AUTHOR QUERY FORM

Book: Lysaker-1611078
Chapter: CH018

Please e-mail your responses and any corrections to:
E-mail: E.Taylor@elsevier.com

Dear Author,

Any queries or remarks that have arisen during the processing of your manuscript are listed below and are highlighted by flags in the proof. (AU indicates author queries; ED indicates editor queries; and TS/TY indicates typesetter queries.) Please check your proof carefully and answer all AU queries. Mark all corrections and query answers at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file http://www.elsevier.com/book-authors/science-and-technology-book-publishing/overview-of-the-publishing-process) or compile them in a separate list, and tick off below to indicate that you have answered the query.

Please return your input as instructed by the project manager.

Uncited references: References that occur in the reference list but are not cited in the text. Please position each reference in the text or delete it from the reference list.

Couture et al. (2011)

Missing references: References listed below were noted in the text but are missing from the reference list. Please make the reference list complete or remove the references from the text.

<table>
<thead>
<tr>
<th>Location in Chapter</th>
<th>Query / remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU:1, page 305</td>
<td>Please check and confirm the shortened running head?</td>
</tr>
</tbody>
</table>

To protect the rights of the author(s) and publisher we inform you that this PDF is an uncorrected proof for internal business use only by the author(s), editor(s), reviewer(s), Elsevier and typesetter MPS. It is not allowed to publish this proof online or in print. This proof copy is the copyright property of the publisher and is confidential until formal publication.
Experimental Usage of Oxytocin to Combat Deficits in Social Cognition in Schizophrenia

Cumhur Tas, Elliot C. Brown, Cristina Gonzalez and Martin Brüne
LWL-University Hospital, Division of Cognitive Neuropsychiatry and Psychiatric Preventive Medicine, Ruhr-University Bochum, Bochum, Germany; International Graduate School of Neuroscience (IGSN), Ruhr-University Bochum, Bochum, Germany

Chapter Outline

Introduction 303
Translational Work on the Effect of Oxytocin on Social Cognition 305
Oxytocin in Human Social Cognition 306
Oxytocin in Schizophrenia 307
Potential Pathways to Improve Social Cognitive Deficits in Schizophrenia by Oxytocin 309
Limitations and Future Directions 310
References 311

INTRODUCTION

The human brain, as the most complex organ that has ever evolved, gives us tremendous capacities to maintain fruitful social relationships. For many years, the idea of uncovering the magic potion for successful social interaction has received interest from many scientific disciplines, including psychology, psychiatry, philosophy, and neuroscience. Oxytocin, an evolutionarily conserved neuropeptide that has been well-known for its role in parturition and lactation, has attracted scientific attention for its function in the regulation of early infant–caregiver relationships and social interaction more generally. It is...
Social Cognition and Metacognition in Schizophrenia

thus referred to as a ‘prosocial hormone’ that is relevant for the formation of trustful social bonds through secure attachment (Choleris et al., 2013).

Some of the prosocial effects of the oxytocinergic system have been attributed to its stress-reducing and social ‘buffering’ effects. According to the social buffering hypothesis, gregarious animals downregulate stress responses through social interaction with genetically related individuals or allies. In essence, when conspecifics are engaged in social interaction, their neuroendocrine stress response gradually decreases, while an increase in social reward-related activity is concurrently observed as a response to the secretion of oxytocin from the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus (Neumann and Landgraf, 2008).

In support of these findings, histologic studies have discovered oxytocinergic pathways in higher-order prefrontal structures and other brain areas such as the amygdala that are responsible for the regulation of human social interaction in terms of fight or flight or, more generally speaking, approach and avoidance (Neumann and Landgraf, 2008). Oxytocin, it seems, has the potential to increase approach and decrease avoidance behavior, which may make it an interesting substance for improving social interaction in clinical populations, in which dysregulation of affiliation versus assertiveness coin the clinical picture.

Schizophrenia is a term for a number of heterogeneous syndromes or disorders of which one outstanding commonality is the impairment of patients in social functioning. Poor social functioning is associated with a broad range of negative symptoms such as avolition, apathy, and social withdrawal, as well as with positive symptoms such as delusions and hallucinations. Moreover, social dysfunction in schizophrenia seems to be tightly linked with social cognitive deficits, which statistically act as a marker of core schizophrenia symptoms and social functioning (Couture et al., 2010). Of note, recent targeted psycho-social interventions have demonstrated that social cognition is a remediable domain, and improvement in social cognitive skills ultimately impacts on the severity of social dysfunction in schizophrenia (e.g., Tas et al., 2012). Since current pharmacologic treatment using antipsychotic drugs has relatively little impact on social cognition in schizophrenia, the hope is that oxytocin may have the potential to enhance patient’s social cognitive capacities and helps to ameliorate the core symptoms associated with these disorders, including blunted affect, social withdrawal, suspiciousness, and paranoid ideation, possibly by means of stress reduction, which is why oxytocin has been deemed a ‘natural antipsychotic’ (Caldwell et al., 2009).

Accordingly, this chapter aims to present an overview of oxytocin studies spanning animal work and experimental use of oxytocin in patients with schizophrenia, to discuss potential mechanisms underlying the effects of oxytocin on symptoms and social cognition in schizophrenia, and to highlight limitations and the prospects of future research in this domain.
TRANSLATIONAL WORK ON THE EFFECT OF OXYTOCIN ON SOCIAL COGNITION

Animal and human studies suggest that oxytocin improves several aspects of social cognition, including the formation of social memories, attachment, fear conditioning, trust, empathy, social and emotion recognition, and theory of mind (Domes et al., 2007; Ferguson et al., 2001; Hurlemann et al., 2010; Kirsch et al., 2005; Kosfeld et al., 2005; Strathearn et al., 2009). The possibility to modify the oxytocinergic system genetically and to carry out pharmacologic intervention studies in animals has produced new insights into the brain mechanisms involved in social cognition. Although the complexity of the human brain cannot be directly compared to a rodent brain, animal models provide valuable information regarding the most basic levels of information processing.

Numerous studies have shown that central administration of oxytocin or oxytocin agonists increase social memory formation in rodents. One widely used test to assess the levels of social memory formation is the social recognition test, in which animals are first presented with a stimulus animal, followed by an interexposure interval (IEI), and finally a re-exposure to the same animal with the addition of a novel one. In the re-exposure part of the experiment, the tested animal spends more time sniffing and investigating the novel animal, if it remembers the first encounter. Administration of oxytocin in the olfactory bulb, the medial preoptic area of the thalamus and the septum of rats increases the time they spend socially investigating the novel animal after the IEI (Dluzen et al., 1998; Popik and van Ree, 1991; Popik et al., 1992). Interestingly, another study showed a dose-dependent U-curve response of oxytocin on social memory (Benelli et al., 1995). In this study, low doses of oxytocin injected into the cerebral ventricles improved social memory formation while high doses had no beneficial effect. In line with these findings, pretreatment with oxytocin antagonists abolished the improvement by low doses, and increased social memory when high doses of oxytocin were administered. Taken as a whole, these studies suggest that oxytocin in the brain modulates social memory, and that a U-curve dose response might be responsible for the observed effects.

Genetically manipulated animals in which the oxytocin receptor gene (OTR) was knocked out (KO) provide further information relevant to the effects of this neuropeptide on social behavior. For instance, one study in oxytocin KO mice found that they failed to recognize conspecifics after repeated exposures, despite normal behavior in other memory-associated tasks. This effect was fully reversible by oxytocin administration (Ferguson et al., 2001). In line with these findings, intraventricular oxytocin antagonist treatment in wild-type mice produced the same effects seen in oxytocin KO mice (Ferguson et al., 2000). Moreover, intracerebral oxytocin administration in OTR KO mice reduces aggression and improves social and learning deficits (Sala et al., 2011).
More specifically to schizophrenia, studies have found that oxytocin ameliorated social deficits in a mouse model of schizophrenia, in which the animals received the N-methyl-D-aspartate (NMDA) antagonist phencyclidine (PCP), a potent psychotomimetic agent (Lee et al., 2005). Similarly, oxytocin administration in the central amygdala can reverse social impairments in a rat model of schizophrenia that mimicked prenatal stress (Lee et al., 2007). In prenatally stressed animals decreased oxytocin messenger ribonucleic acid (mRNA) was found in the PVN of the thalamus and increased oxytocin binding was observed in the amygdala. Consistent with these experiments, oxytocin KO mice that were treated with psychotomimetic drugs such as amphetamine, apomorphine, or PCP showed altered prepulse inhibition (PPI) responses, which reflects a deviation in the startle response that has also been found in patients with schizophrenia (Caldwell et al., 2009). In rats, the impaired PPI response produced by PCP was normalized by the administration of oxytocin (Feifel and Reza, 1999; Lee et al., 2005). Interestingly, clozapine, but not haloperidol, has the potential to increase the secretion of oxytocin in rats, which may, in part, account for its ‘atypicality’ (Uvnas-Moberg et al., 1992).

In addition to the effect of oxytocin on social memory and social behavior, other studies have shown oxytocin to be implicated in modulating the response to stressful stimuli. For instance, Windle and colleagues (1997) demonstrated that ovariectomized rats that were given oxytocin injections into the cerebral ventricles had reduced plasma corticosterone responses to white noise stress. Another study reported decreased adrenocorticotropic hormone (ACTH) and corticosterone release in rats treated with oxytocin, in addition to decreased c-Fos mRNA expression in the PVN, the ventrolateral septum, and some sub-regions of the dorsal hippocampus in response to stress (Windle et al., 2004). Finally, one study in sheep showed that infusion of oxytocin in the posterior pituitary and the PVN reduced the cortisol response to a stressful event (a barking dog), and that lactating sheep had a lower cortisol response (Cook, 1997). This suggests that oxytocin attenuates stress-induced physiologic and behavioral responses by modulating the hypothalamic-pituitary-adrenal (HPA) axis.

To sum up, animal studies demonstrate that oxytocin impacts social behavior and social cognition, partly due to its stress-reducing properties. However, evidence from research in rodents and pigs also suggest some caution in investigating oxytocin as a therapeutic agent in humans, because the administration of low-dose oxytocin over a 10- to 12-week period produced increased aggressiveness and dysfunctional HPA axis in these animals (Bales et al., 2012; Rault et al., 2013).

**OXYTOCIN IN HUMAN SOCIAL COGNITION**

Intranasal oxytocin administration exerts measurable effects on a broad range of social cognitive abilities. For example, oxytocin increases trust, trustworthiness and attractiveness, cooperation, defensive (but not offensive) aggression toward
out-group, generosity, socially reinforced learning, and empathy, among others (De Dreu et al., 2010; Hurlemann et al., 2010; Kirsch et al., 2005; Kosfeld et al., 2005; Theodoridou et al., 2009; Zak et al., 2007). Furthermore, intranasal oxytocin has also been found to improve the ability to recognize emotions from an image showing the eye region of a face only (Domes et al., 2007). Interestingly, the positive effects of oxytocin were more pronounced for difficult expressions, suggesting that this neuropeptide may increase emotional salience.

With regard to the interaction of oxytocin with the HPA axis in humans, it was shown that both social support and oxytocin independently attenuated the cortisol responses induced by a social stress test (Heinrichs et al., 2003), whereby the combination of social support and oxytocin yielded the lowest cortisol response. Compatible with these findings, Pierrehumbert et al. (2012) demonstrated that subjects’ attachment style can predict cortisol response to stress and oxytocin levels, where high cortisol reactivity and low oxytocin levels were related to more insecure attachment representations. These findings seem to be encouraging with respect to the rationale of utilizing oxytocin for treating symptoms associated with schizophrenia.

### OXYTOCIN IN SCHIZOPHRENIA

To examine the role of oxytocin in relation to social cognition and symptomatology, one needs to distinguish between studies measuring the association of peripheral oxytocin with cognition and symptom profile from research into the experimental administration of oxytocin adjunct to antipsychotic medication.

In the 1980s, a few studies produced conflicting results regarding differences in blood or central nervous system (CNS) levels of neuropeptides between schizophrenia and other clinical populations. Linkowski et al. (1984), for example, reported lower levels of neurophysins (carrier proteins of oxytocin) in the CNS of patients with schizophrenia compared with patients with major depression or bipolar disorder, and healthy controls (Linkowski et al., 1984). Conversely, another study demonstrated higher CNS levels of oxytocin, but not vasopressin, in patients with schizophrenia compared with healthy controls (Beckmann et al., 1985), a finding that could not be reproduced in a later study (Glovinsky et al., 1994).

More recent studies demonstrated reduced oxytocin serum levels in patients with schizophrenia, which predicted their ability to correctly identify facial emotions (Goldman et al., 2008). In trust-dependent interactions, healthy controls showed increased plasma levels of oxytocin, whereas this effect was absent in patients with schizophrenia (Kéri et al., 2009).

With regard to the symptomatology, one study found that higher oxytocin serum levels in patients with schizophrenia were associated with reduced symptom severity compared with patients with lower oxytocin serum levels (Rubin et al., 2010). In addition, the same study group found that women with schizophrenia who had higher plasma levels of oxytocin evaluated emotions as
more positive, although there were no differences in terms of plasma oxytocin levels between men and women (Rubin et al., 2011). One study by Walss-Bass et al. (2013) examined the association of plasma oxytocin levels with theory of mind and emotion perception in schizophrenia. The authors created a so-called ‘waiting room task’ consisting of 26 videos of people in a room who were looking at a camera with varying duration, gaze direction (direct or indirect), and facial expression. It turned out that social cognitive task performance correlated only in patients with delusional beliefs, but not in patients without delusions. Notably, similar correlations were also present in healthy participants in this study, hence these findings do not appear to be specific for paranoid schizophrenia (Walss-Bass et al., 2013).

As regards the experimental administration of oxytocin for treating patients with schizophrenia, the first systematic study was conducted by Bujanow who, back in 1974, already envisioned a role of oxytocin in the treatment of schizophrenia when stating “the neurophysiological matrix of schizophrenia is a central functional organizational scheme related to reduced stress and drives and the biochemistry of pineal gland is closely related to that”. In this early study, oxytocin was randomly given (versus placebo) to acute and chronic patients with schizophrenia, and was found to lead to symptomatic improvement and reduce hospitalization rates (Bujanow, 1974). Following this ground-breaking – though at that time under-recognized – research, later studies have focused on the question whether or not intranasal administration of oxytocin can ameliorate symptoms and/or improve social cognition.

With respect to schizophrenia symptoms, Feifel and colleagues (2010) found that oxytocin administration over a 3-week period twice daily improved both positive and negative symptoms in schizophrenia and also reduced the Clinical Global Impression score significantly. Similarly, Pedersen et al. (2011) reported a reduction in the Positive and Negative Syndrome Scale score after a 2-week treatment with oxytocin given adjunct to antipsychotics, where, in addition, the ability to appreciate the mental states of others (theory of mind) improved. With regard to emotion recognition, Averbeck et al. (2011) found an improved recognition of emotions upon intranasal oxytocin administration in schizophrenia patients. Notably, the effect of oxytocin on emotion recognition was more pronounced when the stimuli were particularly difficult to interpret and negative in content (i.e., anger and fear). Along similar lines, MacDonald et al. (2013) found that patients receiving oxytocin were more accurate in determining the emotional mental states of people whose faces were cropped in a way that only the eyes remained in view. Likewise, Davis et al. (2013) studied patients’ performance on simpler compared with more difficult social cognitive tasks under oxytocin versus placebo, whereby oxytocin improved accuracy only in the more advanced tasks comprising the detection of sarcasm and empathetic perspective-taking.

Lastly, social perception has been proposed to be another subdomain of social cognition in which oxytocin administration has shown some effects.
Fischer-Shofty et al. (2013) found that, following the administration of oxytocin, patients with schizophrenia improved their ability to recognize kinship in video-clips that were presented to participants as part of the Interpersonal Perception Task (Costanzo and Archer, 1989). Interestingly, healthy controls did not show any improvements following the administration of oxytocin, which may suggest that the effect of oxytocin is more prominent in participants with deficits in social cognitive skills relative to healthy populations.

**POTENTIAL PATHWAYS TO IMPROVE SOCIAL COGNITIVE DEFICITS IN SCHIZOPHRENIA BY OXYTOCIN**

Despite these encouraging findings of oxytocin administration on social cognition and behavior, most effect sizes in the above-mentioned studies were moderate to small. Previous factor analyses and studies using model-based statistical approaches based on behavioral tests successfully identified the interdependency of subdomains of social cognition. General principles of prefrontal cortex activity, for example, suggest that bottom-up processes such as emotion perception impact on top-down cognitive processes such as theory of mind and metacognition. In support of this assumption, evidence suggests that oxytocin acts as a neuromodulator that primarily targets subcortical structures, which in turn may affect the high cortical areas that are responsible for social decision-making, empathy, theory of mind, and metacognition (Meyer-Lindenberg et al., 2011; Sofroniew, 1980).

The amygdala appears to be one of the brain region that are most sensitive to oxytocin manipulation (Hurlemann et al., 2010). Several functional magnetic resonance imaging (fMRI) studies reported correlations between amygdala activity and the accurate identification of emotions, which was modifiable by oxytocin administration (Domes et al., 2007; Gamer et al., 2010). In addition, several studies in healthy populations found that the misinterpretation of sensory input at the level of the amygdala might negatively influence higher-order theory of mind skills (Corden et al., 2006; Kreifelts et al., 2010; Mier et al., 2010).

Rosenfeld and his colleagues (2011) proposed an emotional model in which oxytocin and amygdala activity played a center-role to understanding social behavior and social cognition in schizophrenia. In brief, they put forth the idea that, while the core features of schizophrenia rely heavily on dysfunctions in the dopaminergic circuits, the network activity involved in the fine-tuning of social behavior, which is centrally controlled by the amygdala via oxytocinergic pathways, could further impact on social impairments in schizophrenia. Specifically, they hypothesized that the impairments in the dopaminergic reward system, the amygdala and oxytocinergic neurons engender a neural milieu that improperly assigns emotional salience to environmental stimuli and hence causes misinterpretations that lead to inappropriate social approach and avoidance responses. Such misinterpretations concerning the
salience and intensity of emotional stimuli often lead to an aberrant activation of the amygdala, which leads to a stimulus being appraised as threatening. Consequently, such threatening stimuli activate the autonomic nervous system and the HPA axis as an initial alarm systems. Conversely, the oxytocinergic system can dampen the activation of the amygdala, the autonomic nervous system, and HPA axis and can thus contribute to the prevention of false alarm biases. Critically, such oxytocinergic activity occurs more often when the stimuli is appraised as socially rewarding and prosocial. In the absence of this activity, an aberrant activation in amygdala would affect the functionally interconnected prefrontal areas that are responsible for theory of mind and social perception and hence distort social cognitive capacities.

Taken as a whole, it seems parsimonious to assign oxytocin a role in the modulation and expression of social cognitive skills and the symptomatology in patients with schizophrenia. Therefore, more research into the clinical use of oxytocin for improving social cognitive deficits and psychotic symptoms in schizophrenia is warranted.

**LIMITATIONS AND FUTURE DIRECTIONS**

Schizophrenia is a group of heterogeneous disorder with multiple clinical expressions. Negative findings of current pharmacologic studies propose that there may not be one ‘magic bullet’ to cure schizophrenia. Focusing on social cognition as a treatment strategy has been found to be one potential strategy for improving social functioning in this disorder. Studies have found beneficial effects of oxytocin on symptom severity and social cognitive skills in schizophrenia. However, clinical studies in schizophrenia have limited the use of oxytocin to at best several weeks. For example, Modabbernia et al. (2013) found in an 8-week randomized trial superior improvement in positive, negative, and general symptoms in schizophrenia when oxytocin was given in addition to risperidone, as compared with risperidone alone. To date, there is no information about follow-up examination after the termination of oxytocin treatment. Another limitation pertains to the lack of knowledge about long-term effects of oxytocin. Moreover, the short half-life of oxytocin makes it difficult to produce stable serum (or CNS) levels (McCullough et al., 2013). In addition, it is far from being clear which patient profiles would respond to oxytocin treatment and which would not. Along similar lines, a general consensus has also not yet been reached for the most effective dose titration of oxytocin, although no severe side effects have been observed following oxytocin administration in humans (MacDonald et al., 2011). Another important point that needs to be clarified is the influence of endogenous oxytocin faculties on the effects of external administration. For instance, patients with lower basal oxytocin levels may benefit more from oxytocin administration. Conversely, patients with normal peripheral levels of oxytocin may benefit less from such treatment strategies. Finally, genetic research has found associations
of autism with polymorphic variation of the OTR, and a few studies have pointed to the possibility that the genetics of oxytocin are also related to schizophrenia (Montag et al., 2012; Tellis et al., 2012).

It is evident that oxytocin studies will expand our understanding of schizophrenia and underline the importance of the social dimension of schizophrenia. The current state of the art may suggest the use of oxytocin administration as an augmentation therapy for treating social cognitive deficits, and perhaps to increase patients’ potential to benefit from social cognitive training. Considering the limited effects of current antipsychotic pharmacologic agents on social cognition and functioning, oxytocin may provide new hope for improving the social capabilities of our patients.

REFERENCES


Chapter  |  18  Experimental Usage of Oxytocin


Abstract
Exciting new research has revealed that the administration of oxytocin can improve empathetic abilities, increase trustworthiness and other attachment-related behaviors, and reduce social anxiety in both healthy and some clinical populations. A growing body of work has explored the potential therapeutic benefit of oxytocin for improving deficits in social cognition in schizophrenia. The aim of this chapter is to review the current state of this work, including current limitations and issues for future work.

Keywords
emotional salience, oxytocin, schizophrenia, social cognition