration, 7 and 14 days after shock exposure, respectively. The single administration of OXT immediately after shock exposure, on the other hand, enhanced contextual fear behavior at day 2, inducing an increase in fear memory consolidation [49••]. The authors speculated that the long-term anxiolytic effect of repeated and chronic OXT administration could be the product of an OXT-mediated increase in extinction memory consolidation during re-exposure to the trauma context in safer conditions [49••].

Another advantage of the translational OXT research is the use of conditioned association experiments to examine the acquisition, learning, and extinction of anxiety [50, 51], ascertaining that OXT is highly implicated in the moderation of conditioned association and fear learning [52].

Table 1 summarizes the most recent rodent studies investigating the anxiolytic properties of OXT.

Misconceptions in OXT Research

A controversial issue in the OXT-anxiety literature is the occurrence of acute anxiogenic effects following OXT administration. To settle this misconception, Macdonald et al. referred to the similarities seen with the serotonin reuptake inhibitors [53]. Furthermore, Tol et al. warned against the risk of impairing fear learning with the use of strong short-term anxiolytics (as with benzodiazepines) [54]. Hence, the potential long-term benefits of chronic OXT use should be assessed carefully before dismissing it because of its anxiogenic acute effects.

Another challenging aspect is whether OXT crosses the blood brain barrier (BBB) or could it be that its effects follow a downstream mechanism triggered by peripheral signaling,

Table 1 Summary of recent rodent studies investigating the anxiolytic properties of oxytocin

Authors	Subjects	Objectives and parameters	Main findings
Li et al., 2016 [57]	Male and female mice. Oxytocin receptor interneuron is a class of medial PFC interneurons sensitive to OXT, modulating sociosexual behavior only in female mice [8].	Optogenetic activation of oxytocin receptor interneurons.	Activation of oxytocin receptor interneurons in male, but not female, mice strongly regulates anxiety-related behaviors.
Sánchez-Vidaña et al., 2016 [96]	31 young adult male rats.	Investigating the effect of repeated OXT treatment on hippocampal cell proliferation, dendritic maturation of new neurons and social/emotional behaviors. OXT v/s PBO, daily for 2 weeks, assessed by behavioral tests.	OXT increases social behaviors and reduces anxiety- and depressive-like behaviors. OXT promotes cell proliferation, differentiation, and dendritic complexity of new neurons in hippocampus.
Smith et al., 2016 [30•]	Female prairie voles.	OXT injection in PVN	Ante-stress OXT injections inhibits stress activation of HPA axis via recruitment of GABAergic neurons. Post-stress OXT treatments seem ineffective.
Ayers et al., 2016 [97]	157 male rats.	Baseline pre-fear conditioning startle responses firstly measured (Rats categorized as low or high startlers). Subcutaneous OXT injection to all rats.	OXT reduced background anxiety only in rats with low pre-fear startle responses (phenotype of high trait anxiety in rats and humans with distress disorders).
Huang et al., 2014 [47]	Adult male mice.	Chronic and acute IN OXT administration.	Chronic IN OXT administration produced a selective reduction in social behaviors towards same and opposite sex, and towards familiar and unfamiliar subjects. Acute IN OXT administration increased social behaviors towards opposite sex, did not alter them with male familiar mice, and reduced them with male unfamiliar mice.
Sabihi et al., 2014 [45]	Male and female rats.	OXT injection into the prelimbic medial PFC to determine whether the effects of OXT on anxiety-like behavior are sex dependent and to evaluate the specificity of OXT.	Although endogenous OXT in prelimbic medial PFC does not regulate anxiety, exogenous OXT applied to this site reduces anxiety-related mice behavior independent of sex.

GABA γ aminobutyric acid, *HPA* hypopituitary-hypophysis-adrenal axis, *IN* intranasal, *OXT* oxytocin, *PFC* prefrontal cortex, *PBO* placebo, *PVN* paraventricular nuclei

since only low levels of OXT are measured inside the brain after relatively large peripheral administration. In this review, it is clear that both cerebrospinal fluid (CSF) and plasma OXT levels can be correlated with behavioral changes; however, what remains unanswered is whether the peripheral OXT levels are indicative of central OXT. An even more enigmatic hurdle is the analogy between OXT and vasopressin (VP), differing by only two amino acids, where this latter also mediates either potential peripheral or central effects of OXT at the fear circuit. This matter can eventually be figured out once a positron emission tomography ligand for the OXTR is tested.

Inconsistent Gender Effects

Albeit the abundancy of recent research in rodents [55] and humans [8, 12•, 56, 57] strongly supporting the earlier observations that dissimilarities in hormonal balance and brain circuitry between males and females can contribute to complex behaviors, the exact mechanisms underlying the gender biases in the manifestations and response to treatment in social and emotional disorders are still poorly understood. The disparate gender effect of OXT on higher-order circuits regulating anxiety is still far from being elucidated and appears to be highly brain region- and species-specific [58••]. Since most anxiety disorders are twice as prevalent in females [59], this sex difference in OXT effects once explored and resolved might shed some light on the gender-specific brain circuitry disparity.

An illustration of this differential anxiolytic effect specific to the male gender was illustrated by Weisman et al. who examined plasma OXT levels in 473 healthy adults (41.5% males) and found a link between those levels and low trait anxiety only in men [60]. Another example is the findings by Bredewold et al. that only female rats' social play was affected by OXT injection into the lateral septum [61]. Conflicting data with opposite effects between sexes on brain activation during human social interaction have also been reported [62], whereas other authors found similar effects in both sexes [63]. Moreover, compared to gender differences in the OXT peptide synthesis, the differences in its receptor system are even more cryptic, generally displaying higher OXT expression in females, whereas in males its receptor expression is higher. [58••]. Further examples of these gender discrepancies are discussed in the specific sections of this review.

Specificity of OXT Effects

Pertaining to the specificity of the OXT action, Evans et al. suggested that the anxiolytic effects arising in a social setting might be specific to this cue. In other terms, the enhanced sense of social approval resulting from the administration of OXT could be the product of a positive processing bias emerging from the complex interaction of OXT on higher-order social function in the instance of social stimuli [64]. Additional investigations over this nuance are warranted to better understand the situations under which IN OXT is prosocial. The use of non-social control conditions would also be helpful in confirming the specificity of its effects.

Furthermore, social stimuli can sometimes be misleading, signaling both safety and danger in certain ambiguous situations. An active area of research is addressing this issue of a possible nonspecific effect (increasing social salience in general) versus a more specific effect on the processing of stimuli with a certain valence (e.g., happy vs. fearful faces) [65]. An additional example of this specificity is the differential moderating effects of OXT influenced by the perception whether a social partner is thought to be a member of the in-group or outgroup [66]. In fine, since it appears that selective OXTR activation in the PFC versus the amygdala could generate contrary effects on fear extinction, the OXT treatment mechanisms could become better apprehended by understanding how OXT dosing can differentially affect regional OXTR [67].

Intranasal Application of OXT in Humans

The question whether OXT given intranasally could be considered a reliable measure for the assessment of its functions (with the absence of alternatives in human research) has been a matter of debate. Born et al. asserted that neuropeptides when given intranasally crossed the BBB [68]. Moreover, a critical review of the impact of OXT IN on social and behavioral process reported considerable positive results [69]. More recent studies further supported the adequacy of the IN delivery system suggesting a direct nose-to-brain route for OXT [5, 70]. However, Walum et al., in their analysis of IN-OXT studies, warned that such studies are frequently underpowered and hence a high probability that the reported effects are an overestimation [71]. In order to minimize the effects of anatomical variations in IN OXT uptake, Guestella et al. proposed a protocol standardizing OXT administration [72].

Human Imaging Studies

For the past few years, functional magnetic resonance imaging (fMRI) has been extensively used to investigate the behavioral and cognitive effects of OXT, and the neural correlates of its effects [73]. It has been shown that OXT induces activity in cortical and subcortical regions in both sexes, although gender-specific differences in these responses have also been reported [12•, 74, 75]. The seminal meta-analysis by Wigton

et al. is a perfect example of the explicit emotional processing tasks in women, after OXT administration, resulting in an increased activity in the temporal lobes and the amygdala, while implicit emotional processing in men had the opposite effect [12•]. Sripada et al. have demonstrated an increase in the functional coupling of the ventromedial PFC and the amygdala stimulated by IN OXT administration in healthy men [76]. Dodhia et al. replicated this effect in patients suffering from SAD [77]. Another MRI study using IN OXT suggested that OXT might act by limiting the control of the amygdala while concomitantly increasing the medial PFC function to facilitate the extinction of conditioned fear, thus reproducing a top–down control over the fear response [78].

OXT and General Anxiety: Human Research

In the sections herein, it is crucial to keep in mind additional technical limitations in particular the lack of a radioligand for the OXTR, the lack of a centrally active OXT antagonist in human research, the limited understanding of the functional role of OXT genetic variants, and the limited understanding of the relationship between central OXT system activity and peripheral OXT levels. Indeed, the pharmacodynamics, pharmacokinetics, and mechanism of action of IN OXT are still not fully understood. Although the treatment of anxiety disorders should optimally consist of chronic, multiple doses over weeks, few clinical trials of chronic OXT in humans were conducted.

The scant studies that are in line with this pharmacological standard of care have produced initial positive results in GAD [79] and a negative outcome in obsessive compulsive disorder (OCD) [80, 81]. Most reports, however, have assessed the effect of single-dose OXT in various models of anxiety, in both healthy and mentally ill individuals, and have shown positive, neutral, and negative effects on different parameters of anxiety. Feifel et al. supported a beneficial effect of daily OXT administration in GAD patients over 3 weeks, particularly in males [79]. It is clear that additional studies assessing the effect of chronic or repeated OXT administration in GAD are warranted.

Social Stress and Social Anxiety

A recent meta-analysis demonstrated a significant impact of IN OXT in reducing cortisol levels during stressful laboratory tasks that had a social-evaluative component [82]. Wirth et al. went further by stating that no effect of OXT was seen on basal cortisol in the absence of an acute stressor [83]. The stress dampening effect of OXT administration seems to be amplified by a social cue. In line with those results, Neumann et al. reported that under nonreproductive and stress-free conditions where basal OXT activity is low, there is no anxiolytic effect of endogenous OXT using an OXTR antagonist. They concluded that endogenous OXT might be responsible of regulating anxiety in the setting of psychosocial or physiological stressors rather than a baseline maintenance of a basal level of anxiety [4••]. An elevated OXTR binding in regions associated with the fear circuitry, notably the dorsolateral septum, central amygdala, hippocampus, and the median raphe nucleus in social fear suggests a significant association with changes in the brain OXT system. The modifications in OXTR binding have been found to be reversed following social fear extinction [35•].

OXT in PTSD and Social Anxiety Disorder: Human Research

Several human studies examined the OXT system in relation to both PTSD and SAD. IN OXT versus placebo demonstrated an enhanced social fear extinction [78, 84] and enhanced extinction recall [85]. Male PTSD patients were found to have lower salivary OXT levels compared with male trauma-exposed controls [86].

As is the case in translational research on rodents, single versus repeated administration of OXT have demonstrated opposite results in humans. In a recent multicenter randomized double-blind placebo-controlled clinical trial (RCT) assessing the efficacy of IN OXT in recently trauma-exposed emergency department (ED) patients (N = 107), the repeated administration proved to be a promising early preventive intervention for PTSD for individuals at increased risk of its development whereas a single OXT administration acutely increased amygdala reactivity to fearful faces and attenuates amygdala-PFC functional connectivity [87••]. Similarly, a single systemic injection of OXT was enough to impair reconsolidation of social fear memories after reactivation of learned fear [88]. A study by van Zuiden reported beneficial effects of OXT only in trauma-exposed subjects with high acute PTSD symptoms [89••]. Apparently, the nature of the threat (social vs non-social, predictable vs unpredictable) is also an important moderator of the effectiveness of exogenous OXT in humans. Furthermore, the timing of the OXT exposure relative to cue presentation is another determinant of the response to OXT administration [85]. All in all, those studies demonstrate that OXT can be a potentially effective treatment of PTSD owing to its reconsolidation blocking effects.

Several studies assessing plasma OXT levels, OXTR gene methylation and SNPs, and the effect of IN OXT on SAD symptoms have been undertaken. For example, a decreased baseline OXT plasma level has been reported in patients with SAD [90]. Ziegler et al. found that a decreased OXTR methylation (likely to result in increased expression and less

Table 2 Summary of recent human studies of oxytocin in anxiety disorders

Authors	Subjects	Objectives and parameters	Main findings
Frijling et al., 2017 [87••] van Zuiden et al., 2016 [89••]	Recently trauma-exposed emergency department patients. - (Range N = 37–41) - Adult ED patients, 12 days post-trauma. M/F = 1 (N = 107, 53 OXT, 54 PBO).	- fMRI study assessing acute effects of single administration of OXT on functional fear circuitry - RCT assess the efficacy of repeated IN OXT v/s PBO administration early after trauma for preventing PTSD symptom development up to 6 months post-trauma.	- Single OXT administration acutely increased amygdala reactivity to fearful faces, attenuating amygdala-PFC functional connectivity. - Repeated IN OXT administration early post-trauma reduced PTSD symptom occurrence in recently trauma-exposed ED patients with high acute PTSD symptoms.
Koch et al., 2016 [98, 99]	Unmedicated male and female police officers with (n = 37, 21 M) and without PTSD (n = 40, 20 M).	RCT, cross-over fMRI study examining OXT administration on amygdala reactivity towards emotional faces v/s PBO.	PTSD patients showed more dampening of amygdala reactivity on exogenous OXT, benefiting from its administration.
Gorka et al., 2015 [92]	17 Generalized SAD males, 18 HC.	RCT, within-subjects design. fMRI study assessing amygdala response to fearful faces following acute IN administration of OXT or PBO.	During processing of fearful faces, OXT enhanced functional connectivity between amygdala and the bilateral insula and cingulate gyrus.
Notzon et al., 2016 [100]	Healthy probands (N = 388; 219 F, 169 M).	Gene–environment interaction approach. Assessment for anxiety in social situations depending on attachment style and OXTR rs53576 A/G genotype.	Strong association between less secure attachment and social anxiety. Stronger negative influence in A allele carriers of the gene.
Tabak et al., 2016 [101•]	125 students (90 F, 35 M).	RCT, between-subjects design. Investigation whether social anxiety moderates effects of OXT v/s PBO on social and non-social working memory.	OXT decreased social working memory performance in individuals with higher levels of social anxiety. Effects not observed for non-social working memory.
Acheson et al., 2013 [85]	44 local community, healthy participants M/F = 1.	RCT, assessing acute effects of OXT (v/s PBO) in fear-potentiated startle task of fear conditioning and extinction, tested for extinction recall 24 h later.	OXT did not facilitate extinction, but may facilitate fear extinction recall. OXT treatment can be used to enhance consolidation of fear extinction training.
Lebowitz et al., 2016 [102]	50 youth (55% F) suffering from anxiety disorders. (2/3 GAD 2/3 SAD, 1/3 Sep. AD, and 1/3 PD and SP).	Salivary OXT measurement and correlation with multi-method anxiety symptoms assessment and family accommodation.	Youth with Sep. AD, an interpersonal disorder in nature, had significantly lower salivary OXT levels than for other anxiety disorders.
Radke et al., 2017 [103]	52 healthy males.	RCT, between-subjects design, fMRI study during social approach-avoidance task. OXT v/s PBO.	OXT modulates task-related activity associated with emotional control in amygdala. Compared to PBO, OXT decreased amygdala activation during approach (when perceiving threatening scenes and faces) but not during avoidance of angry faces in male healthy subjects.
Cavalli et al., 2017 [104]	Healthy individuals (N = 52, 28 F, 24 M).	RCT, between-subjects design, IN OXT v/s PBO, administered 45 min before the acquisition phase of both cue and context conditioning (order of cue and context conditioning counterbalanced across subjects).	Reduction in early fear acquisition following OXT v/s PBO in nucleus accumbens for both cue and context conditioning.

ED emergency department, *F* feminine, *fMRI* functional magnetic resonance imaging, *GAD* generalized anxiety disorder, *HC* healthy controls, *IN* intranasal, *M* masculine, *OXT* oxytocin, *OXTR* oxytocin receptor, *PBO* placebo, *PD* panic disorder, *PFC* prefrontal cortex, *PTSD* posttraumatic stress disorder, *RCT* randomized clinical trial, *SAD* social anxiety disorder, *Sep. AD* separation anxiety disorder, *SP* specific phobias

binding potential) in 110 unmedicated patients with SAD was associated with symptom severity, elevated stress-induced cortisol responses, and increased amygdala activity [23•]. Promising results on improvement in self-evaluation of public performance was seen in patients with SAD who received IN OXT either alone or in combination with exposure therapy [91]. Additional reports assessing regional neuronal activity patterns and amygdala-prefrontal connectivity in response to emotional faces after administration of IN OXT conferred similar positive results [77, 92]. In fragile X patients, who demonstrate high levels of social anxiety, IN OXT improved eye gazing and reduced cortisol in response to a social challenge [93]. A selection of the most recent studies investigating the anxiolytic properties of OXT in human anxiety disorders is listed in Table 2.

Conclusion

There is a substantial body of evidence supporting the significant, complex and nuanced, modulatory role of the OXT system in different heterogeneous aspects of anxiety and anxiety disorders that stretches out to expand our understanding beyond the description of OXT as simply *anxiolytic.* In light of this review, our hopes for the development of new therapeutic options for some specific anxiety disorders using OXT stand high, especially if its effects turn out to be of long-lasting action and to have an adequate side-effect profile. It might also be that OXT treatment could prove more beneficial if it is conceived to target traits and dimensional anxiety like social cognition and interpersonal deficits rather than sticking to diagnosis-related approaches. It is also fitting to expect its initial use as an add-on to other treatments rather than being devised as monotherapy. Furthermore, its ability to increase feelings of trust could prove useful in facilitating therapeutic alliance, enhancing response to treatment and improving compliance.

However, many considerations should be thought-out before reaching firm conclusions on the clinical utility and efficacy of OXT. Despite the wealth of the aforementioned data, many questions regarding the pharmacokinetics and pharmacodynamics of IN OXT remain unanswered. Larger, more adequately powered RCT are crucial to identify appropriate dosing strategies for the various indications of use. Other highly relevant questions for future investigations are the exact mechanisms of action of OXT, its interaction with other pharmacological interventions, the correlation between peripheral and central OXT, and the increased concentration in the CSF when administered intranasally, and whether the effects are maintained at long-term follow-up.

Of particular focus in recent research has been the opposing, anxiolytic or anxiogenic, effects of OXT in fear and extinction memory consolidation depending on administration frequency and timing relative to fear conditioning [49••], and whether the conditioned stimuli are social or not [35•]. Further investigations of those observations are of critical importance to improve understanding and handling of OXT in its therapeutic aspects. Moreover, the dose-response effects of OXT administration on anxiety, alluded to by Peters. et al., are to be thoroughly examined as well [48•]. In regard to the sex differences in the OXT system, we believe that this is far from being well understood and no firm conclusions can be drawn.

The many studies available to date, implying a possible association between polymorphisms of the OXT peptide and receptor system and anxiety disorders, advocate a role of the former in the pathophysiology of the latter. However, it is clear that each finding constitutes no more than a tiny additive role in the complex genetics and gene–environment interactions underlying the different anxiety phenotypes. In addition, alike the HPA and serotonin systems, we can expect that the diverse aspects and particularities of the OXT system will help improve our understanding of the genetics, epigenetics, and nature of human anxiety and stress-related disorders.

In summary, the evidence for the role of OXT in general anxiety, stress-related disorders, and social fear, in addition to its many pro-social effects, is compiling. In fine, we found no conclusive evidence for the effectiveness of OXT in the treatment of OCD, rather a potential involvement of the OXT system in the etiology of OCD repetitive behaviors has been raised [94, 95]. Future rigorous research is needed in order to better ascertain the specificities and nature of the OXT role, allowing more accurate translation of findings into a comprehensive understanding of the underlying pathophysiology of anxiety disorders, leading the way to the development of effective treatment strategies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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