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Review

Oxytocin system in neuropsychiatric disorders: Old concept, new insights

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Abstract: Oxytocin (OXT) is a neuropeptide that plays a pivotal role among species peripherally and centrally. It recently has attracted much attention for its involvement in anxiety-related behavior, stress regulation, social behavior and various neuropsychiatric disorders. OXT is one of the important mediators of emotional and social behaviors such as maternal behavior, fear extinction, social support, happiness, and trust. It is also involved in learning and memory process. The recent progresses in OXT system have put this neuropeptide as an important psychotherapeutic intervention for various psychiatric disorders such as stress, anxiety disorders, social phobia, postpartum depression, bipolar disorder, autism, and schizophrenia. In this review, we highlight OXT's contributions to various physiological functions and psychological disorders and discuss its potential use as a therapeutic agent.

Key words: oxytocin; stress; anxiety; fear; autism; schizophrenia; neuropsychiatric disorders

神经精神疾病中的催产素系统：老概念，新见解

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摘 要：催产素(oxytocin, OXT)是一种神经肽，在各物种的中枢和外周神经系统中都起着关键作用。由于它参与焦虑相关行为、压力调节、社会行为和各种神经精神障碍，近年引起大量关注。OXT是介导诸如母性行为、恐惧消退、社会支持、幸福与信任之类的情感和社会行为的重要物质之一，也参与学习和记忆过程。OXT系统的最新进展已将此神经肽用于心理治疗干预各种神经精神疾病，如压力、焦虑障碍、社交恐惧症、产后忧郁症、躁郁症、自闭症和精神分裂症等。本综述着重概括OXT对各种生理功能和心理问题的贡献，并讨论其作为治疗药物的潜力。

关键词：催产素；压力；焦虑；恐惧；自闭；神经精神疾病
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1 Introduction

Oxytocin (OXT), a neuropeptide found in all vertebrate mammals, plays a pivotal role peripherally and centrally [1]. Peripheral action of OXT is of great importance, as it is involved in the regulation of reproductive behavior [2], parturition and lactation in females [3]. The peripheral action of OXT is controlled by OXT mainly secreted from the pituitary gland, because peripheral OXT has the poor penetration of the blood-brain barrier (BBB) [4]. Clinically, OXT is used during the delivery and lactation [5] as it is involved in the smooth muscle contraction of uterus and breast. OXT receptors (OXTr) are found in the gut, gastrointestinal tract, heart, testes, uterus, corpus luteum, placenta, amnion, kidney, pancreas, thymus, adipocytes [6] and involved in the regulation of water balance, bone density, and appetite [7].

The central activity of neuropeptide OXT mainly depends on OXT produced from hypothalamus [4]. Preliminary studies revealed that OXTr are widely distributed in various brain regions including bed nucleus of the stria terminals (BNST) [8], limbic structures, central nucleus of the amygdala [9], prefrontal cortex (PFC) [10],

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hippocampus, nucleus accumbens, septum and certain brain stem nuclei [11]. Recently, the neuropeptide has attracted much attention for its role in anxiety-related behavior, stress regulation, sleep/wake patterns, social behavior and mental health [12]. More importantly, the recent progresses in OXT system have put this neuropeptide as an important treatment target for various psychiatric disorders, like anxiety disorders, stress, postpartum depression, bipolar disorder, social phobia, autism and schizophrenia [13].

The advancement in research revolutionizes our knowledge as recent fMRI studies revealed the insights of central OXT physiology [14, 15]. As breastfeeding mothers show an extended release of OXT, there is accumulating evidence that neuropeptide release during lactation decreases the stress response and social anxiety [16]. The pharmacological activation of central OXT through intranasal administration has been shown to positively affect core symptoms of autism spectrum disorders (ASD), especially socio-communicational deficits [17].

Many studies in humans have found the link between central activity and peripheral release of OXT [18], but the mechanism of this correlation is still unknown. These days the research has focused on developing agonists and antagonists of OXTr that can easily penetrate through BBB, because OXT once secreted from the pituitary gland, cannot re-enter the BBB [19]. It has been suggested that intranasal OXT bypasses the BBB and passes from clefts in the nasal epithelium to reach the cerebrospinal fluid (CSF) [20, 21].

Several studies in line confirm the association of peripheral and central OXT. Studies on humans showed that high plasma OXT levels are associated with enhanced social behavior in ASD [22]. Another study links high plasma OXT with a social challenge, such as a distressed pair-bond relationship [23]. Stressful stimuli, such as conditioned fear stimuli, restraint stress [24] and several other psychosocial stressors are found to increase peripheral OXT levels [25]. However, higher plasma and salivary OXT is positively linked with the parents' and child's social behavior and communication [26]. Here we focus on the involvement of neuropeptide OXT in various psychological conditions such as stress, anxiety disorders, social phobia, autism and schizophrenia (Fig. 1) and discuss its potential use as a therapeutic agent.

2 The role of OXT in emotional and social behavior

Researchers for decades studied happiness as an

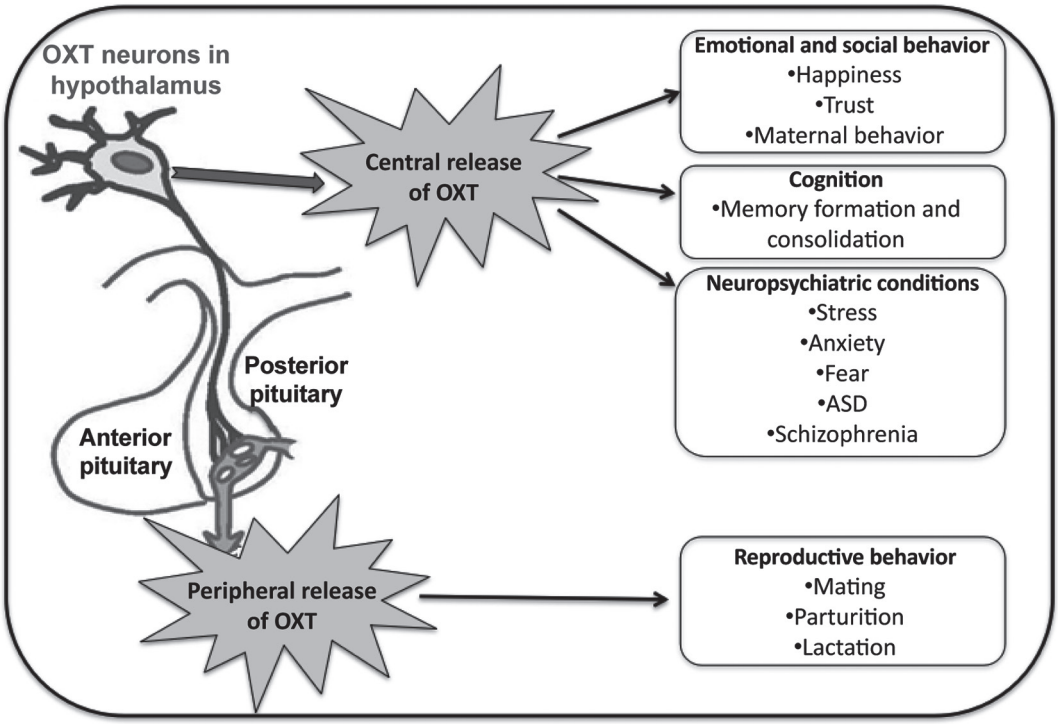

Fig. 1. Schematic diagram summarizing the central and peripheral roles of oxytocin (OXT). ASD: autism spectrum disorders.

emotion. Previously, there were two kinds of perceptions, one is that happiness occurs because of genetics and inherited factors while the second one is related to the environmental factor like high income, being active during life, education or having more friends. Recent studies have found that happiness is the outcome of multiple factors occurring due to the interaction between various endogenic and exogenic factors, and OXT is one of the important endogenic mediators [27]. The brain's emotion circuitry is a complex network that involves hippocampus, PFC, amygdala, anterior cingulate cortex and insular cortex; these structures are directly or indirectly connected to each other and involved in the emotion regulation. The presence of OXTr in these regions influences the notion that the OXT is one of the important mediators of emotional behavior such as maternal [3] and social behavior [28]. Furthermore, it has been shown that OXT enhances positive social interactions [29], social support and trust [30]. Collectively it assumes that OXT is involved in happiness regulation. Human studies revealed that the intranasal administration of OXT promotes trust across different tasks [31]. In addition, OXT is also involved in processing and regulation of emotional information [32].

A recent study demonstrates that intracerebroventricular (ICV) injections of OXT are associated with maternal behavior [33]. Similarly, impaired maternal behavior has been observed in OXTr knockout mice [34]. Further association between OXT and maternal behavior is also explored by using different agonists and antagonists of OXT [35]. Disruption in central OXT activity due to lesion and OXT antagonist also impairs maternal behavior [36]. Importantly, OXTr in nucleus accumbens is involved in the induction of maternal behavior in prairie voles [37]. As discussed earlier, OXT system is positively linked to parental behavior, in the same way, increased OXT levels in peripartum are associated with improved mother-infant relationship [38]. Moreover, early life insult seems to influence the OXT system later in life, i.e. adult women who experienced childhood abuse in their earlier life had decreased CSF OXT level [39].

Along with maternal care such as feeding, nest building and grooming of pups [40], OXT also facilitates prosocial behavior [41]. Clinical studies on healthy adults and neuropsychiatric patients demonstrate the effects of OXT on social cognition and emotional behavior. The results showed improved theory of mind and emotional empathy in healthy adults [42], and these results are also consistent with the autistic patients in addition to improve affective speech comprehension [43, 44]. Taken together, both animals and humans studies have suggested that OXT enhances prosocial behavior.

Research has revealed that OXT is also involved in fear extinction. Amygdala is the main structure that regulates the fear responses, and OXT normalizes amygdala activity to reduce fear response by acting on central amygdala [45], which in turn inhibits excitatory flow from the amygdala to brainstem [9]. In addition, studies in rodents show that OXT inhibits the fear response by activating an inhibitory circuit within the amygdala [46]. These results are also consistent with human studies [47]. Moreover, the hyper-sociability behavior is associated with decreased amygdala activation [31], while increased amygdala activation is linked with social phobia and social avoidance [48]. In conclusion, OXT modulates functional network related to fear process by reducing amygdala activation (Fig. 2).

3 The role of OXT in cognition

Memory is one of the important consequences of brain function. For decades, scientists have focused on the phenomenon related to memory process. Several studies suggested the role of many neuropeptides in memory formation and OXT is thought to be one of the key neuropeptides that are involved in memory process [49]. The hippocampus is an important brain structure involved in memory formation and consolidation. As we discussed earlier, OXTr is largely expressed in the hippocampus, so it could be supposed that OXT may play a vital role in memory consolidation.

Correspondingly, a number of studies investigated the involvement of OXT in memory consolidation, and reported that OXT administration improves memory impairments [50]. Similarly, OXT treated hippocampal slices significantly sustain longer long-term potentiation (LTP) and have higher levels of phosphorylated CREB, and OXT also improves reference memory when centrally administered [51]. Thus, it is suggested that OXT acts directly on the hippocampus to enhance memory.

Besides this, there are some contradictory studies regarding OXT's role in memory. As OXT was injected into the structure involved in attention and memory i.e. nucleus basalis of Meynert (NBM), rats showed impaired spatial memory in Morris water maze (MWM) [52]. Moreover, injection of an OXT antagonist, atosiban, into NBM blocks the OXT-related impairments sug-

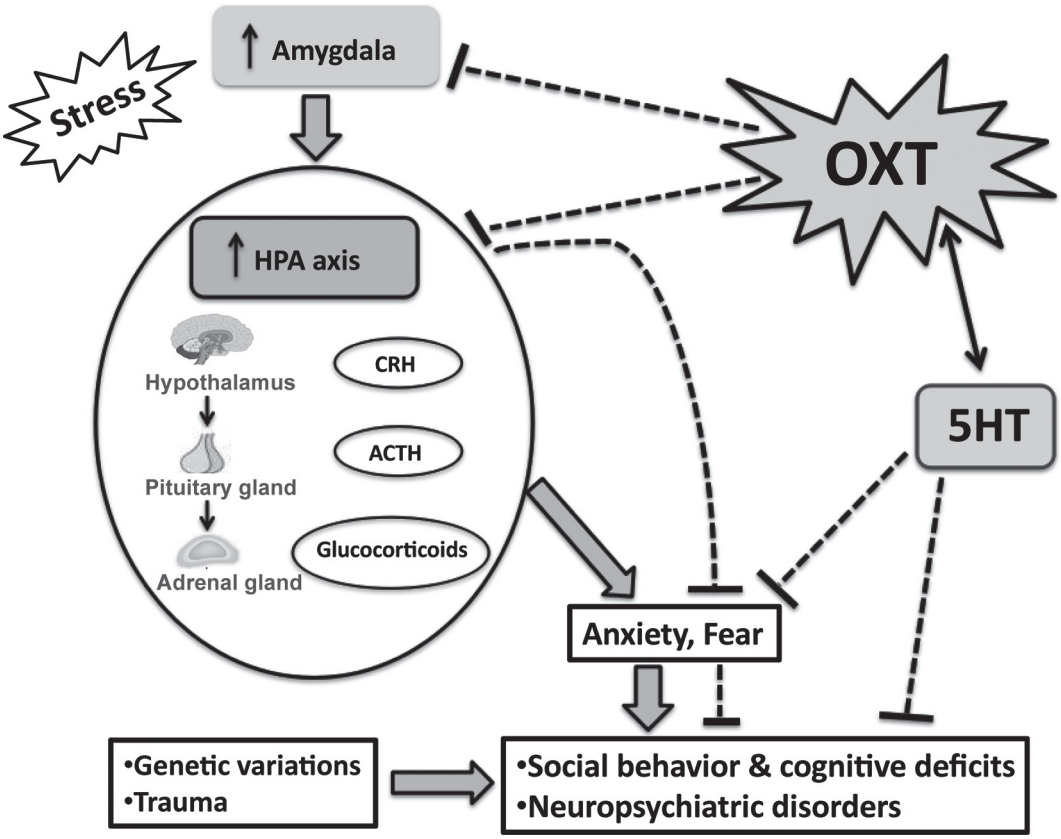

Fig. 2. Integrative model of the interactions of oxytocin (OXT) with stress, anxiety, fear and neuropsychiatric disorders. The activation of amygdala and hypothalamic-pituitary-adrenal (HPA) axis in response to stress induces anxiety, fear and social behavior deficits. The HPA axis and amygdala activation is prevalent in numerous neuropsychiatric disorders i.e. panic disorder, acute stress disorder, generalized anxiety disorder (GAD), social phobia, autism and schizophrenia. The altered OXT system and its variants have been observed in these neuropsychiatric disorders and these disorders are also linked with serotonin (5HT) dysfunction. OXT decreases amygdala activity and HPA axis over-activation by inhibiting the stress hormones, such as corticotropin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoid, thus improves social behavior deficits, anxiety behavior and various neurological conditions. OXT release or therapy positively affects the core symptoms of these disorders directly or by interacting with 5HT.

gesting that OXT exerts inhibitory spatial memory effects via NBM [52]. Furthermore, human studies in both males and females also show that OXT might be involved in spatial memory impairments. In this context, a recent study demonstrates that OXT induced memory impairments in individuals with higher levels of social anxiety [53], and another study on this issue reveals that when given to pregnant females to induce labor, OXT impairs the cognition and may be a risk factor for bipolar disorder in offspring [54].

In contrast, OXT gene knockout mice do not show any memory impairment in MWM, suggesting that OXT might not be involved in memory formation [55]. These contradictory studies about OXT's role in memory remain one of the important challenges for neuroscientists and further research is needed to explore the notion.

4 Neuroendocrine role of OXT

4.1 Stress regulation

Research has suggested that OXT plays a pivotal role in stress regulation through modulating the function of hypothalamic-pituitary-adrenal (HPA) axis [56]. As we know that HPA axis is the main neuroendocrine stress system, however, both inhibitory and excitatory effects of OXT have been found on HPA axis during the stress condition [57]. Furthermore, exogenous OXT administration significantly inhibits the stress-induced activity of HPA axis [58], in the same way, endogenous stimulation of OXT during lactation also has an inhibitory influence on stress response, such as decrease in basal plasma levels of adrenocorticotropic hormone (ACTH) and cortisol [59].

In addition, human studies also support the idea that

OXT causes relaxation state and reduces biological response to stress [60]. The authors show that OXT in combination with social support resulted in low salivary cortisol concentration and decreased the anxiety. For instance, a recent study reported that OXT attenuates the death of pancreatic beta cells in islets exposed to cytotoxic stresses [61]. Similarly, high plasma OXT levels have been found to decrease norepinephrine levels, reduce vasoconstriction and sympathetic reactivity in a response to stress, suggesting a direct link between OXT and stress regulation [62].

Besides this, central OXT controls stress responses by inhibiting HPA axis in gender-independent manner [63]. Several other studies also link OXT to stress regulation in rodents. For example, different stressful stimuli, such as conditioned fear stimuli and restraint stress, induce central and peripheral OXT release [24, 64]. In short, brain OXT might be involved in the control of neuroendocrine stress responses (summarized in Fig. 2).

As we discussed earlier, OXT has stress regulation effects in both rodents and humans. The effects of OXT on stress regulation are due to its direct or indirect inhibitory influnces on the amygdala [9, 65]. Moreover, neuroimaging studies revealed that intranasal OXT administration not only reduces amygdala activity [66], but also decreases functional coupling between the amygdala and brainstem [9, 67]. The neuropeptide OXT is currently attracting considerable attention as a result of the discovery of the amazing behavioral functions it regulates, especially in the context of social interactions and stress regulation. The collection of studies presented above supports the notion that OXT exerts beneficial effects and plays an important role in the modulation of stress regulation.

4.2 Interaction of OXT and serotonin system

OXT interacts with the monoaminergic, specifically serotonergic pathway to exert its anxiolytic and antidepressant effects. Furthermore, a recent study also confirmed the link between OXT and serotonin (5HT) [68]. Serotonin originates specifically from the raphe nuclei of the brainstem and projects to the paraventricular nucleus of hypothalamus (PVN) [69]. It is also shown that a large number of OXTr is expressed within raphe nucleus [70]. The stimulation of serotonin release activates hypothalamic OXT neurons [71], hence serotonin modulates OXT release and exaggerates OXT related neuroendocrine responses. In addition, OXT also mediates the effects of selective serotonin reuptake inhibitors (SSRI) [72]. Related to this phenomenon, it has been reported that some SSRI such as citalopram and fluvoxamine play their antidepressant role via OXT release [73]. Acute administration of citalopram [74] and fenfluramine (5HT agonist) [75] significantly increases plasma OXT level. Therefore, it is suggested that OXT release is an important aspect of the pharmacological actions of SSRIs.

As discussed earlier, OXT is involved in the pathophysiology of various psychiatric illness, such as panic disorder, post-traumatic stress disorder, depression, obsessive-compulsive disorder (OCD), schizophrenia, and autism [76], while these disorders are also linked with serotonin dysfunction [77]. In this regard, the OXTr could be a potential therapeutic target. Therefore, further research is needed to explore the link between serotonin and OXT system in neuropsychiatric disorders.

4.3 Anxiety behavior

Brain OXT is an important regulator of anxiety behavior. A recent study confirmed the role of OXT, particularly in central amygdala and hypothalamic PVN, regarding the modulation of anxiety behavior [78]. Nowadays, research has focused on the therapeutic use of OXT against various anxiety related disorders. In this context, a study conducted on rats shows that OXT exerts its anxiolytic effects via activation of extracellular signal-regulated kinase 1/2 (ERK1/2) pathway [79]. However, OXTr agonist treatment activates ERK1/2 cascade specially in the hypothalamus, which may provide therapeutically relevant mechanisms. The anxiolytic role of OXT is further confirmed in various studies using OXTr antagonist [80], OXT deficient mice [81], and OXT treated animals showed a reduced anxiety behavior in the elevated plus maze.

Human studies also reveal the association of OXT with anxiety behavior regulation. fMRI studies on normal humans with no history of psychiatric disorders suggest that fear stimuli activate the amygdala while OXT administration decreases its activity. This amygdala activation is associated with the increased anxiety behavior while the decrease in its activity by OXT is related to anxiolytic behavior [67]. Physiologically, breast suckling is involved in increasing plasma OXT levels, decreasing cortisol level, or attenuating anxiety behavior, and is also associated with positive mood state [82]. By contrast, women who experienced childhood abuse in their earlier life had increased anxiety level and decreased CSF OXT concentration [39]. Simi-

larly, intranasal administration of OXT improves symptoms of social impairments in patients with social anxiety disorder [47, 83]. This anxiolytic effect of OXT may be because of the projections of a large number of PVN OXT neurons to the various limbic brain regions including medial preoptic area, olfactory bulb, anterior hypothalamus, substantia nigra and amygdala. In short, it is clear that OXT is responsible for reducing the anxiety-like behavior.

5 The role of OXT in neuropsychiatric disorders

5.1 ASD

ASD is a group of developmental disorders with the specific pattern of abnormalities in communication, impairments in social cognition and repetitive behaviors [84]. Until now, there has been no effective treatment of ASD because it is a multifactorial disorder and its symptoms vary among patients. However, new therapeutic targets are being established because of advancement in the field of genomics and neuropathology of ASD. With regard to this, OXT signaling pathway is extensively studied to improve the social deficits in ASD and thought to be a potential therapeutic target for drug discovery [85]. Various mouse lines have been developed to study the link between OXT and ASD. OXT knockout mice show the similar social deficits that are found in ASD animal models, while OXT therapy rescues the social behavior and repetitive behavior in both OXT knockout and CD38 knockout mouse models [55, 86]. In addition to this, intravenous OXT administration in ASD patients is able to improve the repetitive behavior [87] and increase the ability to remember spoken words [44]. Hence, OXT pharmacotherapy brings a promising treatment for repetitive and affiliative behaviors in ASD patients.

Several other studies have argued that there might be a link between OXT system and ASD pathophysiology. Likewise, the association of decreased OXT level has been found with deficits in social behavior in ASD patients [88]. Recent studies demonstrate that OXT is involved in regulation of social behavior [41, 89], therefore social deficits in ASD patients may be because of the disruption in OXT system. Moreover, it is suggested that OXT system and variants of OXTr [90] are involved in the etiology of ASD. Similarly, single nucleotide polymorphisms (SNPs) in OXT [91] and OXTr genes are also found in patients with ASD. Currently, research has focused on molecular mechanism underlying the association between OXT system and ASD.

However, clinical trial related to the association of OXT system and ASD reveals that synthetic OXT significantly improves social behaviors, specifically affective speech comprehension and repetitive behavior in ASD patients [92]. The authors show three possible mechanisms of OXT's action on ASD social symptoms; attenuate anxiety (inhibitory effects on the HPA axis and amygdala in the response to social stimuli), improve affiliative enthusiasm (interaction with the dopaminergic pathway and several regions of the social brain) and social stimuli salience. Moreover, another trial on autistic patients reports that OXT administration effectively reduces core symptoms of ASD especially social behavior deficits [93]. These clinical trials also prove the link between OXT system and ASD in humans. Hence, OXT might be a promising target for ASD drug discovery. Further research is needed to examine the optimal dosage, safety and efficacy of OXT therapy in ASD patients.

5.2 Schizophrenia

Schizophrenia is a chronic neuropsychiatric disorder characterized by a group of complex symptoms, i.e. negative symptoms (social behavior deficits), cognitive impairment (impaired working memory, attention, and disorganized thinking) and positive symptoms (hallucinations, delusions, and disorganized speech) [94]. As schizophrenia is a heterogeneous disorder, various neurotransmitter and neuropeptide systems are positively involved in its pathophysiology. OXT is found to be an important mediator that positively affects the symptoms associated with schizophrenia. Moreover, OXTr is widely expressed in the brain areas that are affected in schizophrenia, such as substantia nigra, basal ganglia, hippocampus, amygdala, septal nucleus and the nucleus of solitary tract [95]. Thus, expression of a large number of OXTr in these areas proves it to be an important therapeutic agent for the drug discovery in schizophrenia.

A recent study shows that OXT system is disrupted in schizophrenic patients [96]. Similarly, elevated plasma OXT levels are also found in patients with schizophrenia [97]. Recent studies suggest that SNPs of the OXT and OXTr genes are linked with symptom severity in patients with schizophrenia [98, 99]. OXT gene polymorphism (*rs2740204*) is involved in the negative symptoms of schizophrenia, and human studies find that this gene variant is significantly linked with clozapine

(serotonin agonist) treatment response [100]. These findings support the idea that OXT system works as an antidepressant and antipsychotic via attenuating the therapeutic response of serotonin. Furthermore, fMRI studies reveal that dysregulation of OXT system is associated with the social and cognitive deficits in schizophrenia [101] and exogenous OXT infusion significantly improves social cognition and social interaction in schizophrenia [102].

Several animal models exist to investigate the association of OXT system and neuropsychiatric disorders. For example, OXT and OXTr knockout mice have been extensively used to study the impact of disrupted OXT system in schizophrenia. Furthermore, OXT system is an important candidate against cognitive deficits that are reflective in schizophrenia. Besides cognitive deficits, impaired sensorimotor gating is also a common outcome of schizophrenia [103] and prepulse inhibition (PPI) of the startle reflex (defensive response to intense stimuli) is a tool to measure sensorimotor gating across species. Schizophrenic patients display reduced PPI of the startle reflex and OXT infusion rescues PPI in brown Norway rats that naturally have low PPI [104]. Clinical studies suggest that intranasal administration of OXT could be a beneficial candidate in schizophrenia as it is found to improve social behavior and cognitive dysfunctions in schizophrenic patients [105]. Similarly, a group of schizophrenic patients that received 3-week adjunctive treatment with intranasal OXT show improved verbal memory and positive and negative syndrome scale (PANSS) scores [106].

Briefly, these findings suggest that disrupted OXT system might be an underlying mechanism of negative, positive and cognitive symptoms of schizophrenia. In conclusion, it leads to the hope that OXT might be used as potential therapy to rescue the all three symptoms domains of schizophrenia.

6 Conclusion

In summary, molecular, cellular and behavioral studies determine a role of OXT neural pathways in learning and memory, social behavior, anxiety, stress and various neuropsychiatric disorders (Fig. 1). However, there is a contradiction between the effects of OXT on learning and memory, which needs further exploration. The pharmacodynamics of OXT administration is still unclear. In particular, further research is required to investigate the mechanism by which OXT penetrates the brain following various routes of administration. These findings are fascinating and important but research in this field is in its adolescence. Therefore, further research is needed to elucidate the specific mechanisms through which OXT exerts these effects. We also need advanced approaches to translate laboratory studies into clinical outcomes. Human and animal models tremendously demonstrate the critical role of OXT system in neuropsychiatric disorders especially bipolar disorder, social phobia, autism, and schizophrenia. We now have the tools to test the above prediction that OXT can work as a therapeutic agent. In near future, it is hoped that we will gain a better understanding of the underlying neural mechanisms of OXT's antipsychotic role and provide new avenues for drug discovery in neuropsychiatric disorders.

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