Oxytocin in the socioemotional brain: implications for psychiatric disorders

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The neuropeptide oxytocin (OXT), highly conserved during evolution, is an important modulator of social and emotional processes across many species. During the last decade, a large body of literature has revealed its effects on different aspects of social behavior, including social stress and anxiety, social memory, affiliation and bonding, emotion recognition, mentalizing, empathy, and interpersonal trust. In addition, as impairments in these social domains can be observed in a number of neuropsychiatric disorders, such as autism, social anxiety disorder, depression, schizophrenia, and borderline personality disorder, the role of OXT in mental disorders and their treatment has been intensively studied. The present paper gives a short overview of these lines of research and shows how OXT has become a promising target for novel treatment approaches for mental disorders characterized by social impairments.

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Introduction

During recent years, the neuropeptide oxytocin (OXT) has attracted enormous interest in neuroscientific research on social and emotional processes. Given the generally increased interest in social cognition in the area of psychiatric research, the number of publications focusing on OXT in the context of mental disorders has also increased markedly in recent years. The role of OXT in the context of childbirth and lactation has long been studied; however, two lines of research have motivated investigation into the role of OXT in social behavior. First, animal research initiated by Insel and Young[1] on the role of OXT in maternal behavior and bonding revealed that OXT in the central nervous system modulates social behavior. Second, in human research, a startling paper by Kosfeld et al[2] showed that the intranasal application of OXT—originally developed to support lactation in breastfeeding mothers—increases interpersonal trust in an economic trust game. Since publication of that paper in 2005, the overwhelming increase in the number of studies on OXT's role in social behavior is not surprising. The present paper gives a brief overview of the research on OXT and socioemotional processing in humans and of

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Selected abbreviations and acronyms

ASD	*autism spectrum disorder*
BPD	*borderline personality disorder*
DA	*dopamine*
HPA	*hypothalamo-pituitary-adrenal*
IU	*international unit*
OXT	*oxytocin*
OXTR	*oxytocin receptor*
RMET	*Reading the Mind in the Eyes Test*

its importance in understanding social deficits and corresponding treatment in psychiatric disorders.

Neurophysiology of the oxytocin system

Evolutionarily speaking, OXT is a very ancient neuropeptide, conserved in many species ranging from invertebrates to mammals.[3]

In mammals, OXT, together with its sister neuropeptide arginine vasopressin (AVP), is synthesized in magnocellular neurons located in the paraventricular and supraoptic nuclei of the hypothalamus. From there, via axonal processing, OXT is transported to the posterior pituitary, where it is stored in secretory vesicles for release into the portal vascular system to exert its peripheral effects on target organs, the uterine and mammary glands, via general blood circulation. However, in addition to this well-known neuroendocrine pathway, other brain pathways enable OXT to act as a neuropeptide. For the central effects of OXT, aside from the potential impact of diffusion of extracellular OXT to other brain regions, OXT neurons directly project from the hypothalamus to a large number of brain regions related to social and emotional processing. Outside a number of forebrain regions, projections are particularly found in the amygdala, the hippocampus, and the nucleus accumbens.[4] OXT neuron projection targets fit nicely with brain regions known to contain OXT receptors (OXTRs).[5] However, these findings were exclusively attained in rodents; much less is known about the distribution of OXTRs in humans. Recently, initial studies in nonhuman primates identified brain regions with OXT binding sites, including the amygdala, the hippocampus, and the anterior cingulate cortex (ACC),[6,7] highly consistent with the suggested role of OXT in social and emotional processing.

Neurobiology of oxytocin effects in the human brain

Although the exact distribution of OXTRs in the human brain remains unknown, human neuroimaging studies have shown impressive accordance with regard to the effect of OXT challenge on brain activation during social cognitive tasks. In all such studies, OXT was administered intranasally, a method known to successfully deliver neuropeptides to the brain,[8] although it remains unclear how the blood-brain barrier is crossed by these molecules. In an initial study looking at the effect of intranasal OXT (27 international units [IU]) on brain activation during the perception of socioemotional stimuli, we found a significant attenuation of amygdala activation after OXT challenge as compared with placebo.[9] In addition, the functional coupling between the amygdala and the brain stem was significantly reduced. Those results agree well with animal studies showing an OXT-related reduction in social fear, also shown to be modulated by the amygdala and downstream projections to brain stem regions.[10] This first evidence for an important modulatory effect of OXT on the amygdala was replicated in a number of studies using different social cognitive or emotional paradigms. Almost all studies found a reduction in amygdala activation after intranasal challenge with OXT (for an overview, see Wigton et al[11]). However, since most studies were conducted exclusively in males, an unresolved question is whether the findings can be generalized to females. While one study using visual stimuli of emotional faces found an increase in amygdala activation in females,[12] another study using infant cries as a social emotional stressor reported a decrease.[13] However, though researchers understandably prefer to study males rather than females due to multiple problems related to the menstrual cycle, a clear understanding of gender differences is nonetheless necessary, particularly when focusing on OXT as a potential treatment for mental disorders.

In addition to the unresolved gender issue, the very strong evidence for OXT effects on the amygdala do not necessarily mean that this brain structure is the main site of OXT action. Aside from existing knowledge[10] suggesting an important role for this structure, and thus a priori definition of this region of interest creating a sort of spotlight effect in many studies, most of the paradigms used are also specifically suited to identification of effects in limbic structures, particularly

the amygdala. However, consistent with the findings of OXTR distribution in the primate brain,[6,7] some studies also find effects of OXT in visual areas, particularly the fusiform gyrus.[14,15] One can assume that OXT effects will be found in many areas of the brain involved in social processing, sometimes referred to collectively as the social brain;[16,17] more sophisticated experimental paradigms and analysis might uncover these effects in the future. Particularly when looking at behavioral studies, OXT can be concluded to play an important role in a wide range of social cognition.

Oxytocin and social cognition

Before OXT in human social behavior attracted much interest, a number of studies looked at the role of the OXT system in different species, including mice, rats, voles, sheep, and monkeys (for an overview, see Insel and Young[1] and Donaldson and Young[3]). However, the discovery that intranasal OXT was a suitable tool for investigating OXT effects in humans allowed many of the findings from animal research to be confirmed in human studies. Such studies looked at a number of social cognitive functions, including social stress and anxiety, social memory, affiliation, emotion recognition, mentalizing, empathy, and interpersonal trust.

Social stress and social anxiety

Prior to discovery of its important role in affiliation and bonding, OXT was shown to modulate fear and stress-related systems like the hypothalamo-pituitary-adrenal (HPA) axis in rodents.[18] In humans, the suckling of a newborn increases OXT release in the mother's brain, subsequently reducing plasma levels of the stress hormones adrenocorticotropic hormone (ACTH) and cortisol.[19,20] Therefore, it is naturalistic to test the stress-dampening effect of OXT in breastfeeding women. Interestingly, breastfeeding before stress exposure reduces ACTH and cortisol responses to psychosocial or physical stress in postpartum lactating women, compared with nonlactating women.[21,22] This stress-buffering effect of OXT was confirmed through intranasal OXT challenge in humans[23] and primates.[24] However, meta-analysis showed a significant cortisol-reducing effect of OXT during stress only for laboratory tasks producing a clear HPA-axis response.[25] Such tasks are mainly those having a social-evaluative component.[26] Consistently, while social processes seem to boost the effect of OXT on stress-hormone secretion, there is no effect of OXT on basal cortisol in the absence of an acute stressor.[27] In line with those results, the stress-dampening effect of OXT treatment is specifically amplified when combined with social support.[28] Such interrelation between OXT and social interactions was also demonstrated in an interesting study of romantic couples engaged in conflict discussion. The authors found a reduced cortisol response and an increase in positive communication after intranasal OXT challenge.[29]

Besides increased social stress, social fear can also be established through conditioned social fear responses, which animal[30] as well as human research[31] has shown can be modulated by OXT. Both have found that OXT administration facilitates extinction of the conditioned fear response. In humans, intranasal OXT (24 IU) challenge after Pavlovian fear conditioning leads to a faster decrease in conditioned electrodermal responses; however, this effect is observed for both social and nonsocial conditioned stimuli.

OXT also modulates another characteristic of social anxiety: increased attentional bias toward socially relevant stimuli. While individuals with high social anxiety show increased vigilance to stimuli associated with social threat, such as emotional faces, this bias can be significantly reduced by intranasal application of 24 IU of OXT.[32]

To summarize, OXT exerts its effects on different information processing levels associated with social anxiety via a more general stress-dampening effect during social stress, modulation of fear conditioning, and modulation of attentional processes associated with social anxiety.

Social memory

The importance of the OXT system for social memory was convincingly demonstrated by Ferguson et al[33] in an impressive paper demonstrating a specific lack of social memory in genetically mutated mice missing the OXTR gene. These homozygotic knockout mice show a dramatic failure to develop social memory for conspecifics while showing an intact nonsocial olfactory memory. In addition, while treatment with OXT rescued social memory in the knockout mice, giving an OXT antagonist to the wild-type animals mimicked the social-memory deficit. A similar phenotype is observed in a CD38

knockout mouse.[34] CD38 is a transmembrane protein that stimulates the secretion of OXT in the brain. These CD38 knockout mice show reduced plasma OXT levels and reduced social recognition, which can be reversed by the administration of OXT or CD38.

These findings have been replicated in human studies that show an enhancement in face memory after intranasal OXT challenge, either through improved encoding of memories[35] or by increasing the familiarity of stimuli.[36] In addition, intranasal administration of OXT after learning social stimuli improved the recognition of face identity, but not expression.[37] However, a memory-enhancing effect was not observed in all studies looking at social memory.[38] Furthermore, OXT has been described as an "amnestic peptide,"[39] as in the context of nonsocial memory, OXT has a memory-impairing effect. These contradictory results could be due to the well-known interaction between OXT and cortisol via the OXT modulatory effect on the HPA axis. Since cortisol can also have a memory-enhancing or -impairing effect, depending on the context,[40] it is reasonable that OXT could differentially influence memory depending on the specific circumstances (see ref 41 for a discussion of these relationships).

Affiliation

Given the well-established role of the OXT system in pair bonding and attachment in animals, it seems obvious to look at OXT's role in human affiliative behavior. Affiliation and bonding are the social processes most closely related to the role of OXT in reproductive behavior. During mating, OXT secretion increases,[42] leading to an increased attachment between the mating partners after the sexual act, most likely through a dopaminergic, reward-related pathway.[43] However, this OXT-dopamine (DA) interaction during pair bonding is not restricted to mating. Males seeing the face of their female partners show an increased activation of reward-related dopaminergic brain regions after intranasal application of 24 IU of OXT.[44]

During breastfeeding, maternal OXT secretion is increased and the OXT is transferred to the child via the mother's milk; this may further increase mother-child bonding.[45] Interestingly, in many rodents, OXT secretion during labor changes the mother's behavior from avoiding to approaching pups,[46] and in humans, OXT levels in mothers seem to be positively correlated to the quality of mother-child interrelations.[47] Although the biological basis of OXT in mother-infant relations is obvious, there is also evidence for an important role of OXT in the attachment and affiliation between father and children. The OXT level in adults from both sexes correlates significantly with the amount of parental bonding (to mother and father).[48]

The role of OXT in parent-child relations is not only reflected in the association between basal OXT levels and relation quality, but also in the differences in OXT secretion during interpersonal interaction and the amount of bonding. Parents having a high level of body contact with their children in a 15-minute "play and touch" session show markedly larger increases in salivary OXT levels than parents experiencing lower levels of touch,[49] mimicking what is seen in rodents with respect to licking and grooming behavior.[50] Importantly, the amount of licking and grooming also shapes the OXT system of the pups, establishing a mode of transgenerational propagation of OXT-related social behavior via epigenetic mechanisms.[51] Such influences from parental social behavior on the functionality of the OXT system in children was also shown in a study investigating children who grew up in a very aversive, socially deprived environment in East European orphanages. Once in adoptive families, the children showed markedly lower urinary levels of OXT after social interaction with their adoptive mother as compared with normally reared biological children of the same mothers.[52]

Interestingly, it is not only social behavior that shapes the OXT system of the next generation; the parental OXT system is also associated with the responsivity of their offspring's OXT system and social behavior, further emphasizing the importance of this system for cross-generational transmission of social behaviors. Children of fathers who were treated with OXT, leading to higher salivary OXT levels and increased positive interaction behavior, also showed increased salivary OXT levels and more engagement in social interaction.[53]

The application of intranasal OXT does not only influence parent-child bonding, but also male-female bonding. In one study, social touch from a female experimenter was rated as being more pleasant and activated more limbic brain regions in heterosexual males after intranasal application of 24 IU of OXT.[54]

Overall, there is clear evidence for the crucial role of OXT in attachment, bonding, and social affiliation

in different types of social relationships. Furthermore, the OXT system is an important target for the effect of developmental influences on social behavior and for epigenetic influences modulating the cross-generational transfer of this behavior.

Emotion recognition, empathy, and mentalizing

Key components of social cognition are the ability to correctly recognize states and intentions of other individuals and to be able to empathically feel what they feel. Much evidence shows that OXT increases the ability to recognize emotional expressions in faces.[55] However, evidence about the influence of valence shows some inconsistencies. While some studies found a specific effect of OXT on the recognition of happy faces,[56] others found a specific effect for the recognition of fear.[57] Interestingly, these effects were not only observed during a normal presentation of faces, but also for a very short, masked presentation.[58]

The Reading the Mind in the Eyes Test (RMET)[59] requires the ability to detect emotional states from pictures exclusively depicting the eye region of different individuals. While some use this test for emotion recognition, it covers additional social cognitive functions, namely mentalizing or theory of mind. In this specific paradigm, adminstration of 24 IU of OXT also improves performance.[60] This effect is specifically observed in individuals with higher alexithymia[61] or reduced empathy abilities[62] and points to the role of OXT in empathy. Intranasal application of OXT has been shown to increase emotional, but not cognitive empathy, potentially by an amygdala-dependent mechanism.[63] The effect was not observed for empathy for pain.[64]

Overall, OXT is an important modulator for social cognitions that influence an individuals' ability to successfully behave in interpersonal interaction. Therefore, OXT is very interesting for research in the context of psychiatric disorders.

Trust

An important interpersonal process, repeatedly discussed in the context of OXT, is trust. In an experimental setting, trust is usually measured by means of an economic trust game.[65] In such a game, involving two players, an investor can transfer a share of his money to a trustee. This money is tripled and the trustee can return money to the investor. If the investor trusts the trustee and the trustee himself plays fair, the investor can increase his own balance by investing money. The amount of invested money can therefore be used as a measure of trust. As shown in the literature, a single intranasal dose of OXT (24 IU) significantly increases trust, but not risk, behavior.[2] The relationship between trust and OXT has been reinforced through genetic analysis[66] showing that a common variant of the OXTR gene modulated the amount of invested money in the trust game.

There is some discussion whether trust as measured in the trust game is a good proxy for interpersonal trust as it occurs in everyday interactions. Therefore, it is interesting to see that OXT also increases other kinds of interpersonal trust. After a single intranasal application of OXT (32 IU), study participants have more confidence that private information is in good hands with their interaction partners[67] than after receiving placebo. Furthermore, if trust is betrayed, OXT increases the willingness of participants to attribute this behavior to nonpersonal causes.[68]

On the neural level, such OXT-related maintenance of trust after betrayal is modulated by reduced activation of a network consisting of the amygdala, and midbrain structures, as well as the dorsal caudate.[69] That finding supports the assumption that the trust-increasing effect of OXT is driven by a reduction in fear and reduced feedback-related learning during interpersonal interaction.

While all the studies reported here support a prosocial, cooperation-supporting role for OXT in social behavior, there is some evidence that this is modulated by contextual factors. The effect has been shown to be restricted to interaction with familiar persons[70] and/or to in-group members, whereas cooperation with out-group members was even found to be reduced after the application of intranasal OXT.[71] This influence of the social context on the OXT effect was also partly supported by a recent meta-analysis.[72] While a significant medium-sized trust-increasing effect was found in in-group members, it was not significant for out-group members. However, notably, there is no meta-analytic evidence for a trust-reducing effect of OXT for out-group members.

In general, there is very good evidence for a trust-inducing effect of OXT, making the substance a promising candidate for supporting prosocial behavior in mental disorders associated with interpersonal distrust.

Oxytocin in psychiatric disorders and their treatment

Given the restricted treatment options in psychiatry, it is not surprising that OXT has been used as an experimental treatment option. As early as 1972, a letter from the Russian psychiatrist Bujanow[73] was published in the *British Medical Journal*, reporting that intravenous OXT injections to treat schizophrenia patients had "some rapid therapeutic effects" and "prevented some hospitalizations." A second letter from the author 2 years later supported this approach[74]; however, it would take longer for OXT to enter the focus of neuropsychiatric research. Bujanow's report was rather anecdotal and did not include any theoretical considerations. In contrast, around 20 years later, initial ideas for OXT as a treatment option were published and used at least a phenomenological perspective: referring to the animal literature on the relation between OXT and affiliation and the symptomatology of the disorder, Modahl and colleagues[75] speculated in a letter to the editors of the *Journal of Autism and Developmental Disorders* about a potential role for OXT in autism. A number of years would pass before the first empirical investigation about the relation between alteration of the OXT system and autism spectrum disorders (ASDs).[76] In that study, Modahl and colleagues reported a significantly lower level of OXT in plasma of autistic patients than controls. Although plasma OXT cannot be directly interpreted to reflect central OXT levels and although these results could not be replicated in another study looking at the plasma OXT response to acute stress in autism,[77] Modahl's paper[76] was a kind of initiation of OXTR in psychiatry research. Meanwhile, a large and constantly growing number of studies on OXT can be found for almost any psychiatric disorder including schizophrenia, depression, anxiety disorders, and personality disorders. This research is mainly driven by the hope that OXT might offer a new mechanism for the treatment of such disorders, particularly the treatment of social and emotional deficits common in psychiatric disorders, which makes sense from a domain-specific view of psychiatric nosology.[78]

Autism spectrum disorder

Given the prominent role of OXT in attachment, bonding, and social interaction, it is not over-reaching to assume a relation between the neuropeptide and autism, as social impairments have been regarded as a central feature of the disorder since the initial description by Leo Kanner and up to the currently used diagnostic criteria for ASD. Besides initial evidence about reduced plasma levels of OXT in autism,[76,79] most evidence for an important role of the OXT system in this disorder comes from genetic studies. The OXTR gene is an obvious candidate to investigate for associations with ASDs. Not only is the OXTR gene located at a suggestive linkage peak for the disorder,[80] but a number of association studies suggest a relation between different variations of the OXTR gene and ASD.[81-85] Although there are some negative[86] or ambiguous findings,[87] and although the OXTR gene did not produce a significant signal in a genome-wide association study (GWAS) analysis of autism,[88] there is now meta-analytic evidence for an association between this gene and autism.[89]

Another interesting candidate gene for ASD in the context of OXT is the CD38 gene. CD38 is reported to be involved in OXT secretion in the central nervous system and influences social behavior in mice.[34] In human studies, a common single nucleotide polymorphism, associated with ASD in two samples, has been identified.[90,91] Furthermore, the risk allele for autism of this genetic variant is associated with a lower expression of CD38 in lymphoblastoid cells,[90] which should result in reduced secretion of OXT in the brain. On the brain level, the genetic risk variant is associated with increased activation in the fusiform gyrus and reduced activation in the left amygdala while perceiving social stimuli and faces with a gaze directly pointed toward the observer.[15] Both brain areas have been found to be altered in ASD during social perception.[92]

These strongly supportive findings for an important role of OXT in ASD also led to studies looking at OXT as a potential treatment in autism. The first study in this context was published in 2003.[93] In that study, an intravenous infusion of OXT reduced repetitive behaviors in ASD patients. In a second report on that study, the authors added evidence that this treatment also improved the comprehension of affective speech.[94] However, that positive finding is somewhat puzzling because there is no explanation of how the substance reaches the brain to exert its central action when given intravenously. Therefore, newer studies used the intranasal application route. These proof-of-concept studies usually used a single administration of OXT at a dose between 18 and 42

IU compared with placebo in a double-blind crossover design. There is some evidence that such a treatment improves social cognition in patients, such as emotion recognition and mentalizing,[95] visual scanning of faces, positive interaction behavior in a virtual game,[96] and eye-gaze frequency during social interaction.[97] Interestingly, the latter study, conducted in a group of patients with fragile X syndrome, showed that improvement in eye-gaze behavior was accompanied by a decrease in salivary cortisol, suggesting that OXT treatment acts by reducing stress during social activity. These findings fit nicely with others showing an increase in amygdala activation in ASD during direct eye gaze,[98] assuming that the positive effect of a single dose of OXT on social cognition in autism might be associated with its stress- and anxiety-reducing effect during social interaction.

However, while those single-dose treatments produced very promising results, effects are less clear when looking at rare studies that tested prolonged treatment with intranasal OXT. In those studies, the primary outcomes were more clinically relevant measures, such as an improvement in global clinical impression, autistic symptoms,[99] or mother-child interaction.[100] Whereas in one study[99] OXT was administered as two daily doses over 6 weeks, in the other study, 12 to 24 IU were given once a day for 4 days.[100] Aside from such large differences in the treatment scheme, neither study found a main effect of the substance on primary outcome measures. However, Anagnostou and colleagues,[99] using the 6-week treatment, found a very strong effect on performance in the RMET,[59] replicating the first study on a single-dose application in ASD.

Taken together, initial treatment studies with OXT in ASD reveal some promising effects on experimental measures of social cognition, but evidence is missing for a sustainable effect on clinical measures.

Anxiety disorders

Given the clear anxiolytic effect of OXT, particularly in the context of social fear and anxiety, another clinical condition that enters the focus of OXT research is anxiety disorder. However, while there is a large body of basic research on the relation between OXT and social anxiety, the evidence for a pathogenetic role of OXT in social anxiety disorders is missing. In contrast to ASD, in social anxiety disorder, there is no evidence for an altered plasma level of OXT.[101,102] However, even more puzzling, while increased anxiety symptoms are associated with higher plasma OXT levels,[102] social anxiety disorder patients showed lower levels than controls after social interaction in a trust game.[101] Nevertheless, some treatment trials with OXT for anxiety disorders exist, including a pioneer study on the effect of intranasal OXT for the treatment of posttraumatic stress disorder (PTSD) in veterans.[103] However, the authors found only a nonsignificant tendency toward a reduction in physiological stress responses during imagery of personally relevant combat situations. That finding provides evidence that OXT might be a reasonable add-on for behavioral therapeutic treatments of anxiety disorders, allowing the patients to deal with more anxiety-related situations. That idea was tested in another study combining a repeated application of OXT or placebo with a group-exposure therapy in patients with social anxiety disorder.[104] Whereas there was no substance effect on the reduction in subjective symptoms, possibly due to a generally high reduction in symptoms in both groups, patients treated with OXT reported a subjectively better appearance and performance during the testing situations, consisting of public speech. In a neurobiological approach, a stronger OXT-related attenuation of an initially increased activation of limbic structures was found in social anxiety disorder patients engaged in watching emotional faces.[105] OXT treatment in social anxiety disorder might be more helpful in reducing the social stress level than anxiety symptoms in patients, which might then predispose anxiety patients to better benefit from a psychotherapeutic exposure treatment.

Schizophrenia/psychosis

Aside from the desire to improve treatment of schizophrenia through uncovering new biological pathways, elucidating the role of OXT is of interest both clinically and biologically speaking. Clinically, OXT treatment could be useful for particularly treatment-resistant negative symptoms, such as social withdrawal and anhedonia, as well as increased social anxiety. Biologically, in light of the dominating DA hypothesis of psychosis, it could be argued that the clear interaction between the DA and the OXT system suggests a role for OXT in the disorder. On the molecular level, DA receptors can be found on OXT neurons in different brain regions[106] and OXT and DA receptors are colocated in regions

of the mesolimbic DA system,[107] also important in the context of psychotic symptoms. In addition, dopamine-OXT-receptor heteromers in the rat striatum have recently been proposed, possibly constituting a molecular mechanism underlying these OXT-DA interactions[108] and encouraging testing for OXT effects on psychotic symptoms. While some early studies reported increased plasma levels of OXT in schizophrenia,[109] this finding could not be replicated in later studies reporting no differences in OXT levels in cerebrospinal fluid (CSF)[110] or even diminished levels in plasma.[111] These inconsistencies might be due to different effects of OXT on positive versus negative symptoms. While there is some evidence for an association between increased OXT and positive symptoms,[112] negative symptoms might be associated with reduced plasma OXT either at basal levels[111] or after social interactions.[113]

Hints for successful treatment of schizophrenia symptoms with OXT come from animal research showing a positive effect of OXT in prepulse inhibition (PPI)[114] as well as in a chronic phencyclidine (PCP) treatment model of schizophrenia[115]; in the former, reversing the PPI deficit; in the latter, the PCP-induced social deficit. The first methodologically sound study in patients was published in 2010.[116] Using up to 40 IU of intranasal OXT daily for three weeks as an add-on to a stable neuroleptic medication, the authors found a reduction in positive and negative symptoms, as well as in global clinical impression in 15 schizophrenia patients. Initially revealed in a double-blind crossover study, those findings were replicated in a double-blind parallel-group study[117] showing not only a reduction in general psychotic symptoms, but also an improvement in different social cognitive measures in patients treated with OXT for 2 weeks. The strongest effects were reported in a double-blind placebo-controlled study of 40 schizophrenia patients who were on stable monotherapy with resperidone and received either placebo or up to 40 IU OXT as adjunct therapy over 8 weeks.[118] The authors report a large additional effect of OXT on general psychopathology, positive symptoms, and negative symptoms.

These studies show evidence of a twofold effect of OXT in the treatment of schizophrenia: while it seems to boost the antipsychotic effect on positive symptoms over a prolonged treatment, probably through an OXT-DA interaction pathway, it also improves negative symptoms, probably via a more general, disorder-independent mechanism. While the reduction in psychotic symptoms seems to require a longer treatment period, the improvements in social cognition, such as emotional face recognition, are observed even after a single dose of OXT, either on the behavioral[119] or on the neural level,[120] where it exerts its effect mainly in the amygdala. However, it is less clear whether this effect is specific to schizophrenia, as improvements in social cognition were observed in healthy participants as well.[121] Altogether, there is no doubt that the treatment effects of OXT in schizophrenia are among the most impressive in the field of psychiatric disorders.

Depression

Given the very well–documented effect of OXT on the HPA axis and the important role of this axis for depression, it is not surprising that a large body of literature looks at the role of the OXT system in mood disorders. First attempts to approach the question of such a relationship investigated OXT levels in patients suffering from mood disorders, particularly from depression. However, as results are inconsistent in those studies, a clear relationship cannot be postulated. There is some evidence that female patients show reduced OXT levels whereas male patients might show even increased levels.[122] Generally, the relationship between OXT level and depression is complex and it can be assumed that multiple interactions with other neurotransmitter systems such as serotonin and DA play an important role.

A significant association has been reported between the rs53576 polymorphism on the *OXTR* gene and depression.[123] However, whereas the G allele was associated with depression, negative emotionality was associated with the A allele of this genetic variant.[124] Thus, the impact of *OXTR* genotypes on depression appears complex and one could speculate that it would involve gene/environment interactions.[125] Not only does early life stress lead to reduced CSF levels of OXT,[126] there is also some evidence for an interaction between *OXTR* genotype and early adverse events increasing the risk for mood disorders.[127,128] Interestingly, this effect seems to particularly impact postpartum depressive symptomatology.

Evidence for the importance of *OXTR* gene/environment interactions also comes from a very recent study showing reduced DNA methylation of exon 1 of the *OXTR* gene in depressed females, and that this is modulated by the *OXTR* rs53576 genotype.[129]

Regarding treatment, initial evidence for an antidepressant effect of OXT came from an animal study demonstrating reduced immobility in mice after a forced-swim test, matching the effect of traditional antidepressants.[130] Despite those promising animal results, there is no report of successful treatment with OXT in human depression. Indeed, the rare clinical studies treating depressed patients with OXT are not very promising. There is only one case report in the literature showing a decrease in depressive symptoms after a 1-week treatment with 8 IU of OXT as an adjunct to escilopram.[131] Also, a single administration of 40 IU of intranasal OXT was reported to augment neural activity in limbic regions of depressed patients during the RMET.[132] However, in postpartum depression, administration of 24 IU of intranasal OXT for 1 week was shown to increase sad mood in patients.[133] This speaks for a specific role of OXT in postpartum depression, as delivery itself is associated with a strong secretion of OXT.

In summary, there is no evidence that OXT would be a good option for the treatment of depression.

Borderline personality disorder

Disturbances in social processes, particularly in interpersonal interactions, are a key symptom of borderline personality disorder (BPD), which should stimulate interest in research of the relation between BPD and OXT,[134] also encouraged by this clinical picture and the lack of sufficient symptom-specific pharmacological treatment options. However, compared with other psychiatric disorders, research focusing on OXT and BPD has had a rather late start.

Recently, initial evidence was published showing a reduced plasma OXT level in female BPD patients.[135] That study also replicated former findings of a significant negative correlation between OXT level and the amount of childhood trauma, but did not find a mediating effect on the relation between childhood trauma and BPD symptoms according to OXT level. In a study with the so-called "cyber-ball" game,[136] it was shown that the experience of social exclusion leads to a decrease in plasma OXT level in BPD, but not in controls, leading to a more pronounced group difference,[137] an effect unrelated to cortisol responses. That finding supports the assumption of deregulated rather than generally reduced secretion of OXT in BPD. Therefore, treatment trials with OXT seem promising. However, results from initial studies, all using a single dose of intranasal OXT, are contradictory. In two independent studies, OXT reduced trust and cooperation in BPD patients,[138] in strong contradiction to what was found in healthy participants.[2] However, in the same sample as used for the trust study,[138] the cortisol response to a psychosocial stressor was attenuated.[139] In addition, a single dose of 26 IU of intranasal OXT normalized the behavioral and neural (amygdala) hypersensitivity to social threats in BPD patients.[140] These somewhat puzzling results suggest that trust and social stress/anxiety in BPD patients are not modulated through the same mechanism. That conclusion needs much more elaboration, but nevertheless seems to indicate that a simple explanation that trust-increasing effects of OXT are generated via a reduction in fear must not be sufficient.

Conclusions

The tremendous amount of research on the role of OXT in social and emotional processing and its importance for understanding and treating mental disorders has revealed many interesting new insights, but many inconsistencies as well. Nevertheless, there is cumulating evidence for an important modulatory effect of OXT in the context of social stress, social anxiety, social cognition, and psychosis. Such evidence is mostly consistent with neurobiological observations of the central OXT system and its interactions with other brain systems identified to be modulated by OXT. These domain-specific effects and their neurobiological underpinnings warrant efforts to test OXT as a new treatment option for a variety of psychiatric disorders. *Figure 1* briefly summarizes these findings on different levels.

Unfortunately, treatment approaches have thus far differed to a great extent. The minority of studies investigate the effect of long-term treatment or uses clinical symptomatology as a primary outcome measure. More studies use the single intranasal administration approach and look at more general social cognitive functions. It is not surprising that these treatments lead to effects that can also be observed in healthy controls. Nevertheless, these findings indicate that OXT treatment, possibly with the exception of positive symptoms in schizophrenia, should follow a mechanistic approach rather than a diagnosis-related one, targeting social cognitive and interpersonal deficits, which are observed in a number of neuropsychiatric disor-

ders. Therefore, OXT could be a model substance for the development of new treatments that are oriented to the Research Domain Criteria (RDoC) approach,[78] an idea that is also supported by a recent meta-analysis showing significant effects only in cross-diagnosis analyses.[141] Furthermore, OXT seems to be more suitable for use as a potential add-on to other treatments rather than constituting a new pharmacological option for monotherapy. This idea should be considered in particular when thinking about pharmacologically supported psychotherapy, where OXT might be a useful treatment supplement.[142]

However, there are a number of unresolved issues in OXT research. First, we still suffer from the lack of tracers that would allow us to map the distribution of OXT receptors and its occupancy in the human brain in vivo. Second, many studies in the clinical context refer to peripheral OXT levels, while the relationship between peripheral and central OXT is still not entirely clear, although there is some evidence for a correlation of both under stress conditions in rats.[143] In addition, although we know that the OXT system is sexually dimorphic, most of the human research, particularly in the area of intranasal administration, was conducted in males. Furthermore, there are some inconsistencies regarding the role of OXT in social processes as well as in the treatment of social deficits, supporting the assumption that the beneficial effects of OXT might be restricted to specific conditions. A more or less naive approach to simply test the effect of OXT in many different conditions must be replaced by more sophisticated approaches to identify the specific circumstances that create an adjuvant effect of the substance. Finally, regarding OXT treatment, it remains unresolved whether prolonged administration leads to effects comparable to those seen after a single administration. While there is no doubt about the safety of single-dose treatments, this is less clear for repeated administration over a longer period. Nevertheless, one can expect the very vital and productive field of OXT research to reveal much more interesting findings of particular importance for the field of clinical neuroscience and neuropsychiatric disorders. ❑

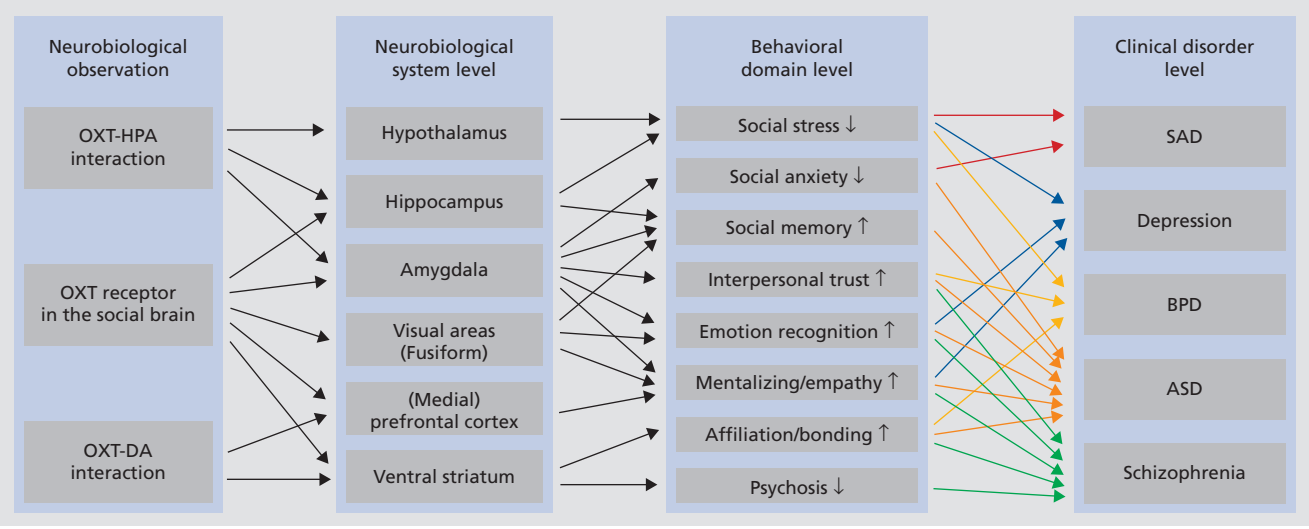

Figure 1. Summary of the role of oxytocin on different descriptional levels and its relation to neuropsychiatric disorders. ASD, autism spectrum disorder; BPD, borderline personality disorder; DA, dopamine; HPA, hypothalamo-pituitary-adrenal; OXT, oxytocin; SAD, social anxiety disorder

La oxitocina en el cerebro socioemocional: repercusiones en los trastornos psiquiátricos

El neuropéptido oxitocina (OXT), muy bien conservado durante la evolución, es un modulador importante de los procesos sociales y emocionales en muchas especies. Durante la última década, bastante literatura ha revelado sus efectos sobre diferentes aspectos de la conducta social, incluyendo el estrés social y la angustia, la memoria social, la filiación y el vínculo, el reconocimiento de las emociones, la mentalización, la empatía y la confianza interpersonal. Además, se ha estudiado extensamente el papel de la OXT en los trastornos mentales y su tratamiento ya que las alteraciones en estos aspectos sociales pueden observarse en varios trastornos neuropsiquiátricos como el autismo, el trastorno de ansiedad social, la depresión, la esquizofrenia y el trastorno de personalidad borderline. Este artículo entrega una pequeña panorámica de estas líneas de investigación y muestra cómo la OXT ha llegado a ser un objetivo promisorio para las nuevas aproximaciones terapéuticas para los trastornos mentales caracterizados por alteraciones sociales.

L'ocytocine dans le cerveau socio-émotionnel : implications dans les troubles psychiatriques

L'ocytocine (OXT), neuropeptide très bien conservé au cours de l'évolution, est un modulateur important des processus sociaux et émotionnels dans de nombreuses espèces. Ces 10 dernières années, de nombreux articles de la littérature ont montré ses effets sur différents aspects du comportement social dont le stress et l'anxiété sociaux, la mémoire sociale, l'affiliation et la création de lien, la reconnaissance des émotions, la mentalisation, l'empathie et la confiance interpersonnelle. De plus, le rôle de l'OXT dans les troubles mentaux et leur traitement a été très étudié car des déficits dans ces domaines sociaux sont observés dans de nombreux troubles psychiatriques comme l'autisme, l'anxiété sociale, la dépression, la schizophrénie et la personnalité «borderline». Dans cet article nous faisons une brève revue de ces axes de recherche et montrons comment l'OXT est devenue une cible prometteuse de nouveau traitement pour les troubles mentaux caractérisés par des troubles sociaux.

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