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Title: **The Other Face of Oxytocin: Role of Oxytocin in Neuropsychiatric Disorders**

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Abstract

The neuropeptide oxytocin (OXT) is well-known for its role in pregnancy and lactation. However, its role extends beyond the reproductive system. In fact, the role of OXT in neuropsychiatric disorders has long been studied. OXT is largely associated with social behavior and stress reduction, and so it is to no surprise that it is thought to be involved in the pathophysiology of neuropsychiatric disorders. Many studies have investigated how abnormalities in the OXT system give rise to symptoms and socio-cognitive deficits many patients with neuropsychiatric disorders exhibit. Understanding the patho-physiology of these disorders enables the development of more efficacious therapeutic agents which target the abnormalities and give rise to less adverse effects.

In this review we summarize the literature available to date about the role of OXT in schizophrenia, autism spectrum disorders (ASD), addiction to drugs of abuse and anorexia nervosa (AN). Although these disorders are very Sept.arate and different entities, they all have something common in their pathology; they are associated with deranged OXT systems. Although many studies have been conducted to determine the exact role of OXT in these disorders and how OXT can be used to treat these disorders, research is still in its infancy. Further research is required to be able to standardize OXT as a therapeutic agent, determine its effects and safety, both in short-term and long-term use.

Keywords: oxytocin, schizophrenia, autism, addiction, anorexia nervosa, therapeutic

Introduction

Oxytocin (OXT) is a polypeptide composed of nine amino acids. Its synthesis occurs in the magnocellular cells of the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus. It is stored and released from the posterior pituitary. Smaller quantities of OXT are synthesized by the parvocellular cells of the PVN of the hypothalamus[1].Other regions which may synthesize OXT are the bed nucleus of the stria terminalis, lateral amygdala and the medial preoptic area[1–3].

The role of OXT in humans is extensive; it is involved in pregnancy and labor, lactation and response to stress. It is also cardio-protective and plays a role in the cardiovascular system. It is also famous for its role in pair bond formation, parental care as well as social recognition.

Since OXT has been found to exert an anxiolytic effect as well as play an important role in recognizing emotions and social behavior, it is thought that it also plays a role in neuro-psychiatric disorders characterized by deficits in social cognition and increased stress and anxiety. Such neuropsychiatric disorders include schizophrenia, autism Spectrum Disorders (ASDs), drug addiction and anorexia nervosa (AN).

Schizophrenia

Schizophrenia is a psychotic disorder which affects an estimated 51 million people all over the world[4]. As shown in Table 2, the symptoms of schizophrenia are classified into two categories; positive symptoms and negative symptoms, with impaired emotional face recognition being heavily implicated in the disorder[5]. Being a very complex disorder, it is still vaguely understood, however one possible cause of schizophrenia is the dysregulation of chemical systems, one of which being the OXT system[4,6]. The extent to which the OXT system is disrupted affects how severe the symptoms are. For this reason, administration of OXT to schizophrenic patients to counteract the imbalance is deemed as a possible treatment for schizophrenia[4].

Current anti-psychotic drugs relieve the positive symptoms, but are not very effective in improving the negative symptoms. However, new treatment involving OXT can help improve the negative symptoms associated with schizophrenia since OXT is involved in all symptom domains[4].

Symptoms of Schizophrenia	
Positive Symptoms	**Negative Symptoms**
Hallucinations	Social withdrawal
Delusions	Inability to feel pleasure

Lack of Coordination (dysmetria)	Cognitive impairments i.e. disorganized thinking, impaired memory & lack of attention
Eye tracking dysfunction	Speech disturbances
Saccadic Eye movements	General lack of drive

Table 1: Classification of symptoms exhibited by schizophrenic patients (adapted from[4,7])

Schizophrenia is caused by the combination of a disrupted dopaminergic system, a malfunctioning amygdala and dysregulation in the OXT system[8]. Further research shows that hypoactive N-methyl- D-aspartate (NMDA) receptors also play a role in bringing about the negative symptoms associated with schizophrenia[4,9]

Emotions and social behavior are mainly controlled by a part of the brain called the amygdala, which is found near the front end of the hippocampus. It serves as an integration center for various sensory inputs such as sense of smell, sight, taste[10] and also fear[8].

The amygdaloid complex is made up of three subnuclei; the medial group, the basal-lateral group and the central-anterior group[10]. It forms several networks with the ventral tegmental area and the closely positioned nucleus accumbens; two dopaminergic structures. The interactions between the amygdala and the dopaminergic structures are important for the proper identification of stimuli[8].

In animal studies, OXT receptors (OXTR) have been found in abundance in the central-anterior group of the amygdaloid complex, as well as in the basal-lateral and medial group, however in much smaller amounts. Some OXTRs have also been identified in the hippocampus and the nucleus accumbens[8]. The exact pattern of distribution of OXTRs in the human brain has not yet been determined[11]. However, studies have found that the administration of intranasal OXT is associated with a decrease in amygdalar activation following exposure to a socioeconomic stimulus which elicits fear[11,12]. This suggests a link between OXT and the amygdala.

Hyperactivity of the amygdaloid complex is associated with social impairment and increased social angst; both characteristics of schizophrenia. Abnormalities in the amygdala impair the detection of stimuli and cause it to respond inappropriately, thus bringing about social impairments. For instance, schizophrenic patients are not able to respond adequately to harmful situations because of the abnormally low activity of their amygdala. However, they may respond aggressively to non-harmful situations because of the abnormally high activity of the mygdala[13]. Low activity of the amygdala means that there is little amygdalar response to a stimulus, whereas high activity of the amygdala means that the amygdalar response to a stimulus is strong[13].

OXT has been found to be anxiolytic, i.e. it helps to reduce stress and anxiety and increases relaxation[13–15]. A higher concentration of OXT in the plasma is associated with a decrease in the plasma norepinephrine concentration, a decrease in the amount of vasoconstriction as well as a reduction in the sympathetic response in reaction to stress; all of which are mechanisms which contribute to the anxiolytic effect of OXT[15]. The anxiolytic property of OXT is also thought to be brought about by the increase in transmission of gamma Aminobutyric acid

(GABAergic) inhibitory interneurons found in structures belonging to the limbic system. A decrease in the number of GABAergic inhibitory interneurons may be part of the patho-physiology of oxytocin-related social cognition impairment in schizophrenic patients[8].

A post-mortem study showed that the schizophrenic brain has a lesser amount of OXTRs in the temporal cortex compared to that of a healthy human brain, as well as a decreased binding affinity of OXTRs in the vermis[16]. This defect in the OXTR contributes to the pathophysiology of schizophrenia.

Schizophrenic patients have a plasma concentration of OXT which is lower than that found in healthy individuals. The lower the concentration of OXT, the more severe the negative symptoms of schizophrenia are, as measured on the Positive and Negative Syndrome Scale (PANSS)[17 18]. Single nucleotide polymorphisms (SNPs) in the OXT and OXTR genes modulate an effect on the extent to which the symptoms of schizophrenia are severe[4]. Also, there is a correlation between the size of the OXT gene and the size of the amygdala[12], which is found to be 6% smaller in volume in schizophrenic patients compared to healthy individuals[8].

Dopamine and OXT are also related; dopamine is thought to have a role in the release of OXT from the paraventricular nucleus (PVN). Furthermore, antagonizing dopamine transporters leads to a decrease in both the expression and the affinity of OXTRs[8]. Schizophrenic patients are thought to have an imbalance in the dopamine system, such that there is a surplus of transmission of dopamine in the mesolimbic pathway, and a lack of transmission of dopamine in the pre-frontal cortex[4].

OXT as a Supplement for Anti-Psychotic Drugs

Most of the antipsychotics currently being used to treat schizophrenic patients, i.e. the typical antipsychotics, are dopamine receptor (D2) antagonists. They are based on the dopamine hypothesis of schizophrenia described earlier. The problem with these typical antipsychotics is that while they improve most positive symptoms, they are not capable of improving the negative symptoms[4]. They have a very high affinity to D2 receptors, and as a result, their binding is not limited only to the limbic system, leading to many side effects, such as tremors as seen in Parkinson's disease[19].

Other atypical antipsychotic drugs are more effective at improving positive and, to a lesser extent, negative symptoms[4], as well as bring about less side effects. Having a lower affinity for D2 receptors, and an affinity for D3 and D4 receptors which are solely found in the limbic system, these atypical antipsychotics are constricted to work in the parts of the brain which are involved in schizophrenia[19].

Irrespective of the atypical antipsychotics being able to help relieve negative symptoms, both typical and atypical antipsychotics are unable to improve social cognition in schizophrenic patients[20]. Recent studies trying to find an ideal therapeutic for improving social cognition in schizophrenic patients have been focusing on the administration of intranasal OXT as a supplement to antipsychotic drugs[21].

Although OXT can be used as a therapeutic for all patients, patient gender should be taken into consideration in order for effective management of OXT. Since the OXT system is regulated by estrogen and progesterone, changes in the levels of these hormones throughout the menstrual cycle in females may be associated with changes in the presentation of symptoms[18].

When intranasal OXT was administered to healthy individuals, functional magnetic resonance imaging (fMRI) showed a reduction in the activation of the amygdaloid complex when participants were exposed to fearful faces, and an increase in the activation of the amygdaloid complex when participants were exposed to happy faces[18]. Increased activity in the amygdala may be the reason why schizophrenic patients perceive neutral or non-harmful faces as being threatening[22].

Similar studies were also carried out on male schizophrenic patients[9]. Patients chosen were those who had been receiving stable doses of antipsychotics for at least four weeks. Any patients who were receiving treatment for mood swings were excluded from the study since there is still not enough knowledge on the relationship between drugs which stabilize moods and the OXT system[20]. The patients were administered a maximum of 40 International Units (IU) of intranasal OXT for 3 consecutive weeks, during which they were monitored. This study conducted by Feifel *et al*. showed improvement of both positive and negative symptoms after the third week of intranasal OXT administration[23]. Furthermore, after the third week of the study, participants underwent the California Verbal Learning Test and the Letter Number Sequence test in order to examine if the participants experienced any loss of memory as a result of intranasal OXT administration. Results showed that the participants who had been receiving intranasal OXT did not experience any memory loss. Also, participants who had been administered intranasal OXT did better on two subtests than participants who had been administered a placebo[23].

Results of a randomized, double-blind, placebo-controlled experiment which studied the effect of intranasal OXT as an adjunct to risperidone for a period of 8 weeks also showed that intranasal OXT ameliorated the positive symptoms of schizophrenia. Statistics show that OXT may also have an ameliorating effect on negative symptoms and total psychopathology scores however these effects are unlikely to be clinically significant[11,24].

A similar study conducted by Woolley, Chuang *et al*. aimed to find the effect of intranasal OXT on different aspects of social cognition; mainly on automatic social cognition and on controlled social cognition[20]. Automatic social cognition is described as being 'reflexive', due to its immediate and unconscious nature. On the other hand, controlled social cognition is described as being 'reflective' since it involves conscious thinking and occurs over a longer period of time than automatic social cognition [20].

The participants of this study included both schizophrenic patients, as well as healthy individuals as controls. After participants of the study had randomly received 40 IU of intranasal OXT or of saline solution as a placebo, tests regarding social cognition were carried out. The "Reading the Mind in the Eye Test" (RMET) together with Emotional Evaluation Test (EET) and Simple Sarcasm Exchanges (SSR) test, was used to evaluate the effect of intranasal OXT on automatic social cognition. Social Inference Enriched (SI-E) test was used to evaluate the effect of intranasal OXT on controlled social cognition[20].

Results from this study show that intranasal OXT had a positive, ameliorating effect on controlled social cognition in schizophrenic patients, compared with the healthy controls. The results also show that intranasal OXT did not have any effect on automatic social cognition in both the schizophrenic patients and the healthy individuals. Since controlled social cognition is associated with an improved quality of life, this study affirms the use of intranasal OXT as a supplement for antipsychotic drugs used to treat schizophrenic patients[20]

The positive ameliorating effect intranasal OXT brought about on controlled social cognition in schizophrenic patients is probably to do with the fact that OXT improves working memory, helps patients remain interested in social communication and also enhances non-social cognition, resulting in the augmentation of social cognition. While the reason why OXT was ineffective in ameliorating automatic social cognition remains undetermined, the results concerning healthy individuals were probably due to the high concentrations of intranasal OXT used in the study (40IU), which led to OXT binding to both OXT and vasopressin receptors; the effects of which counteracted each other[20].

OXT as an Anti-Psychotic Therapeutic Drug

A study carried out by Caldwell, Stephens *et al*. aimed to prove that OXT has natural properties of antipsychotic drugs. The experiment was carried out on laboratory mice which had the OXT gene switched off and on laboratory mice which had a functional OXT gene[9]. The mice were administered doses of amphetamine (Amp), apomorphine (Apo) and phencyclidine (PCP) in order to induce a reduction in the Prepulse Inhibition (PPI) of the startle reflex; a reduction seen in schizophrenic patients[9,20]. Apo is a D1 and D2 receptor agonist; Amp brings about the release of dopamine and then prevents its reuptake, and PCP is an N-methyl-D-aspartate receptor (NMDAr) antagonist[9].

Results of this study show that there was a greater change in the PPI of the startle reflex in the knockout mice than in the mice with the switched-on OXT gene. This implies that OXT may indeed have a role as a natural antipsychotic as it prevents alterations of PPIs when chemical systems are disrupted. It also gives rise to the possibility of OXT being used an anti-psychotic to treat disruptions in PPIs[9]. Furthermore, the greatest reduction in PPI was observed in the knockout mice which were administered PCP. PCP affects the glutamatergic system, which as explained above, is a cause for the negative symptoms of schizophrenia if it is low in activity. This observation leads to the hypothesis that there is a link between OXT and the glutamatergic system[9]. However, more research has to be done in order to identify and establish this link.

Schizophrenic patients also experience a low latent inhibition (LI)[25,26]. LI refers to the process by which our brain takes more time to process and give meaning to familiar stimuli than it does for unfamiliar stimuli[26]. This process is important to allow human beings to adapt to new situations. People having a low LI treat familiar situations as if they were unfamiliar. Since LI is targeted by anti-psychotic drugs, and OXT is thought to have anti-psychotic properties, it is likely that OXT can be used as a possible treatment for low LI. This was investigated in a study conducted by Feifel, Shilling *et al*. Brown Norway rats were used in this study to see how they would react to unpleasant flavored water, depending if they had been pre-exposed to the flavored water or not. The rats were either administered a saline solution as a control, or else they had different doses of OXT injected into their peripheral circulation[26].

Results showed that there is a correlation between OXT and a high LI. In fact, rats which had previously been exposed to the unpleasant flavored water and had been administered OXT, drank more flavored water than those rats which had not been previously exposed to the unpleasant flavored water[26]. This indicates that OXT targeted directly the LI; it increased the loss of the aversive taste brought about by the pre-exposure to the unpleasant water without actually changing the unpleasant taste itself[26]. Also, the dose of OXT which had the best results in increasing LI was the lowest dose out of the three used; 0.02mg/kg. This is probably because

when higher doses were used, OXT ended up binding to vasopressin receptors, bringing about a counteractive effect[26].

Schizophrenia is a very complex disorder involving various factors including OXT. OXT plays a very important role in schizophrenia. OXT plays a role in its etiology in its severity and also in its treatment. Although there is still a lot of research to be done, it is evident that administering OXT to schizophrenic patients will be a huge step towards improving their overall health and lifestyle.

Autism Spectrum Disorder

Autism is a developmental disorder which is characterized by a multitude of shortcomings in social behavior[27]. Approximately 1% of the worldwide population is affected by this genetic disorder[28]; with every 1 in 1000 individuals being autistic[27]. It is a disorder which typically affects more males than females, with a ratio of males: females of 5:1[29].Autism is considered to be a spectrum disorder because its symptoms' severity may vary over a wide range in different individuals identified with autism[28].

Although it has been established by various studies that genetics play a vital role in the etiology of autism, different gene mutations have been identified in different cases of autism. In fact, each gene mutation identified as a cause of autism is associated with no more than 1 to 2% of autism spectrum disorder (ASD) cases[30,31].

According to the Diagnostic and Statistical Manual of Mental Disorders, ASD symptoms are classified into two domains which comprise symptoms associated with impairment in social communication and those associated with restricted and repetitive interests and behaviors[28,29]. In order for an individual to be diagnosed as autistic, the above mentioned symptoms must be observed in the individual at an early age during childhood[28].

Atypical antipsychotics are the current treatment given to ASD patients. Although these drugs have been proved to ameliorate symptoms such as hyperactivity and tantrums, they do not target the main deficits in social behavior associated with autism[28].

New studies have been focusing on the neuropeptide OXT, which has been largely associated with social behavior. As well as trying to determine the role of OXT in the etiology of ASDs, studies are also focusing on the role of OXT as a potential therapeutic for ASDs[31].

Autistic individuals exhibit a variety of abnormalities; they exhibit mutated genes, abnormal brain structure and composition as well as altered levels of neuropeptides such as OXT. There is such a wide range of clinical presentations of autism that no single factor can be pinpointed as a cause of this developmental disorder.

Autistic patients tend to have an enlarged brain as well as abnormal cellular composition of the brain tissue. Abnormalities of the cerebellum are largely associated with the clinical presentation of ASDs. Such abnormalities include underdevelopment of the cerebellar vermis, cerebellar hemispheres as well as a decrease in the amount of Purkinje cells in the cerebellum. Cerebellar activation in autistic individuals is in excess during straight forward skills which require little cognitive ability. However, it is somewhat reduced when the individual is performing tasks which require great cognitive ability, accuracy and attention[31]. Mutations in the Tuberous Sclerosis (Tsc1) and neuroligin-3 (Nlgn3) genes are associated with ASDs. Deletions of the latter gene

are related to blocked metabotropic glutamatergic receptor-dependent long term depression (MGluR-LTD) at synaptic junctions between Purkinje cells and parallel fibers. This blockage in MGluR-LTD is related to the deficiencies in motor coordination seen in autistic individuals[31]

Abnormal cellular composition of the frontal and temporal lobes of the cerebral cortex is often identified in autistic individuals. These brain regions are associated with social and language development, therefore malformations of these regions are often considered to play a role in the pathological physiology of ASDs[31,32]. Other brain regions which exhibit abnormalities in ASDs are the amygdala and the hippocampus, both of which are associated with social behaviors. Whilst some studies concluded that the abnormalities include an increase in the volume of these subcortical brain regions, others concluded that autistic individuals exhibit a decrease in the volume of the amygdala and hippocampus[31].

There is a high concentration of OXTRs in the amygdala and so any mutations in OXT and OXTR genes are thought to account for the deficits in social behavior observed in autistic individuals. In fact, mutations in the OXTR gene and the CD38 gene, thought to be involved in the release of OXT, have been associated with ASDs[33]. However not all studies found a correlation between SNPs in the above-mentioned genes and ASDs[33,34]. The reason for this discordance is probably due to the diversity between the individuals who participated in this study and those who participated in the studies which support the hypothesis[33].

A study conducted by Gregory *et al*. 2009 suggested that the gene for OXTR is silenced in autistic individuals. The silencing of the gene is due to the excessive methylation it undergoes due to a mutation[33].

Studies show that autistic individuals do not undergo the normal developmental increase in OXT levels. In fact, autistic individuals exhibit depressed levels of OXT in the bloodstream[27,35–37]. Findings which show elevated levels of the precursor of OXT, OXT-X, in the bloodstream offer the possibility that the reason why autistic individuals exhibit lower levels of OXT in the plasma than normal is because of a malfunction occurring in the synthesis of OXT [36].

An inverse relationship between plasma OXT levels in autistic individuals and their social behavior was observed, such that those autistic individuals who had the highest plasma OXT levels exhibited the worst forms of social behavior deficits[27,37]. Healthy individuals who have higher levels of OXT have better social abilities than healthy individuals with lower levels of OXT. Thus, the effect of OXT on social abilities in autistic individuals is opposite the effect it has on healthy individuals. Defects in the gene encoding OXT or in the processing of OXT could account for the decreased plasma OXT concentration in autistic patients, whereas defects in the gene encoding OXTR could account for the positive correlation between high OXT levels and worse social behavior deficits[37].

OXT may also serve as the link between the social capacities of autistic children and the autistic traits exhibited by their parents, but further research is required[37].

OXT as a Potential Therapeutic for Autistic Individuals

In an experiment conducted by Andari, Duhamel *et al.* individuals were asked to play a computer game of ball-tossing between 4 participants, three of which were fictitious players who were

given the roles of good, bad and neutral players. The game was played with a healthy subject, an autistic patient under a placebo and an autistic patient who was administered OXT. Similarities were observed between the healthy subject and the patient who was administered OXT, in that they were both biased in throwing the ball towards the good player. The patients who were given the placebo showed no marked bias to any one of the players. Also, patients who were administered OXT developed more trust towards the good player rather than the bad player, whereas patients under the placebo showed no difference in their attitudes towards the good and the bad players. Patients given the OXT infusion were able to distinguish between the players who reciprocated the ball toss and the players who did not reciprocate the ball toss. This shows that OXT, apart from increasing trust, also increases the motivation to interact socially, which subsequently helps to improve the learning process[36]

Another experiment conducted to investigate how OXT modulates the way autistic patients looked towards human faces showed that OXT increased to a certain extent the fixation of the patient on the eye region and decreased the saccadic eye movement associated with social stress and anxiety. This may be due to the suppressive effect OXT has on the activation of the amygdala, thereby reducing the response to fear[36].

OXT is also associated with the repetitive behavior observed in autistic individuals[38]. 15 autistic off-medication adults were given continuous infusions of either OXT or of a placebo. The infusions were administered over 4 hours, during which the dose of the infusion was gradually increased, with the subjects being closely monitored to ensure their wellbeing. Throughout the administration of the infusions, at every hourly interval, the subjects were observed for six different; the necessity to know, repetitiveness, ordering, necessity to tell or ask, self-harm and touching. The participants were given a rating based on how they scored for each behavior. The same experiment was carried out 2-3 weeks later with the same 15 participants[38].

Results showed that generally, participants given the OXT infusion exhibited a decrease in repetitive behavior as well as a decrease in the number of different repetitive behaviors. No decrease in repetitive behavior was observed in the placebo group; with 6 of the subjects exhibiting an increase in repetitive behavior. One subject who had received OXT exhibited an increase in repetitive behavior [38]. It must be taken into consideration that this study was conducted on a small number of subjects and it did not include autistic children. Therefore, although its results support the use of OXT as a potential therapeutic in autistic individuals, it has several limitations[38].

Studies have shown that OXT not only increases the social cognition of autistic individuals but it also helps autistic individuals to retain more the social cognition[33,39]. Studies investigating the performance of autistic individuals in the RMET before and after OXT administration showed that the participants who had been given OXT scored better on the RMET than those who had been given a placebo[33,40,41]. The study carried out on individuals aged more than 16 showed that the participants showed an improvement for items considered to be difficult[40], whereas that carried out on individuals younger than 16 showed an improvement for items considered to be easy[41]. This may be because children and pre-teens can continue to improve on skills they have not yet fully mastered however developing adults are unlikely to continue improving skills they have already mastered [33].

One of the mechanisms by which OXT may improve ASD social symptoms is by inhibiting the hypothalamic-pituitary-adrenal (HPA) axis and the amygdala on exposure to social stimuli. OXT may also interact with the dopaminergic pathway as well as several parts of the brain forming the social brain, thereby increasing the individual's will to interact socially. A third possible mechanism is by enhancing the ability to detect social stimuli[15,42,43].

OXT is not labelled as an ASD therapeutic drug; however, it has been prescribed to autistic individuals as an off-label drug, with the aim of ameliorating the social deficits associated with ASDs [44].

Human studies show that while OXT has been administered for long-term treatment to male patients without any adverse effects, there is hesitancy when it comes to prescribing OXT to autistic females. This hesitancy is probably due to the well- known effect OXT has on lactation and uterine contractions[44]. However a case report documented by Kosaka, Munesue *et al*. shows the marked improvement in the aggressive, self-harming and irritable behavior of a 16-year-old girl who had been receiving long-term treatment with intranasal OXT infusions. No signs of a disrupted menstrual cycle and ejection of milk were recorded in this case report[44.]

Nevertheless, an animal study conducted by Bales et al. (2012) shows the possibility of adverse effects associated with long-term OXT therapy. While intranasal infusions of OXT initially improved social behavior in prairie voles, over time, deficits in the prairie voles' partner preference behavior started being observed, suggesting that it might not be all that safe to use OXT as a long-term therapeutic[33].

Further research conducted on larger groups of patients needs to be conducted in order to establish further the efficacy and safety of OXT therapy for ASD patients, as well as standardize a method of administration, which dosages are safe to use and the optimal duration of therapy. Determining which patient groups more likely to benefit from OXT treatment would be ideal[45].

Although ASDs are complex, multifactorial disorders, repetitiveness and deficits in social behavior exhibited by autistic individuals can be targeted using OXT. Further research must be carried out in order to fill in the gaps in current research and have a better understanding of how OXT can be used as a therapeutic drug for ASDs without causing any harmful effects.

OXT & Addiction

Addiction to alcohol and illicit drugs is a worldwide problem. According to a study carried out by Gowing, Ali *et al*. the number of people addicted to alcohol estimates to 240 million people worldwide. The same study shows that the number of intravenous drug users (IVDUs) adds up to approximately 15 million people worldwide [46]

Alcohol and drug addicts tend to exhibit deficits in social behavior. OXT, being largely affiliated with social behaviors, is thought to play a role in the development of tolerance and addiction. Another hypothesis supporting this premise is that negative experiences endured in early childhood may affect the development of the OXT system[47,48]. Furthermore, the OXT system is linked to the dopamine system, as well as the immune system and the autonomic nervous system; systems which are abnormal in addicts [48].

The Role of OXT in bringing about the Prosocial Effects of Drugs

OXT plays a role in bringing about some of the prosocial, rewarding effects of drugs of abuse[49]. The prosocial effects brought about by the intake of low doses of 3,4-methylenedioxy-methamphetamine (MDMA/ ecstasy) are thought to be due to the release of OXT from the SON and PVN of the hypothalamus following activation of the $5HT_{1A}$ receptor. In fact, MDMA users are found to have higher plasma OXT levels than normal[49,50]. Dehydration and high temperatures seem to promote the release of OXT from the SON and PVN of the hypothalamus[51,52]. In fact, it has been observed that people who make use of MDMA prefer to do so under warm conditions[52,53].

OXT is greatly associated with the mesolimbic dopaminergic system. The interaction of OXT with the DOPA system in the nucleus accumbens is a component in the development of both social reward, such as pair bonding, as well as drug reward[49,52]. An experiment carried out on prairie voles by Anacker & Ryabinin (2010) demonstrated that although the same pathway is involved in social and drug reward, there is preference to social reward over drug reward[52,54]. People with difficult pasts have a higher tendency of taking drugs and alcohol than normal. This may be due to the fact they do not have stable bonds with other individuals making them more susceptible to becoming addicts to drugs and alcohol[52]

The Effect of Drugs of Abuse on the Oxytocin system

Animal studies have shown that chronic use of drugs of abuse is associated with abnormalities in the endogenous OXT signaling system[55]. While acute administration of cocaine resulted in an increased concentration of OXT hormone in the dorsal hippocampus of rodents[56], chronic cocaine administration resulted in decreased OXT concentration in the hippocampus[57] and an increased amygdalar OXTR signaling[58]. Different drugs of abuse affect different parts of the brain [55]. Chronic morphine administration resulted in low OXT concentrations in the hypothalamus and increased receptor binding in the anterior olfactory nucleus, amygdala, piriform cortex and medial Sept.tum[55,59]. Chronic alcohol intake was also associated with decreased OXT levels[55]. On the other hand, ecstasy was associated with increased plasma OXT levels[60] and increased hypothalamic OXT messenger ribonucleic acid (mRNA) levels[61]. It must be taken into consideration that peripheral blood OXT levels do not necessarily reflect OXT levels in the CNS[52]

Addiction is considered to be a form of dysfunctional learning[62], and since studies have shown that OXT inhibits learning and memory consolidation, it may have a role in reversing drug addiction[55]. Early studies conducted by Kovacs *et al*. (1985) showed that OXT inhibits the development of acute tolerance to morphine, and that the degree of inhibition depends on the dose of OXT[57,63]. Later studies have shown that OXT also inhibits the development of chronic tolerance to morphine in a dose-dependent manner[57]. The same OXT-tolerance reducing effect was observed in studies conducted using alcohol as a drug of abuse[55].

Furthermore, OXT not only inhibits tolerance development but also decreases the physical dependency on drugs[57]. OXT also inhibits the development of tolerance to cocaine as well as promotes cocaine sensitization [49,57]. OXT also plays a role in reducing cocaine-seeking behavior by increasing the phosphorylation of the GluA1 subunit of the glutamate receptor in multiple brain regions[55,64]. Also, there seems to be a physical interaction between the glutamate receptor and OXTR[55,64] .

The Role of OXT as a therapeutic agent for addiction

As discussed previously, OXT has a role in decreasing the development of tolerance, reversing tolerance and also relieving drug withdrawal effects. An animal study carried out by Cui, Bowen *et al.* 2001 on cannabis-dependent rats demonstrated how administration of lithium chloride promoted the expression of Fos protein in OXT-immunoreactive neurons located in the SON and PVN of the hypothalamus, and in doing so increased the expression of OXT mRNA in the SON and PVN of the hypothalamus[49,65]. The resultant increase in plasma OXT levels was correlated with a decrease in the characteristic cannabinoid withdrawal symptoms such as panic and confusion[49,65]. When an OXT antagonist was administered 1 hour prior to lithium injection, the rats still exhibited withdrawal symptoms. The same withdrawal symptoms were observed when the rats were administered an OXT antagonist without lithium treatment[65].

Systemically delivered OXT has been shown to reduce the methamphetamine-induced Fos-protein expression in the core of the nucleus accumbens[52,66]. Further, intracerebroventricular (ICV) OXT can also be used to prevent methamphetamine drug relapses brought on by stress. OXT brings about its anxiolytic effect by antagonizing corticotrophin-releasing factor (CRF). CRF brings about the stress response through activation of the hypothalamus pituitary axis. Since OXT has the potential to dampen the response to stress it may be used to prevent individuals from relapsing to substance abuse in times of stress[52,67].

OXT has a significant role in the underlying mechanisms by which addictions develop. Current studies show that there is a lot of potential for OXT to be used in the treatment of addictions. Further research is required to investigate any adverse effects of exogenous OXT administration. Also, if OXT is to be used as a preventative measure to decrease susceptibility to addiction, research must extend beyond the physiology behind addiction and look into philosophical issues such as the consequences it may have on society[52].

OXT & Anorexia Nervosa

Anorexia nervosa (AN) is an eating disorder that affects both males and females. It is most common amongst teenagers and young adults. AN leads to weight loss and muscle wasting. It is also a psychological illness that can be fatal if not taken care of. In fact, apart from causing the affected individuals to have a false perception of the way their body looks, AN is also associated with increased stress and anxiety, as well as changes in social behavior[68.]

It is not surprising that OXT, being highly associated with stress and social behavior, is thought to be involved in the pathophysiology of AN[69]. Furthermore, OXT is thought to have a role in inducing satiety, so it is possible that OXT also plays a role in regulating food intake. Several studies have been conducted to determine whether or not AN patients exhibit alterations in OXT levels.

While treatment of AN is by far very challenging, determining the role of OXT in the patho-genesis of this illness can lead to the development of novel therapies that may aid in recovering AN patients.

OXT Levels in Anorexic Patients

A study carried out by Demitrack, Lesem *et al.* (1990) investigated OXT levels found in CSF of anorexic patients. Results showed that the food-restricting anorexic patients exhibited lower levels of OXT in CSF than the bulimic and the control subjects[70]. After food intake, CSF levels

of the restricting anorexic subjects returned to normal. There was also an increase in OXT levels in the CSF of bulimic anorexic subjects. The rise in CSF OXT levels was associated with food intake[70]. Another study showed that that patients suffering from AN exhibit less overnight secretion of OXT than healthy individuals[71].

Lawson, Holsen *et al.* (2012) aimed to identify whether or not there was a difference in OXT secretion in response to food intake between anorexic patients and healthy individuals. Results showed that the increase in peripheral OXT secretion following a meal was larger in anorexic patients compared to healthy subjects. It was also noted that anorexic patients who had gained weight exhibited a smaller increase in peripheral OXT secretion following food intake compared to those individuals who had not regained weight. This observation may be due to the stimulation of α- MSH by leptin in adipose tissue. α- MSH works at the level of the hypothalamus and brings about inhibition of appetite. It decreases the secretion of OXT in plasma, while at the same time promoting the secretion of OXT in the CSF[72]. Furthermore, there was a correlation between decreased OXT secretions and decreased body fat and bone density [69].

Apart from having decreased levels of OXT, patients suffering from AN also have a decreased level of prolyl endopeptidase (PEP) activity; the enzyme which cleaves OXT [73].

The role of OXT as a therapeutic for Anorexia Nervosa

OXT, being known to exert an anxiolytic effect seems to be a possible therapeutic agent for AN patients who have deranged OXT systems. Kim, Eom *et al.* (2015) studied the effect intra-nasal OXT has on anorexic patients. Results showed that patients who had been administered intranasal OXT were more able to detect emotions compared to those administered a placebo[74.]

Another study showed that AN patient who received intranasal OXT exhibited less fixation on body image and images related to food. The effect of OXT in reducing attentional bias was larger in AN patients who had more socio-cognitive problems verging towards those of ASD patients[75]. Furthermore, another study observed that administration of the intranasal OXT to AN patients attenuated their eating disorder concern[69].

There are many underlying aspects of eating disorders such as anorexia nervosa. It has been established that OXT has a role in the pathophysiology of anorexia nervosa however further research must be carried out, especially since the studies are limited. Understanding the role of OXT in anorexia nervosa is important as it may give rise to new possibilities as to how anorexic patients are treated.

Conclusion

OXT is heavily implicated in the pathophysiology of the neuropsychiatric disorders discussed in this review. Although several studies have been conducted to determine the mechanism behind the dysregulation of the OXT system, there are still a lot of gaps in the knowledge we have so far about it. Further research is needed in order to establish the role OXT plays in these neuropsychiatric disorders and the role it may have as a therapeutic agent to target the social deficits and cognitive impairment associated with these disorders. Also, further research is required in order to determine how safe and efficacious OXT is as a therapeutic agent as well as to determine the best method of administration.

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