Oxytocin and obsessive–compulsive disorder

Mohamed R. Soltan

Department of Psychiatry, Faculty of Medicine, Fayoum University, Fayoum, Egypt

Correspondence to Mohamed R. Soltan MD, Department of Psychiatry, Faculty of Medicine, Fayoum University, PO Box 63514, Fayoum, Egypt. Tel: +20 101 072 3636/20 122 156 2006;
e-mail: dr.mohamedsoltan1979@gmail.com

Received: 22 June 2021
Revised: 30 June 2021
Accepted: 18 July 2021
Published: 24 June 2022

Egyptian Journal of Psychiatry 2022, 43:63–69

Attention has recently been focused on central nervous system neuropeptides as potential mediators of the symptom profile of obsessive–compulsive disorder (OCD). OCD includes a range of cognitive and behavioral symptoms that bear some relationship to dimensions of behavior associated with oxytocin (OT). Increased cerebrospinal fluid levels of the anxiolytic neuropeptide OT have been reported in OCD. OT is a neurosecretory nonapeptide synthesized in hypothalamic cells, which project to widely distributed sites in the central nervous system as well as the neurohypophysis. Central OT affects a variety of cognitive, grooming, affiliative, sexual, and reproductive behaviors in animals. OT is associated with the regulation of complex sociocognitive processes such as attachment, social exploration, social recognition, anxiety, and other stress-related behaviors. Based on these data, we hypothesized that OCD is mediated by OT. The aim of this review is to define possible involvements of OT in the pathophysiology of OCD.

Keywords:
obsessive–compulsive disorder, neurobiology, oxytocin

Egypt J Psychiatr 43:63–69

1110-1105

Introduction

Neurobiology of oxytocin

Oxytocin (OT) is a pleiotropic, peptide hormone with broad implications for general health, adaptation, development, reproduction, and social behavior. Endogenous OT and stimulation of the OT-receptor supports patterns of growth, resilience, and healing (Abramova *et al.*, 2020; Carter *et al.*, 2020).

OT is a 9-amino-acid neuropeptide made primarily in magnocellular neurons of the paraventricular nucleus (PVN) and supraoptic nucleus (SON) and secreted into the peripheral bloodstream from the posterior pituitary. Within the brain, OT that is not routed to the pituitary is synthesized by and transported from smaller, parvocellular neurons located in PVN and elsewhere (Caldwell and Young, 2006).

OT produced in the parvocellular neurons of the PVN projects to several other areas in the brain, including the amygdala, hippocampus, striatum, and brainstem, where it acts as a neuromodulator exerting effects on social behavior (Swanson and Sawchenko, 1980; Castel and Morris, 1988; Peñagarikano *et al.*, 2015). Accumulating evidence highlights the significant role OT plays in the human limbic system, including the amygdala (Bale *et al.*, 2001; Domes *et al.*, 2007).

Once in the bloodstream, OT is defined as a hormone, interacting with distal targets over relatively long timescales. Peripheral OT release is important during parturition and lactation; central OT release can affect maternal behavior and learning and memory (Morris and Ludwig, 2004; Caldwell and Young, 2006).

OT has a key role in female-reproductive functions as well as in social memory in the brain. In our recent Communications Biology article, we reported that OT is transported from the peripheral blood into the brain by the receptor for advanced glycation end products in endothelial cells at the blood–brain barrier. Additionally, we found that oral OT is absorbed by receptor for advanced glycation end products on intestinal epithelial cells at the blood–intestinal barrier (Yamamoto and Higashida, 2020).

Research has recently found that OT also plays an important role in the digestive system, regulating appetite and, indirectly, body weight (Blevins and Baskin, 2015). Besides neural networks, within the last decade, various sets of data have highlighted the possible role of OT and vasopressin, two small neuropeptides composed by nine amino acids and synthesized in the paraventricular and in the SON of the hypothalamus (Buijs *et al.*, 1983; Marazziti *et al.*, 2006), in linking social signals with cognition, behaviors, and reward (Insel and Fernald, 2004).

 DOI: 10.4103/ejpsy.ejpsy_28_21

OT and vasopressin, in fact, have been shown to be involved in the creation of pair bonding in monogamous rodents, such as prairie voles (Insel and Shapiro, 1992), in maternal behavior in rats (Insel and Harbaugh, 1989), in the postpartum acceptance of offspring in sheep (Keverne and Kendrick, 1992), and the relief of distress vocalization in rat pups (Insel and Winslow, 1991).

The relevance of these intriguing findings for humans has not been clarified as yet (Young and Wang, 2004). OT receptors in the human brain are mainly distributed in the substantia nigra, globus pallidus, anterior cingulate, and medial insula, areas that have been shown to be activated in adults while looking at pictures of their partners, or in mothers while looking at their children (Brown, 2005), and belong to the recently hypothesized circuits of the 'social brain' (Adolphs, 2001).

It is interesting to note that OT seems to be released during sexual intercourse and orgasm (Carmichael *et al.*, 1987) and during the application of different relaxation techniques (Turner *et al.*, 1999), so that it is thought to be one of the promoters of attachment and/or mediators in the decrease of the stress responses that are related to positive social bonding (Kosfeld *et al.*, 2005).

Oxytocin and psychiatric disorder

Lower levels of peripheral OT have been reported in some studies on autism-spectrum disorder (ASD), depression, and schizophrenia, although the findings vary (MacDonald and Feifel, 2012; Yamasue *et al.*, 2012; Stavropoulos and Carver, 2013).

An association between the severity of positive symptoms and elevated serum OT levels was shown in patients with schizophrenia (Rubin *et al.*, 2010).

Various studies have suggested that OT reduces aggressiveness, and enhances social relations and interactions in autism (Kuehn, 2011; Kosaka *et al.*, 2012). Intranasal OT, when administered to male patients with autism, enhanced the ability to recognize other individuals' emotions (Guastella *et al.*, 2010).

Serum OT levels were found to have been elevated in manic episodes of bipolar-affective disorder when compared with the levels in healthy controls, emphasizing that the elevation could be associated with increased dopamine levels during manic episodes and is responsible for impulsive behaviors such as hypersexuality and aggressiveness observed in clinical settings (Turan *et al.*, 2013).

In addition, it was reported that plasma OT levels were low in female patients diagnosed with borderline personality disorders, suggesting that decreased OT levels were a result of childhood trauma and attachment, as well as derangements in serotonin and dopamine levels, and could be associated with declined social cognition and impaired award system (Bertsch *et al.*, 2013).

It was reported that men with conduct disorder had higher OT-reactive autoantibody levels compared with men without conduct disorder (Fetissov *et al.*, 2006).

There is evidence in the literature that genes for OT-receptor SNPs rs6770632 and rs1042778 are associated with persistent and pervasive aggressive behaviors in females and males (Malik *et al.*, 2012). OT moderated reactive aggression in women with high-state anxiety (Campbell and Hausmann, 2013; Alcorn *et al.*, 2015).

Moreover, OT causes enhanced emotional recognition and increased empathy (Bartz *et al.*, 2010). OT plays an important role in the modulation of social behavior in both typical and atypical contexts. Also, the quality of early parental care sets the foundation for long-term psychosocial development. Here, we review studies that investigated how OT receptor interacts with early parental care experiences to influence the development of psychiatric disorders (Ilaria *et al.*, 2018).

Evidence from animal studies has demonstrated the significant role that OT and antidiuretic hormone (ADH) play in the regulation of social behavior and cognition (Chang and Platt, 2014). An increasing number of studies have also begun to dissect the roles of OT and ADH in human social behavior (Heinrichs *et al.*, 2009).

These neuropeptides are associated with complex social and emotional processing in healthy people, which if impaired, may account for some of the symptoms present in psychiatric disorders (Meyer-Lindenberg *et al.*, 2011).

Furthermore, there is also growing interest in the potential for synthetic neuropeptides in the treatment of psychosis (Gumley *et al.*, 2014), ASD (Thompson *et al.*, 2006; Uzunova *et al.*, 2015), and affective and anxiety disorders (Griebel *et al.*, 2012).

OT and ADH levels have been recently tested as putative biomarkers in ASD (Boso *et al.*, 2007; Alabdali *et al.*, 2014), psychosis (Goldman *et al.*, 2008; Rubin *et al.*, 2013), bipolar disorder (Turan *et al.*, 2013; Rubin *et al.*, 2014), and major depressive disorder (MDD) (Goldstein *et al.*, 2000; Yuen *et al.*, 2014), as well as in anxiety (Hoge *et al.*, 2012), personality (Bertsch *et al.*, 2013), and eating disorders (anorexia nervosa and bulimia nervosa) (Lawson *et al.*, 2012), with highly heterogeneous and conflicting results (Al-Ayadhi, 2005; Watson *et al.*, 2007; Alabdali *et al.*, 2014).

Oxytocin and obsessive–compulsive disorder

Anxiogenic and stressful stimuli significantly activate the body's OT system, as reflected by increased electrophysiological activity of OT neurons, increased OT gene expression within the SON and PVN, and stimulated peripheral and intracerebral OT release (Wotjak *et al.*, 1998).

For example, exposure of male rats to novelty, forced swimming, or social defeat rapidly increases OT release into blood but also within the PVN and/or SON and in other limbic brain regions, such as the central amygdala or septum (Neumann, 2007).

Similarly, increased OT release into blood and within the PVN and central amygdala has also been found in female rats exposed to psychosocial stress (maternal defeat by an aggressive lactating resident dam) (Bosch *et al.*, 2004).

Magnocellular OT neurons within the PVN (or SON) themselves may provide the neuroanatomical basis for these observations: in addition to their projections to the neurohypophysis, they can also release OT locally within the PVN (or SON) from dendrites and perikarya, as well as from axon collaterals that project to distinct brain regions, for example, the central amygdala (Knobloch *et al.*, 2012).

Recently, there is growing evidence that the neuropeptide OT modulates fear and extinction in humans and rodents through actions in corticolimbic circuits, including the central amygdala (Gunduz-Cinar *et al.*, 2020).

This is an important observation with implications for human studies, as it speaks in favor of peripheral OT measures being a global biomarker for the general activity of the endogenous OT system also, at least partly, reflecting the central (re)activity of an individual's OT system to stress. However, we have to be aware of the fact that plasma OT may, at best, only roughly reflect the temporal dynamics of central release patterns, which was shown to substantially differ from peripheral release patterns of OT (Neumann, 2007).

Further, plasma OT necessarily ignores brain-region-dependent events, which play an important role in the behavioral effects of OT. Paradoxically, while OT is linked to anxiolytic effects and to improvement of repetitive behaviors in autism, elevated OT levels are also putatively involved in the etiology of obsessive–compulsive disorder (OCD)-repetitive behaviors. Clinical trials that investigated the therapeutic use of OT in OCD found no effect of this molecule over the frequency of repetitive symptoms (neither improvement nor worsening) (Den Boer and Westenberg, 1992; Epperson *et al.*, 1996). In contrast, Leckman *et al.* (1994a) reported that levels of OT in ventricular cerebrospinal fluid (CSF) are higher in OCD patients than in healthy controls and identified a positive correlation between higher CSF levels of OT and higher frequency of repetitive behaviors.

Some (Marazziti *et al.*, 2015), but not all (Leckman *et al.*, 1994a), studies have found elevated CSF OT levels in patients with OCD, but a direct correlation between CSF OT levels and OCD severity has not been established (Marazziti *et al.*, 2015). In a 1992 study, CSF-OT of 43 children/adolescents correlated positively with depression, but not with OCD-symptom severity. In a study 2 years later, CSF OT was elevated compared with controls in 22 adult patients with OCD and without history of tic disorders, and in these patients, CSF OT was also positively related to OCD severity, as measured by the Yale–Brown Obsessive–Compulsive Scale (Goodman *et al.*, 1989).

This finding supports an oxytocinergic OCD hypothesis, but a study in 1999 found no CSF OT difference between OCD and control cases and no relation to Yale–Brown Obsessive–Compulsive Scale ratings; however, only 14 patients with OCD were included (Altemus *et al.*, 1999).

Recently, an animal model suggested supporting that OT gives rise to grooming compulsions through links between the PVN and the central nucleus of amygdala (Humble *et al.*, 2013).

There are many different theories as to how OT levels might correlate with specific OCD phenotypes. For

instance, OT has been reported to attenuate memory consolidation and retrieval. It might be that pathological doubting associated with the need to repeatedly carry out checking compulsions is a clinical manifestation of the cognitive effects of a dysregulated OT system in some forms of OCD. Additionally, violent and horrific thoughts, images, and impulses are also common types of obsessions. Central OT injections in mother hamsters were associated with increased maternal aggression toward intruders. A dose–response increase in aggression has also been reported in dominant male squirrel monkeys given intracerebroventricular OT. Blockade of OT receptors reduced aggressive behavior in these same monkeys (McDougle *et al.*, 1999).

Current evidence regarding intranasal OT modulation of social–cognitive processes, behavior, and related neurocircuitry is mixed with some studies suggesting benefits (e.g. improved social perception/interactions, emotion processing), depending on contextual (e.g. social stimuli) and interindividual factors (e.g. age, sex, and clinical status) (Horta *et al.*, 2020).

Thus, given the putative role of OT in 'affiliative/mothering' behavior, with regard to our patient, the pathological doubting she had about being a competent mother with thoughts of possibly harming her baby could be attributed to one manifestation of a pathologically dysregulated OT syndrome (McDougle *et al.*, 1999).

Finally, in the nonpathological state, estrogens can act in a synergistic manner with OT, not only by enhancing its anxiolytic effects, but also by increasing OT-receptor levels in the mouse brain (Acevedo-Rodriguez *et al.*, 2015).

Notably, during peripartum, elevated levels of estrogen are present. Thus, this hypoestrogenism could result in a dysregulated OT system. However, in a subsequent study, Altemus *et al.* (1999) were unable to replicate those findings.

The aforementioned inconsistences in findings relating OT to OCD-repetitive behaviors highlight the potential complexity of such association. The absence of the effects of the acute administration of OT in neither improvement nor worsening of OCD symptoms suggests that current variation of this neuropeptide may not be relevant for the better understanding of OCD etiology (Den Boer and Westenberg, 1992; Epperson *et al.*, 1996). However, despite the lack of significance of current OT levels, prenatal and early natal exposure to high levels of OT could still be potentially related to the future outbreak of OCD-repetitive behaviors. Corroborating this hypothesis, OT has been previously shown to moderate the effects of early social experiences in later life (Cushing and Kramer, 2005).

Oxytocin levels in treated patients

Only three previous studies have investigated OT changes during SSRI treatment in humans (Keating *et al.*, 2013).

In the first of these, 16 children/adolescents with OCD were studied. Clomipramine treatment, ranging between 8.5 and 34 months, caused an overall increase in CSF OT by 11%. Intriguingly, however, the individual clinical response was negatively correlated to CSF OT changes (i.e. those with the least increase in CSF OT were the most improved). Since this study only included treatment responders and no placebo group, conclusion regarding the pharmacological effects of SSRIs on the OT system should be considered with caution (Altemus *et al.*, 1999).

In the next study, plasma OT was measured in 40 patients with MDD before and after successful pharmacological treatment, of which 19 cases were treated with SRIs (venlafaxine or SSRI) in 19 cases. When compared with a control group, the active-treatment patients had significantly lower plasma OT at baseline; however, no difference between pretreatment and posttreatment OT levels was found. All included patients were treatment responders, and the time span between samples was not conveyed (Ozsoy *et al.*, 2009).

A third study was reported on plasma OT at baseline and after 12 weeks of SSRI treatment in 16 adult patients who were successfully treated for MDD. No difference was found (Keating *et al.*, 2013).

Consequently, placebo-treated patients were not used as controls in any of these three studies, nor were responders compared with nonresponders. Two of the studies were for depression, and only one applied a fixed time interval for the second OT sample. Most recently, a study concluded that SSRIs have highly variable effects on plasma OT between individuals. The authors stated that the associations between baseline OT and OCD severity and between OT changes and treatment response support the theories that OT is involved in OCD pathophysiology and that the antiobsessive effects

of SSRIs might be partly exerted through oxytocinergic mechanisms (Humble *et al.*, 2013).

Increased OT activity has been linked to anxiolytic effects (e.g. in the amygdala or the median raphe nucleus) (Humble *et al.*, 2013).

OCD onset is common during the peripartum period, with ranges up to four times the expected rate in the nonperipartum population (Miller *et al.*, 2015).

The acute onset of OCD in the peripartum period might be attributed to the dramatic rise and fall in steroid hormone levels, resulting in serotonergic dysfunction, which is compounded by a predisposition to psychiatric illness. Some research suggests that the rapid increase in OT seen during pregnancy, particularly at nine months, and during the puerperium, might trigger the exacerbation or onset of OCD; however, the exact pathophysiology is unclear, and future research could elucidate this relationship (Brandes *et al.*, 2004).

Clinical trials that investigated the therapeutic use of OT in OCD found no effect of this molecule over the frequency of repetitive symptoms (neither improvement nor worsening). In contrast, a study reported that levels of OT in ventricular CSF are higher in patients with OCD than in healthy controls and identified a positive correlation between higher CSF levels of OT and higher frequency of repetitive behaviors (Leckman *et al.*, 1994a).

However, a subsequent study was unable to replicate those findings (Cappi *et al.*, 2016).

Ultimately, it is unknown whether OT is critically involved in OCD pathogenesis, and, if so, whether the oxytocinergic activity should be increased, decreased, or changed in other ways to improve the clinical state. In various experiments, elevated OT has been linked to relaxed, affiliative situations, implying anxiolytic and antidepressant effects, but, in other experiments, OT is increased in relation to stress. These disparate findings indicate that different segments of the central OT system might act in different direction (Goodman *et al.*, 1989).

In summary, the evidence for the role of OT in a broad range of neuropsychiatric disorders is accumulating, and further research is needed to determine the exact nature of its role and to translate these findings into a better understanding of the underlying pathophysiology of the disorders and effective treatment strategies targeting the oxytocinergic system.

Acknowledgements

The authors thank participants for their participation and cooperation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

Abramova O, Zorkina Y, Ushakova V, Zubkov E, Morozova A, Chekhonin V (2020). The role of oxytocin and vasopressin dysfunction in cognitive impairment and mental disorders. Neuropeptides 83:102079.

Acevedo-Rodriguez A, Mani S, Handa R (2015). Oxytocin and estrogen receptor β in the brain: an overview. Front Endocrinol (Lausanne) 19:690-–714.

Adolphs R (2001). The neurobiology of social cognition. Curr Opin Neurobiol 11:231–239.

Alabdali A, Al-Ayadhi L, El-Ansary A (2014). Association of social and cognitive impairment and biomarkers in autism spectrum disorders. J Neuroinflamm 11:4.

Al-Ayadhi L (2005). Altered oxytocin and vasopressin levels in autistic children in Central Saudi Arabia Neurosciences 10:447–450.

Alcorn J, Green C, Schmitz J, *et al.* (2015). Effects of oxytocin on aggressive responding in healthy adult males. Behav Pharmacol 26(800):798.

Altemus M, Jacobson K, Debellis M (1999). Normal CSF oxytocin and NPY levels in OCD. Biol Psychiatry 45:931–933.

Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM (2001). CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. J Neurosci 21:2546–2552.

Bartz J, Zaki J, Bolger N, Hollander E, Ludwig NN, Kolevzon A, Ochsner KN (2010). Oxytocin selectively improves empathic accuracy. Psychol Sci 21:1426–1428.

Bertsch K, Schmidinger I, Neumann ID, Herpertz SC (2013). Reduced plasma oxytocin levels in female patients with borderline personality disorder. Horm Behav 63:424–429.

Blevins J, Baskin D (2015). Translational and therapeutic potential of oxytocin as an anti-obesity strategy: insights from rodents, nonhuman primates and humans. Physiol Behav 152:438–449.

Bosch OJ, Kromer SA, Brunton PJ, Neumann ID (2004). Release of oxytocin in the hypothalamic paraventricular nucleus, but not central amygdala or lateral septum in lactating residents and virgin intruders during maternal defence. Neuroscience 124:439–448.

Boso M, Emanuele E, Politi P, Pace A, Arra M, di Nemi SU, Barale F (2007). Reduced plasma apel in levels in patients with autistic spectrum disorder. Arch Med Res 38:70–74.

Brandes M, Soares C, Cohen L (2004). Postpartum onset obsessive-compulsive disorder: diagnosis and management. Arch Womens Ment Health 7:99–110.

Brown L (2005). Reward, motivation, and emotion systems. J Neurophysiol 94:327–337.

Buijs RM, DeVries GJ, Van Leeuwen RW, Swaab DF (1983). Vasopressin and oxytocin: distribution and putative function in the brain. Prog Brain Res 60:115–122.

Caldwell H, Young W (2006). Oxytocin and vasopressin: genetics and behavioral implications. In Handbook of neurochemistry and molecular neurobiology 573-607. Springer, Boston, MA. Pharmacology 28:212–219.

Campbell A, Hausmann M (2013). Effects of oxytocin on women's aggression depends on state anxiety. Aggress Behav 39:316–322.

Cappi C, Diniz JB, Requena GL, Lourenço T, Lisboa BCG, Batistuzzo MC (2016). Epigenetic evidence for involvement of the oxytocin receptor gene in obsessive–compulsive disorder. BMC Neurosci 17:1–8.

Carmichael M, Humbert R, Dixen J (1987). Plasma oxytocin increases in the human sexual response. J Clin Endocrinol Metab 64:27–31.

Carter CS, Kenkel WM, MacLean EL, Wilson SR, Perkeybile AM, Yee JR, *et al.* (2020). Is oxytocin 'nature's medicine'? Pharmacol Rev 72:829–861.

Castel M, Morris J (1988). The neurophysin-containing innervation of the forebrain of the mouse. Neuroscience 24:937–966.

Chang S, Platt M (2014). Oxytocin and social cognition in rhesusmacaques: implications for understanding and treating human psychopathology. Brain Res 1580:57–68.

Cushing B, Kramer K (2005). Mechanisms underlying epigenetic effects of early social experience: the role of neuropeptides and steroids. Neurosci Biobehav Rev 29:1089–1105.

Den Boer J, Westenberg H (1992). Oxytocin in obsessive compulsive disorder. Peptides 13:1083–1085.

Domes G, Heinrichs M, Gläscher J, Büchel C, Braus DF, Herpertz SC (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. Biol Psychiatry 62:1187–1190.

Epperson C, McDougle C, Price L (1996). Intranasal oxytocin in obsessive-compulsive disorder. Biol Psychiatry 40:547–549.

Fetissov S, Hallman J, Nilsson I, *et al.* (2006). Aggressive behavior linked to corticotropin-reactive autoantibodies. Biol Psychiatry 60:799–802.

Goldman M, Marlow-O M, Torres I, *et al.* (2008). Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. Schizophr Res 98:247–255.

Goldstein G, Fava M, Culler M, *et al.* (2000). Elevated plasma thymopoietin associated with therapeutic non responsiveness in major depression. Biol Psychiatry 48:65–69.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, *et al.* (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 46:1006–1011.

Griebel G, Beeske S, Stahl S (2012). The vasopressinV(1b) receptor antagonist SSR 149415in the treatment of major depressive and generalized anxiety disorders: results from 4 randomized, double-blind, placebo-controlled studies. J Clin Psychiatry 73:1403–1411.

Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, Hickie IB (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. Biol Psychiatry 67:692–694.

Gumley A, Braehler C, Macbeth A (2014). Ameta-analysis and theoretica lcritique of oxytocin and psychosis: prospects for attachment and compassion inpromoting recovery. Br J Clin Psychol 53:42–61.

Gunduz-Cinar O, Brockway ET, Castillo LI, Pollack GA, Erguven T, Holmes A (2020). Selective sub-nucleus effects of intra-amygdala oxytocin on fear extinction. Behav Brain Res 393:112798.

Heinrichs M, vonDawans B, Domes G (2009). Oxytocin, vasopressin and human social behavior. Front Neuroendocrinol 30:548–557.

Hoge EA, Lawson EA, Metcalf CA, Keshaviah A, Zak PJ, Pollack MH, Simon NM (2012). Plasma oxytocin immuno-reactive products and response to trust in patients with social anxiety disorder. Depression Anxiety 29:924–930.

Horta M, Pehlivanoglu D, Ebner NC (2020). The role of intranasal oxytocin on social cognition: an integrative human lifespan approach. Curr Behav Neurosci Rep 7:1–18.

Humble MB, Uvnäs-Moberg K, Engström I, Bejerot S (2013). Plasma oxytocin changes and anti-obsessive response during serotonin reuptake inhibitor treatment: a placebo controlled study. BMC Psychiatry 13:1–14.

Ilaria C, Atiqah A, Bruno L, *et al.* (2018). Oxytocin receptors (OXTR) and early parental care: an interaction that modulates psychiatric disorders. Res Dev Disabil 82:27–38.

Insel T, Harbaugh C (1989). Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. Physiol Behav 45:1033–1041.

Insel T, Winslow J (1991). Central administration of oxytocin modulates the infant rat's response to social isolation. Eur J Pharmacol 1991; 203:149–152.

Insel T, Shapiro L (1992). Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc Natl Acad Sci USA 89:5981–5985.

Insel T, Fernald R (2004). How the brain processes social information: searching for the social brain. Annu Rev Neurosci 27:697–722.

Keating C, Dawood T, Barton DA, Lambert GW, Tilbrook AJ (2013). Effects of selective serotonin reuptake inhibitor treatment on plasma oxytocin and cortisol in major depressive disorder. BMC Psychiatry 13:1–7.

Keverne EB, Kendrick K (1992). Oxytocin facilitation of maternal behaviour. Ann N Y Acad Sci 652:83–101.

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, *et al.* (2012). Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73:553–566.

Kosaka H, Munesue T, Ishitobi M, Asano M, Omori M, Sato M, *et al.* (2012). Long-term oxytocin administration improves social behaviors in a girl with autistic disorder. BMC Psychiatry 12:1–4.

Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E (2005). Oxytocin increases trust in humans. Nature 435:673–676.

Kuehn B (2011). Scientists probe oxytocin therapy for social deficits in autism, schizophrenia. JAMA 305:659–661.

Lawson E, Holsen L, Santin M (2012). Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypo activation in anorexia nervosa. J Clin Endocrinol Metab 97:E1898–E1908.

Leckman JF, Goodman WK, North WG, Chappell PB, Price LH, Pauls DL, *et al.* (1994a). Elevated cerebrospinal fluid levels of oxytocin in obsessive-compulsive disorder. Comparison with Tourette's syndrome and healthy controls. Arch Gen Psychiatry 51:782–792.

MacDonald K, Feifel D (2012). Oxytocin in schizophrenia: a review of evidence for its therapeutic effects. Acta Neuropsychiatr 24:130–146.

Malik AI, Zai CC, Abu Z, Nowrouzi B, Beitchman JH (2012). The role of oxytocin and oxytocin receptor gene variants in childhood-onset aggression. Genes Brain Behav 11:545–551.

Marazziti D, Dell'Osso B, Baroni S, Mungai F, Catena M, Rucci P, *et al.* (2006). A relationship between oxytocin and anxiety of romantic attachment. Clin Pract Epidemiol Ment Health 2:1–6.

Marazziti D, Baroni S, Giannaccini G, Catena-Dell M, Piccinni A, Massimetti G (2015). Plasma oxytocin levels in untreated adult obsessive-compulsive disorder patients. Neuropsychobiology 72:74–80.

McDougle CJ, Barr LC, Goodman WK, Price LH (1999). Possible role of neuropeptides in obsessive compulsive disorder. Psychoneuroendocrinology 24:1–24.

Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat Rev Neurosci 12:524–538.

Miller ES, Hoxha D, Wisner KL, Gossett DR (2015). Obsessions and compulsions in postpartum women without obsessive compulsive disorder. J Womens Health (Larchmnt) 24:825–830.

Morris J, Ludwig M (2004). Magnocellular dendrites: prototypic receiver/transmitters. J Neuroendocrinol 16:403–408.

Neumann I (2007). Stimuli and consequences of dendritic release of oxytocin within the brain. Biochem Soc Trans 35:1252–1257.

Ozsoy S, Esel E, Kula M (2009). Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. Psychiatry Res 13:249–252.

Peñagarikano O, Lázaro MT, Lu XH, Gordon A, Dong H, Lam HA, *et al.* (2015). Exogenous and evoked oxytocin restores social behavior in the Cntnap2 mouse model of autism. Sci Transl Med 7:271ra8–271ra8.

Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM (2010). Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr Res 124:13–21.

Rubin LH, Carter CS, Bishop JR, Pournajafi-Nazarloo H, Harris MS, Hill SK, *et al.* (2013). Peripheral vasopressin but not oxytocin relates to severity of acute psychosis in women with acutely ill untreated first episode psychosis. Schizophr Res 146:138–143.

Rubin LH, Carter CS, Bishop JR, Pournajafi-Nazarloo H, Drogos LL, Hill SK, *et al.* (2014). Reduced levels of vasopressin and reduced behavioral modulation of oxytocin in psychotic disorders. Schizophr Bull 40:1374–1384.

Stavropoulos K, Carver L (2013). Research review: social motivation and oxytocin in autism-implications for joint attention development and intervention. J Child Psychol Psychiatry 54:603–618.

Swanson L, Sawchenko P (1980). Paraventricular nucleus: a site for the integration of neuroendocrine and autonomic mechanisms. Neuroendocrinology 31:410–417.

Thompson R, George K, Walton J (2006). Sex specific influences of vasopressin on human social communication. Proc Natl Acad Sci USA 103:7889–7894.

Turan T, Uysal C, Asdemir A, Kılıç E (2013). May oxytocin be a triat marker for bipolar disorder? Psychoneuroendocrinology 38:2890–2896.

Turner R, Altemus M, Enos T (1999). Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress. Psychiatry 62:97–113.

Uzunova G, Pallanti S, Hollander E (2015). Excitatory/inhibitoryimbalancein autism spectrum disorders: Implications for interventions and therapeutics. World J Biol Psychiatry 17:1–13.

Watson S, Gallagher P, Smith MS, Young AH, Ferrier IN (2007). Lithium, arginine vasopressin and the dex/CRH test in mood disordered patients. Psychoneuroendocrinology 32:464–469.

Wotjak C, Ganster J, Kohl G, Holsboer F, Landgraf R, Engelmann M (1998). Dissociated central and peripheral release of vasopressin, but not oxytocin, in response to repeated swim stress: new insights into the secretory capacities of peptidergic neurons. Neuroscience 85:1209–1222.

Yamamoto Y, Higashida H (2020). RAGE regulates oxytocin transport into the brain. Commun Biol 3:70.

Yamasue H, Yee JR, Hurlemann R, Rilling JK, Chen FS, Meyer-Lindenberg A, Tost H (2012). Integrative approaches utilizing oxytocin to enhance prosocial behavior: from animal and human social behavior to autistic social dysfunction. J Neurosci 32:14109–14117.

Young L, Wang Z (2004). The neurobiology of pair bonding. Nat Neurosci 7:1048–1054.

Yuen KW, Garner JP, Carson DS, Keller J, Lembke A, Hyde SA, *et al.* (2014). Plasma oxytocin concentrations are lower in depressed vs. healthy control omen and are independent of cortisol. J Psychiatr Res 51:30–36.