Review

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The neurobiological impact of oxytocin in mental health disorders: a comprehensive review

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Abstract

Oxytocin, a neuropeptide, plays a significant role in modulating social behavior and has been widely studied for its potential impact on mental health disorders. This review examines the neurobiological mechanisms through which oxytocin influences mental health and its therapeutic potential in conditions such as autism spectrum disorder, schizophrenia, post-traumatic stress disorder, anxiety, and depression. Oxytocin enhances social bonding, trust, and empathy by modulating neural circuits linked to social interactions. Studies indicate that oxytocin's ability to regulate the hypothalamic-pituitary-adrenal axis plays a vital role in stress response and emotional regulation. Therapeutic applications, particularly intranasal administration of oxytocin, have shown promise in alleviating symptoms and improving patient outcomes. However, personalized approaches are essential to optimize treatment effectiveness. Despite its potential, challenges remain in understanding the mechanisms underlying its effects and identifying the patient populations that would benefit most from such therapies. Future research should focus on elucidating these mechanisms, exploring the long-term efficacy of oxytocin-based interventions, and advancing personalized medicine to maximize its clinical utility.

Keywords: HPA axis, mental disorders, neurobiology, oxytocin, social behavior, therapeutic potential

Introduction

The magnocellular nuclei of the hypothalamus synthesize the hormone oxytocin and subsequently store and release it by the posterior pituitary gland. Oxytocin, a nine-amino acid polypeptide, is primarily a neuromodulator in the brain and peripheral tissues. It is synthesized from prooxyfizine, an inactive precursor. The precursor is subjected to enzymatic degradation, resulting in the formation of oxytocin and neurophysin. Neurophysin plays a role in facilitating the transportation and storage of oxytocin[1]. Oxytocin is activated through further enzymatic hydrolysis of ascorbic acid and distributed for physiological functions[2].

The degradation of oxytocin primarily occurs in the liver and plasma via oxytocinases. The phenomenon substantially impacts a range of physiological systems, including but not limited to the cardiovascular, renal, muscular, and reproductive organs[3-5]. The objective of this study is to consolidate existing research on the involvement of oxytocin in mental diseases, examine its influence on social and emotional mechanisms, and evaluate its potential therapeutic uses in the context of mental health. To support our objective, we have included Table 1, which summarizes key findings regarding oxytocin's role in various neurological and psychological disorders.

HIGHLIGHTS

- Oxytocin enhances social bonding, trust, and empathy through its influence on neural circuits.
- Oxytocin plays a role in autism, schizophrenia, PTSD, anxiety, and depression, modulating symptoms and improving outcomes.
- Intranasal oxytocin shows promise as a treatment for various mental health conditions, with personalized approaches being crucial.
- Oxytocin affects the hypothalamic-pituitary-adrenal axis, playing a key role in stress response and emotional regulation.

Localization and synthesis

Neurohypophysial hormones are classified into the AVP and OT families based on the amino acid at position 8, which determines receptor binding efficiency. OT, a nonapeptide with a disulfide bridge between Cys1 and Cys6, includes a COOH-terminal alpha-amidated tail. Vertebrates universally possess OT-like and AVP-like peptides, reflecting their evolutionary roles in reproduction (OT) and water homeostasis (AVP)[18,19].

OT and AVP are synthesized in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. Precursors, such as preprooxytocin, are processed in neurosecretory vesicles through glycosylation, amidation, and proteolytic cleavage,

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Table 1

Summary of key findings on oxytocin's role in neurological and psychological disorders

Topic	Key findings
Autism	Oxytocin levels are lower in autistic individuals, and its administration reduces repetitive behaviors and improves speech tone comprehension[6].
	Functional neuroimaging supports oxytocin's impact on brain areas relevant to social behaviors in autism[7].
	Endogenous vasopressin levels influence the positive effects of oxytocin on social functioning in autism, although therapeutic benefits for general social behavior are uncertain[8].
Schizophrenia	Lower oxytocin levels are associated with more severe symptoms of schizophrenia, particularly negative and cognitive symptoms[9].
	Genetic studies link variations in oxytocin-related genes to negative symptoms of schizophrenia.
	Higher oxytocin levels are linked to improved social cognition, emotion perception, and working memory, suggesting potential as a supplement to antipsychotic therapy[10].
Post-traumatic stress disorder	Oxytocin promotes the extinction of avoidance reflexes, reduces passive avoidance behavior, and affects memory consolidation and retrieval[11].
	Reduced memory recall and conditioned response in PTSD patients after oxytocin administration suggest alterations in the oxytocin system following trauma may contribute to PTSD development[12].
Disorders of anxiety	Oxytocin's impact on affiliative behavior in animals suggests potential involvement in human emotions and relationships, with implications for anxiety disorders[13].
	Elevated oxytocin levels during pregnancy are associated with reduced prevalence of stress and anxiety disorders, and stress-related oxytocin release may regulate fear and anxiety responses.
Depression	Oxytocin imbalance is prevalent in depression, with lower levels in postpartum depression and potential therapeutic benefits in depressive disorders[14].
	Clinical evidence suggests oxytocin's role in modulating stress response and social behavior, with implications for depressive symptoms and therapeutic response to antidepressant drugs[15].
	Oxytocin's impact on social withdrawal, perception of reality, and therapeutic response to SSRIs indicates its potential as a mediator of depressive symptoms and treatment outcomes.
	Other treatments, such as sildenafil and oxytocin agonists, show promise in alleviating depressive symptoms, possibly by affecting oxytocin release and function[16,17]

yielding OT, neurophysin, and a glycoprotein. These products are transported to the posterior pituitary for release[20,21]. OT, when secreted, acts on distant organs like the kidney and mammary gland, mediating uterine contraction, lactation, and water regulation[22,23].

Triggers such as nursing, labor, dehydration, and stress release OT locally in the PVN and SON, where it acts as a self-neuromodulator. OT influences anterior pituitary hormones, including prolactin, ACTH, and luteinizing hormone (LH). For instance, OT enhances LH secretion and may accelerate ovulation, while it suppresses ACTH under stress, potentially modulating the hypothalamic-pituitary-adrenal axis[24-29].

Peripheral OT is also produced in tissues like the uterus, testis, and heart, with its exact roles and interactions, particularly regarding other hormones, still under investigation[30,31].

The oxytocin-generating system

Hypothalamus-hypophysis

The hypothalamic-neurohypophysial system, composed of the paraventricular (PVN) and supraoptic (SON) nuclei (Fig. 1), is the primary oxy-neurosecretory system[32,33]. Oxytocin is mainly synthesized in the magnocellular regions of the PVN and SON, with their neurons projecting to areas like the medial amygdala and the lateral septum[24]. Magnocellular oxytocinergic neurons release oxytocin into the posterior pituitary, which then enters circulation to act on peripheral organs[34]. Oxytocin does not easily cross the blood-brain barrier, and peripheral stimulation (e.g., milk sucking) may not affect central oxytocin levels[34]. Electrical stimulation of the neurohypophysis releases oxytocin peripherally, while stimulation of the PVN releases it centrally and peripherally[35]. Following hypophysectomy, oxytocin concentration decreases in the blood but increases in the cerebrospinal fluid (CSF), where its half-life is longer than in plasma[36-38]. Local dendritic release of oxytocin also occurs in the PVN and SON, crucial for breastfeeding and postpartum feedback loops[25]. Parvocellular neurons, smaller than magnocellular neurons, project to areas like the vagus motor nucleus and sympathetic spinal centers[30,31,39]. Oxytocin may also play a role in regulating adenohypophysial hormones such as gonadotropins, prolactin, and ACTH, supported by its fibers passing through the hypophyseal portal system to the anterior pituitary[40-42].

Receptor for oxytocin

The oxytocin receptor is a G protein-coupled receptor with seven transmembrane domains. Its activation triggers phospholipase C-β, leading to the production of inositol trisphosphate (IP3) and diacylglycerol (DAG)[42]. IP3 facilitates calcium release, while DAG activates protein kinase C (PKC), phosphorylating downstream proteins. Elevated calcium activates calmodulin, stimulating nitric oxide synthase and guanylate cyclase, which enhance smooth muscle contraction in the myometrium and mammary gland to support parturition and milk ejection[42]

Oxytocin and social behavior

Oxytocin regulates several neuroendocrine reflexes and is essential in developing complicated social behaviors or coordinating behaviors linked to reproduction, partner selection, childcare, or community life. For instance, male and female rats and mice's sexual behaviors are controlled by oxytocin receptors in the paraventricular nucleus[43]. Additionally, oxytocin has potent anti-stress properties and modulates the hypothalamic-pituitary-adrenal axis[44,45]. By stimulating affiliative behavior, the

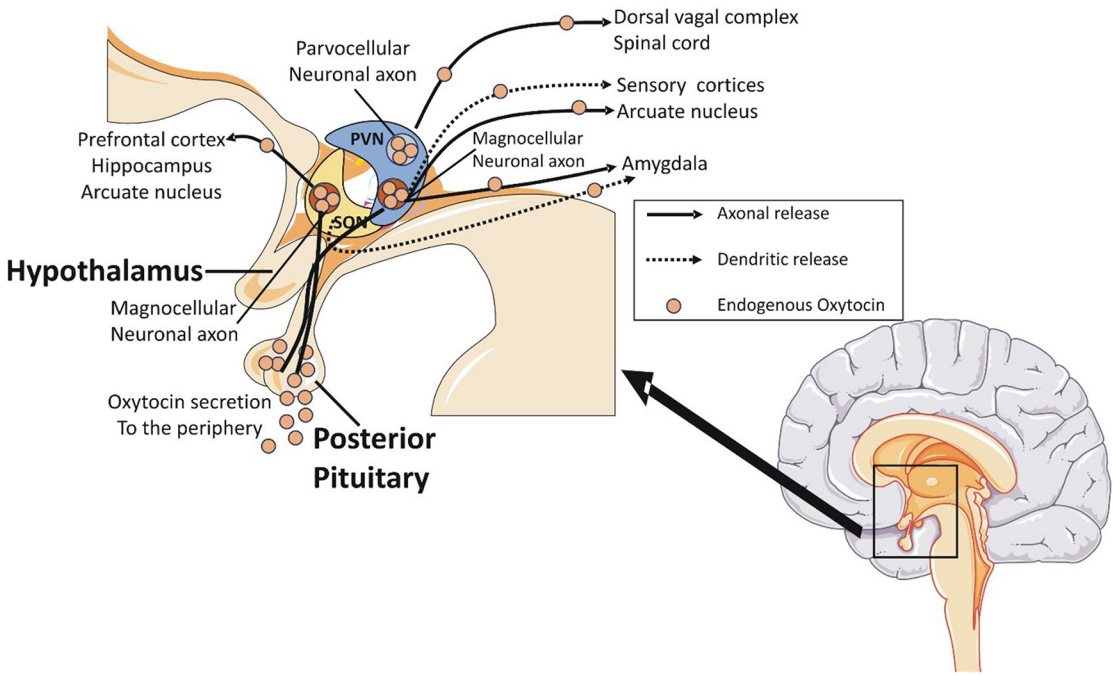

Figure 1. Oxytocin Production and Secretion: Oxytocin, a hormone and neurotransmitter, is primarily produced by magnocellular neurons in the hypothalamus, specifically in the supraoptic and paraventricular nuclei. These neurons send axonal projections to the posterior pituitary, where oxytocin is stored and released into the bloodstream. These neurons also project to various brain regions like the prefrontal cortex, hippocampus, arcuate nucleus, and amygdala, allowing direct release of oxytocin in those areas. Furthermore, oxytocin can be released dendritically, targeting the amygdala and sensory cortices. The ability of dendritically released oxytocin to reach distant brain areas has been a topic of debate, with some studies suggesting it can diffuse via cerebrospinal fluid. In contrast, others propose that long-range axonal projections are the primary delivery method. The distribution of oxytocin receptors, the combination of axonal and dendritic release, and the timing of secretion all contribute to the diverse effects of oxytocin on behavior. While the sites of oxytocin synthesis and axonal pathways are similar across mammalian species, the locations of oxytocin receptor expression vary significantly. This allows for rapid behavioral adjustments to environmental changes. Oxytocin can independently regulate central and peripheral secretion, and its diverse axonal projections help regulate various behaviors.

oxytocin system contributes to social behaviors. Oxytocin has a role in group-related behaviors, such as deciding how to react to a stranger or another group member (Fig. 2).

Oxytocin's primary effects include regulating neuroendocrine responses and generating intricate social and bonding behaviors associated with reproduction and childrearing[46]. Additionally, oxytocin has potent anti-stress properties that may promote pair bonding. One of the most crucial aspects of the oxytocin system is its ability to modulate sex hormones.

Autism and oxytocin

The relationship between oxytocin and autism has been the subject of much investigation over the past 20 years. When Modahl examined the amount of oxytocin in autistic children's blood in 1998, she found that it was much lower than it was in the control group[47]. After oxytocin delivery, autistic repetitive behaviors subsided in 2003 in a different experimental environment. Adults with autism also benefited from this, although these benefits were particularly noticeable in their capacity to comprehend and interpret speech tone[48] accurately.

Functional neuroimaging supports the role of oxytocin in autism, particularly in the mesocorticolimbic system. Studies show that dopamine and oxytocin are linked in these brain areas, crucial for oxytocin's effects in autism. Intranasal oxytocin treatment increased activity in regions like the left premotor cortex and ventral striatum during socio-emotional recognition tasks in autistic individuals, but reduced activity in non-social tasks involving only objects[7]. Additionally, oxytocin enhanced functional connectivity between the ventral striatum and the ventromedial prefrontal cortex, highlighting the importance of mesocorticolimbic areas in its mechanism[49].In autism, where social connection is crucial, the social aspect of oxytocin's activity may have a significant effect. Numerous investigations have been unsuccessful in determining the therapeutic advantages of oxytocin for individuals with autism in terms of general social behavior[50]. Nevertheless, a recent study demonstrated that oxytocin has positive benefits on social functioning in autistic people and that these effects are also impacted by endogenous vasopressin levels[51]. How oxytocin affects social behavior still needs to be fully understood. The subject of specific theories is how oxytocin affects the dynamics of the social response. The capacity of oxytocin to affect sensitivity to external incentives and, hence, directly promote reward-based learning behavior may be a mechanism of action. Preclinical research suggests that oxytocin exerts prosocial effects via the mesocorticolimbic dopamine pathway[52]. The interaction between oxytocin and dopamine in the mesocorticolimbic system causes dopaminergic activity to rise when oxytocin neurons in the ventral tegmental region are activated.

Additionally, after receiving an oxytocin receptor agonist, mice exhibit a reduction in dopaminergic release in the nucleus accumbens, indicating the importance of oxytocin in the mesocorticolimbic transmission of dopamine[53]. Studies have shown that oxytocin does not instantly play a prosocial function, but it

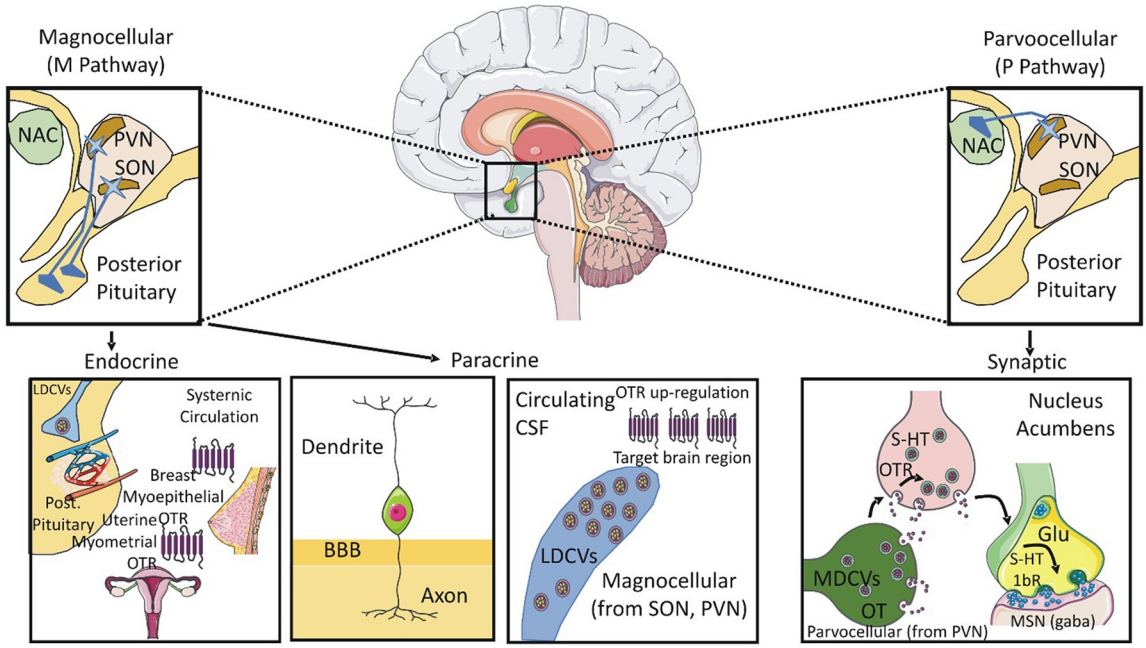

Figure 2. Magnocellular and parvocellular oxytocin (OT) routes in the social brain. Top. The paraventricular nucleus (PVN) and supraoptic nucleus (SON.) of the hypothalamus are where magnocellular (left) and parvocellular (suitable) neuronal subtypes are located. The magnocellular route's endocrine and paracrine release mechanisms are shown on the bottom, while the parvocellular pathway's synaptic release mechanism is shown on the right. B.B.B., blood-brain barrier, cerebrospinal fluid, 5-HT, serotonin, MDCV, medium dense core vesicle, OT, oxytocin, OTR., M.S.N., medium spiny neurone, S.S.V., small synaptic vesicle, 5-HT1bR, serotonin receptor subtype 1b, glutamate. NAc, nucleus accumbens.

does modify how people and animal models respond to certain social cues connected to the conservation instinct. Growing interest in oxytocin's ability to improve social communication deficits has arisen from the need for effective therapies for the symptoms of autism spectrum diseases.

Research indicates that oxytocin administration positively impacts various aspects of social functioning in autism, such as enhanced emotional receptivity and self-confidence[54]. However, core symptoms like restrictive and repetitive behaviors (e.g., hand flapping, object lining, or echolalia) that disrupt social interactions show no significant improvement with oxytocin. Most studies favor antipsychotics for managing these behaviors[55]. A recent meta-analysis also strongly associates low oxytocin levels with autism in children.

Additionally, oxytocin levels in people with autism were identical to those in neurotypical adults, indicating that there may be a higher amount of oxytocin in neurotypical children that may support social interaction and growth, with a reduction in age. In future research, oxytocin therapy in childhood may be the top contender for addressing significant social deficiencies and enhancing cerebral growth in autistic individuals[56]. Human investigations, including those carried out by various experiments, showed that intranasal oxytocin enhanced social cognition and decreased repetitive behaviors in people with autism, in addition to reducing repetitive behaviors in mice. These results highlight the possibility of using oxytocin as a treatment for ASD[57].

Schizophrenia and oxytocin

Other forms of mental disease, including schizophrenia, may include oxytocin. Considering the social deficiencies connected to severe mental disease, this is not altogether unexpected. Significant evidence suggests that oxytocin may be a critical factor in the etiology of schizophrenia because of the inverse relationship between plasma oxytocin levels and the severity of schizophrenia symptoms. More severe symptoms have been linked to much lower oxytocin levels.

Schizophrenia symptoms are linked to lower plasma oxytocin levels, particularly negative and cognitive symptoms, though the exact relevance remains unclear. Low oxytocin levels may be causative, a result of the disorder, or a response to antipsychotic medication[58]. Studies also found no consistent correlation between plasma oxytocin levels and the severity of positive symptoms. Interestingly, female patients with positive symptoms had higher plasma oxytocin levels than male participants[59].

Positive symptoms correlate constantly with oxytocin levels in the cerebrospinal fluid and plasma, whereas negative symptoms have a consistent negative correlation with both[60,61]. This is in contrast to positive symptoms. Furthermore, several genetic studies have linked low oxytocin levels to unpleasant sensations. For instance, a variation of the oxytocin gene (rs2740204) has been linked to negative symptoms in people with schizophrenia. The oxytocin receptor mutations rs53576 and rs237885 have been shown to significantly correlate with negative symptom scores as determined by the PANSS scale (positive and negative schizophrenia symptoms scale)[62]. The rs53576 oxytocin receptor gene variation has been linked to the emotional disengagement characteristic of schizophrenia in several investigations[63].

Higher peripheral oxytocin levels are frequently linked to enhanced social cognition, prosocial behavior, and more excellent emotion perception, which is relevant to the cognitive aspect

of schizophrenia. Higher plasma oxytocin levels have also been linked to more excellent emotion perception, avoidant behavior toward angry faces, and more accurate socially relevant information coding in schizophrenia[9,64]. Additionally, a greater oxytocin level boosts working memory and the efficiency with which information is processed[65]. Intranasal oxytocin may thus be a contender as an addition to antipsychotic therapy for improving negative and positive feelings as well as potentially reversing social cognitive deficiencies[66]. One cannot yet draw a broad conclusion because not all research has found these links. As a result, the importance of oxytocin in schizophrenia is still not entirely understood.

Several studies have shown that oxytocin treatment results in symptom improvement in a range of mental health conditions. For instance, individuals with schizophrenia demonstrated enhanced emotion recognition and social cognition after oxytocin administration[67]. Similarly, in patients with post-traumatic stress disorder (PTSD), oxytocin was effective in reducing conditioned fear responses and improving emotional regulation[13]. These findings suggest that oxytocin may play a significant role in modulating mental health symptoms beyond its well-documented effects on social behavior.

Post-traumatic stress disorder and oxytocin

OT promotes the extinction of an activated avoidance reflex and reduces passive avoidance behavior, as well as memory consolidation and retrieval[68]. Patients with PTSD were shown to have reduced memory recall and conditioned response after receiving intranasal OT[69]. It appears that alterations to the OT system following early traumatic stress and abuse may block brain development and raise the chance of PTSD and, more generally, mental illnesses later in life[70]. It was also hypothesized that increased P.E.P. activity might contribute to the pathophysiology of the behavioral and affective symptoms of PTSD through an increased degradation of different neuropeptides because it was discovered that P.E.P. activity was increased in PTSD patients, especially in those with a concurrent major depression[71].

Disorders of anxiety and oxytocin

Because OT has been shown to impact affiliative behavior in non-human animals, several ideas have been proposed regarding its potential involvement in human emotions and relationships-[72]. Additionally, it is thought that pregnancy, a time when OT levels are elevated, might help avoid several anxiety disorders, including panic disorder. It has been shown that mothers' OT levels are positively correlated with social skills, calmness, and tolerance[73], as well as a decrease in the prevalence of stress and anxiety disorders[7]. Stress-related OT release, which mostly has anxiolytic effects, appears to be an essential regulator of the fear and anxiety response[74-76]. It is interesting to note that OT significantly impacts how the amygdala functions, as it can reduce amygdala activity and its linkage to brain areas responsible for the autonomic and behavioral response to fear[77] when administered intravenously. This is due to the amygdala's role in the biological reaction to threat cues in social interaction. Recent research has connected the pathophysiology of social anxiety disorder to the downregulation of OT receptors, which may assist in explaining the cognitive distortions seen often in this illness's victims[7].

Depression and oxytocin

Studies suggest that neuropeptides regulate affect and are crucial for mood stability and anxiety prevention. Research into the relationship between neuropeptides and monoamines highlights oxytocin's potential role in the pathophysiology of affective disorders. Clinical and animal studies link oxytocin imbalances to depression, demonstrating its positive role in depression management and its frequent dysregulation in depressive states[78]. Oxytocin levels are often lower in postpartum depression compared to controls, and low oxytocin during pregnancy may predict postpartum depression[79,80]. However, the impact of oxytocin administration on the emotional state of pregnant women is inconsistent, with postpartum depression being more commonly associated with oxytocin delivery.

When examining the effects of oxytocin, it's important to consider the multifactorial influences, including hormonal, genetic, and social factors. Some pregnant women may require perinatal oxytocin treatment, which could indicate existing hormonal or neuropeptide deficiencies that make them more prone to depression[81]. Insufficient oxytocin release has been linked to early breastfeeding cessation and postpartum depression[82]. A recent study showed that in women with depressive symptoms, oxytocin released during breastfeeding helps moderate cortisol levels in response to stress[83]. Research suggests that oxytocin may play a role in depressive disorders beyond the postpartum period by promoting social behavior and reducing stress responses. Clinical evidence indicates that severe depression may lead to an imbalanced oxytocin system.

The outcomes of clinical research comparing peripheral cortisol levels with serum oxytocin levels in depressed individuals were dissimilar. While some studies found no appreciable changes between these parameters in depressive patients and control participants[84-86], others found a drop or even an increase in oxytocin levels in depressed patients[87-89]. The decline in oxytocin was significantly more dramatic when fibromyalgia and depression were present. Due to these variations in clinical expression, certain forms of depression may be connected to various amounts of oxytocin. Additionally, even when depressed, somatoform manifestations are associated with a greater oxytocin level. In addition, individuals with social withdrawal as the primary symptom of their depression may have lower levels of oxytocin than other patients, particularly those with impulsivity as their primary symptom. Another crucial factor in understanding variations in the peripheral level of oxytocin is sexuality.

Both in the context of unipolar depression and the presence of bipolar depression, female patients' oxytocin levels were shown to be lower than those of male subjects[90]. Addiction, motivation, survival, nutrition, and sexual activity are all behaviors connected with rewards, and the mesocorticolimbic pathway – where dopamine and oxytocin interact with one another as a primary function – is crucial in accomplishing these behaviors[91]. Oxytocin may be responsible for altering how the depressed person perceives reality, making social interactions appear hostile or unpleasant. As a result, oxytocin system failure may be a risk factor for asocial behavior[92]. According to observations in the literature, oxytocin levels in depressive patients alter both before and after citalopram therapy. After the onset of the therapeutic response, the authors saw considerable alterations. According to the evidence, oxytocin could be a vital mediator of the therapeutic impact of SSRIs[93].

Evidence suggests that sildenafil, commonly prescribed for erectile dysfunction, can also stimulate oxytocin release,

producing an antidepressant effect[16]. Similarly, the oxytocin agonist carbetocin has demonstrated antidepressant effects in animal studies, with results comparable to the tricyclic antidepressant imipramine, as indicated by behavioral changes (e.g., swimming and immobility time)[94]. Additionally, oxytocin treatment may have beneficial effects in treating various mental disorders, including anxiety, schizophrenia, autism, drug addiction, and anorexia.

Despite promising outcomes, several limitations must be considered when evaluating oxytocin as a therapeutic agent. Individual response variability, influenced by genetic factors and receptor sensitivity, makes it difficult to predict who will benefit most from treatment. Additionally, measuring central oxytocin levels complicates understanding its precise mechanisms of action. These challenges highlight the need for more accurate tools and methods in future research.

Conclusion

This review highlights novel insights into the oxytocinergic system's role in mental disorders, emphasizing its multifaceted impact on conditions like autism, schizophrenia, PTSD, anxiety disorders, and depression. We propose innovative perspectives on oxytocin's functions across these disorders, suggesting that its modulation can uniquely influence social behavior, emotional responses, and cognitive processes in each condition. Importantly, our analysis underscores the potential of personalized oxytocin-based therapies tailored to specific symptom profiles in mental disorders. We advocate for further research on elucidating oxytocin's mechanisms in mental health and identifying patient subgroups most likely to benefit from such interventions. This approach could revolutionize treatment strategies in mental health care, moving toward more targeted and effective therapies.

Ethical approval

Ethics approval was not required for this review.

Consent

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Author's contribution

R.P.C.: writing the paper, study concept and design, data collection, and interpretation. Y.S. and H.S.: study concept and design. R.B.: study concept and design. P.G.: editing the paper, study concept and design, data analysis, and interpretation.

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There is no conflict of interest.

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