Oxytocin model of formation of psychotic symptoms and its implications for research on oxytocinergic pathway in schizophrenia

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Summary
There are more and more data to support the dysregulation of the oxytocinergic pathway in schizophrenia. The development of the above branch of knowledge began to evolve alongside the mainstream of studies concerning gene polymorphisms for dopaminergic, glutamatergic and serotonergic systems. Both experimental studies and clinical trials have demonstrated an antipsychotic effect of oxytocin. Starting with the pioneering neuroendocrinobehavioral experiment which demonstrated that oxytocin nasal spray increases the level of trust in healthy volunteers dozens of experiments were carried out confirming the modulatory role of oxytocin for the recognition of emotion, social memory, pro-social behaviours, collaborative behaviours and behaviours that require generosity and altruism. According to, oxytocin model of development of psychotic symptoms – oxytocinergic system dysregulation may affect the incorrect attribution of meaning of emotional information from the environment. This can be manifested in the form of social cognition dysfunction and leads to abnormal social behaviour as withdrawal from social contact, isolation and formulation of paranoid delusions. From the clinical psychiatry point of view it became crucially need for research on selective oxytocin receptor agonists, as they may be used in the treatment of diseases which manifest in social withdrawal, lack of trust and the absence of affiliation behaviour as in schizophrenia.

Key words: schizophrenia, oxytocin, social cognition, oxytocin receptors agonists

Introduction
Research on cognitive function in patients with schizophrenia (neurocognition) has a long history in the development of science in this field. However, social cognition has only recently become a subject of interest to schizophrenia researchers [1]. Studies in this area in relation to schizophrenia appear to be important as social cognition was found among the other factors (such as negative symptoms), which were significantly linked to social dysfunction of schizophrenic patients [2]. One of the first definitions of social cognition was formulated by Brothers as „the ability to become aware of the intentions and attitudes of the other people” [3]. In the studies on schizophrenia there are three main domains of social cognition: theory of mind, style of attribution and
facial emotion recognition [1]. Patients with schizophrenia perform significantly worse on tests of the ability to recognize emotions from facial expressions, than patients with bipolar disorder and healthy subjects in the control group [4]. However, the performance of patients with schizophrenia in the study of the theory of mind clearly correlated with their level of social functioning [5], and appeared to be independent of the level of overall cognitive function [6]. The development of effective pharmacologic strategies that significantly affect the cognitive function impairment in schizophrenic patients is still in its beginning. However, such specific assessment of deficits in social cognition has not yet been incorporated into research standards on new pharmacological strategies in schizophrenia treatment. This is due to the fact that for any of the pharmacological agents, whether aimed at the regulation of dopaminergic, glutamatergic, or serotonergic pathway, scientific evidence concerning their effects on improvement of social cognition or theory of mind had not existed before. In the 90s of the twentieth century it was proved that oxytocinergic system plays a significant role in regulating the creation of relationships, behaviors associated with reproduction and the quality of parental care in rodents [7]. Intensive tests on animals of different species, including primates have shown that oxytocin is a central mediator of prosocial behavior and it is essential for the process of social memory and recognition of social cues [8]. However, the behavior associated with intraspecific communication and relationship forming by individuals of the same species may be responsible for the behavior of social cognition in humans [9]. The number of data confirming the dysregulation of the oxytocinergic pathway in schizophrenia is increasing. The development of the above branch of knowledge began to evolve alongside the mainstream of studies concerning gene polymorphisms for dopaminergic, glutamatergic and serotonergic systems, which inspired a psychopharmacological research for seeking new therapeutic targets in schizophrenia. The purpose of this paper is to present and discuss the latest research in the field of experimental and clinical psychopharmacology and behavioral neuroendocrinology concerning the role of oxytocinergic system in schizophrenia studies.

Experimental studies on the physiological role of hypothalamic hormones

In birds, amphibians and fish single hormone vasotocin regulated affiliate behaviors such as sexual activity and mating sounds [10]. In the course of evolution, inversion and duplication of genes at the level of reptiles has led to the development of two closely related nonapeptides ie arginine-vasopressin and oxytocin and corresponding receptors [11]. In the mammalian brain, with the evolution of the blood / brain barrier, central ‘peptidergic’ communication has been developed, independent of the peripheral effects of the neuropeptides. Thus for the ‘social brain’ a different kind of neurotransmission is characteristic – it is a so called ‘peptidergic’ transmission in contrast to the neuronal synaptic structure of the cerebral cortex [12]. Oxytocin and vasopressin are compounds structurally very similar, the only difference between them is related to the two amino acids. The receptors for oxytocin and vasopressin can be cross-activated by both nonapeptides [11]. Receptors for oxytocin and arginine-vasopressin belong to the family of G-protein coupled receptors. The central effect of oxytocin is mediated by
the oxytocin receptors, which are widely distributed throughout the brain, in a manner characteristic of the species. The largest concentration of oxytocin receptors is found in the mediodorsal nucleus of the hypothalamus, the amygdala, the lateral septum, ventral tegmental area, preoptic area and hippocampus [13].

Additionally oxytocin receptors are widely diffused in most regions of the brain associated with the detection and transmission of olfactory signals, ie primary and secondary olfactory epithelium, the main and additional olfactory bulb and additional olfactory bulb, anterior olfactory nucleus and piriform cortex [14]. For most mammals, including primates, recognition of intraspecific signals (the equivalent of „social cognition” in humans) is mediated by the main and additional olfactory epithelium, which are the gates to the main and additional olfactory system [15]. Oxytocin and vasopressin are released bi-directionally, both axonally and somatodendritically, by giant neurons concentrated in the paraventricular and supraoptic nucleus of the hypothalamus. Both types of transport are regulated in a different way, and there is more and more evidence for the widespread somatodendritic release of both neuropeptides in the brain [16, 17].

Animal studies have demonstrated the importance of oxytocin in modulating stress response and stabilizing the level of anxiety [18]. Animal models also suggest that the central role of oxytocin in mediating complex social behaviors depends on the function of the amygdala. Oxytocin, by affecting the amygdala, weakens the anxiety response [18]. However, oxytocine gene knockout mice (OXT -/-), despite normal olfactory and spatial abilities, show profound deficits in social cognition, which can be compensated by the administration of oxytocin in the central nucleus of the amygdala (medial amygdala) [19]. In addition, it was also shown that oxytocin by acting on the central nucleus of the amygdala inhibits the transmission of the excitation from the amygdala to the centers of the medulla oblongata, where the anxiety response is mediated [20], which confirms its inhibiting effect on the anxiety reaction.

The first study that demonstrated the role of oxytocin and vasopressin in the complex animal social behaviors was carried out in the 70’s of the twentieth century. Cort Pedersen proved that intracerebral administration of oxytocin promotes maternal care behavior in sexually immature female rats, suggesting the importance of this relationship, not only for peripheral physiology of reproduction, but also for the transformation of the brain of the mother towards affiliate behavior, to protect the offspring [21]. In the 90’s it was proved that oxytocinergic system plays an important role in regulating the creation of relationships, behaviors associated with reproduction and mating, and the quality of parental care in rodents [7]. Nowadays, not only proven in experimental studies, but also in humans, the polymorphism of oxytocin and vasopressin receptors is combined with the ability to build relationships, generosity and mating [22], which will be discussed in detail in one of the subsections.

From the conceptualization of the role of oxytocin for prosocial behavior in animals and humans an attempt has evolved to demonstrate the role of oxytocin as a natural antipsychotic. Over the past several years the antipsychotic and counteracting negative symptoms effect of oxytocin has been shown in the animal models of psychosis. Previous experimental studies confirmed that oxytocin may have an antipsychotic effect,
reversing sensory gating deficits caused by the action of amphetamine and MK801 [23],
the effect that is parallel to the effect of atypical antipsychotics. In another experimental
study it was proved that oxytocin gene knockout mice (OXT -/-) are more sensitive in
tests measuring sensory gating, which determines the greater deficit of these animals
while treated with propsychotic agents, especially phencyclidine [24].

Lee et al have shown, however, that social interaction deficits in experimental ani-
malsthat have been subjected to chronic administration of phencyclidine, are reversed
by the administration of oxytocin [25]. It seems, therefore, that there is plenty of evi-
dence from experimental studies confirming the role of dysfunction of oxytocinergic
system in promoting psychotic symptoms and the antipsychotic effect of oxytocin.
The oxytocin model of formation of psychotic symptoms was also created and it will
be discussed further on.

**Neuroendocrinological and genetic research concerning the role
of oxytocinergic system and its implications for research on schizophrenia**

Although it is still not clear how neuropeptides penetrate the central nervous system
by the olfactory epithelium, one study so far has shown that the peptides administered
intranasally can increase the concentration of the test compounds in cerebrospi-
nal fluid as early as 30 minutes after nasal aspiration, reaching significant concentration
levels [26]. Born’s findings gave rise to further studies with intranasal oxytocin and
vasopressin administration. It permitted a clinical assessment of the effects of the two
hypothalamic neurohormones in the series of neuroendocrine-behavioral experiments
and gave the possibility to evaluate the effect of these compounds in comparison to
psychopathological symptoms of mental illness.

Parenteral oxytocin used previously in human studies did not penetrate the blood-
brain barrier in concentrations sufficient to have the central effects [13]. The pioneering
Kosfeld’s experiments in the field of behavioral neuroendocrinology demonstrated that
intranasal administration of oxytocin increases the level of confidence. It resulted in
the higher transfer of money than in the control experiment, with the expectation that
the interaction partner would reciprocate similarly high transfer [27]. Based on the
above and several similar neuroendocrine-behavioral experiments it was found that
oxytocin can affect higher mental processes associated with the level of confidence,
mentalising and cooperation. The circuitry associated with the oxytocin receptors is
considered a potential pharmacological target for social and cognitive functions.

Since then, dozens of neuroendocrine experiments regarding the role of oxytocin in
healthy people have followed. They were focused on the role of oxytocin in recognizing
emotions, social memory, pro-social behaviors, behaviors that require collaboration,
altruism, generosity, response to rejection and many others (For review look at [28]).
However, polymorphisms in the oxytocin and vasopressin receptors have started to
be associated with the development of attachment, the generosity and the quality of
interpersonal bonding [22]. Recently it has been also shown that polymorphisms of the
oxytocinergic genes are associated with the increased susceptibility to schizophrenia
[29] and several oxytocin and vaspressin gene variants associated with the occurrence
of schizophrenia in Arab-Israeli population have been identified [30]. Additionally it is demonstrated that in schizophrenic patients lower concentration of oxytocin in the cerebrospinal fluid is more correlated with negative symptoms and the need for higher doses of neuroleptics [31]. The correlative studies have shown that in women with schizophrenia, higher levels of oxytocin correlate with the recognition of faces as more happy [32], and with lower severity of positive symptoms and with better general psychopathology [33]

**Oxytocin model of formation of psychotic symptoms in schizophrenia**

As shown in experimental studies discussed above amygdala is a key center of the transmission of social cognitive information in animals. The significant role of this structure in the transmission of social information has been confirmed in clinical and neuroimaging studies in humans [34]. The literature has widely documented the role of the amygdala in the analysis of many dimensions of the emotional information [34].

In the experiments with presentation of shapes patients with the amygdala damage can not recognize the social significance of the non-social stimuli. In contrast, a healthy control group finds in them a social and emotional meaning [34]. People with the amygdala damage find presented faces as more trustworthy, compared to healthy people that interpret the same faces as not trustworthy [34].

Facial emotion recognition is one of the best known domains in the field of social cognition in patients with schizophrenia. The majority of patients with schizophrenia demonstrated deficits in the recognition of emotional facial expression, especially in the assessment of negative emotions (that reflect fear), as compared to the control group and those with bipolar disorder [4, 35]. However, neuroimaging studies carried out on healthy people confirmed that oxytocin does not only affect the suppression of the amygdala activation in the presence of unpleasant stimuli, but also increases the activity of the amygdala in the presence of pleasant stimuli [36], which may indirectly modify the learning process (as well as the social learning).

Another issue carrying important implications for the role of oxytocinergic system in the study of schizophrenia are structural connections between the amygdala and the dopaminergic system including such structures as the nucleus accumbens and ventral tegmental area [37].

According to Rosenfeld, the above mentioned structural relationship may bring significant implications for the schizophrenia treatment due to the fact that antidopaminergic agents for the benefit of antipsychotic effect may induce some dysfunction in the field of social cognition [9]. To support this argument, Rosenfeld et al quoted the studies which show that antidopaminergic agents cause the withdrawal of the reinforcing memorization effect of emotional information, versus irrelevant emotional information. The above effect is mediated by the amygdala [9, 38, 39].

There are also studies that confirmed the amygdala dysfunction showing the reduced volume of this structure in schizophrenic patients, compared to healthy subjects. The meta-analysis of 58 studies of structural magnetic resonance imaging (MRI) showed 6% reduction in amygdala volume in patients with schizophrenia compared with
healthy controls [40]. In addition, it was recently demonstrated that for patients with prepsychotic symptoms (meeting the criteria of high risk of developing psychosis) an increased volume of the pituitary gland compared with controls was observed [41].

Both an increased [42–44] and reduced volume of the pituitary gland was observed in schizophrenia patients as compared to the control group [42, 45]. Oxytocin and vasopressin are released by giant neurons concentrated in the paraventricular and supraoptical nucleus of the hypothalamus in the mechanism of neurosecretion. The neurosecretory granules then travel down the long axons through the stalk of the infundibulum to the posterior pituitary where the granules are stored and released into the perivascular space. It is still unclear whether oxytocinergic activation resulting in the increased secretion of oxytocin can trigger morphological changes of the pituitary gland volume. It is rather believed that the change in volume of the pituitary gland in schizophrenic patients in the course of the disease can result from blocking the activity of corticotropin-releasing hormone gene during antipsychotic treatment [46] or the stimulation of prolactin-producing cells [47].

However, neurostructural studies that indicate changes of the pituitary volume in schizophrenic patients compared to healthy subjects may reflect not only a dysregulation of the hypothalamic-pituitary-adrenal axis or dysfunction of the prolactin production by the lactotrophic pituitary cells, but provide indirect evidence for oxytocinergic dysfunction in schizophrenic patients.

Rosenfeld for the first time formulated the oxytocin model of formation of the psychotic symptoms. He hypothesized that “aberrant interactions between dopaminergic reward systems, a dysfunctional amygdala, and the neurohormone oxytocin generate an abnormal neuronal milieu that incorrectly assigns emotional information coming from the environmental stimuli. This deficit in turn results in aberrant social cognition that may ultimately lead to inadequate social responses, from withdrawal and isolation to suspicion and paranoia” [9].

It was also showed that schizophrenic patients with lower concentration of oxytocin in the cerebrospinal fluid expressed more negative symptoms and they required higher doses of antipsychotics [31].

According to Rosenfeld, at this stage of the research it is still not clear how or to what extent changes in the concentration of oxytocin can affect the processing of socio-emotional information [9]. Is is also not clear whether this is caused by the improvement in emotional perception or the improvement of other socio-cognitive functions like those in the theory of mind. The effect of oxytocin may be associated with an increased level of social motivation and hedonia [9], resulting in the increased effort in the searching for social contacts and the greater satisfaction from the social contacts.

**Augmentation of antipsychotic therapy with oxytocin – clinical trials**

The development of the oxytocin receptor ligands is based on the so called ‘reverse pharmacology’, starting from the clinical studies on the new effects of synthetic oxytocin (which differ from the antipsychotic effects of neuroleptics) to the need to
develop the new agonists of this receptor. Oxytocin was laboratory-synthesized by Vincent de Vigneaud in the fifties of the twentieth century [48] and the researcher was awarded the Nobel Prize for this achievement. Since then hundreds of analogues for the both hypothalamic neurohormones were synthesized. Discussing the agonists and antagonists of OXT or AVP studied to date, exceeds the capacity of this paper. However, it is important to note that many of the leading pharmaceutical companies made a number of syntheses of analogs of hypothalamic receptors, but most of them were discontinued at various stages of the research (both at experimental stages, and at I or II phase of clinical trials) [49].

Both Merck and Pfizer discontinued the programs for the development of oxytocin receptor antagonists (for use in obstetrics to prevent preterm birth) at the stage of preclinical studies. At the moment only Glaxo-SmithKline company continues the program for oxytocin receptor antagonists in obstetrics. However, a Pfizer’s oxytocin agonist WAY-267464 was the first synthetic drug from the group of oxytocin receptor ligands, which were tested in the psychopharmacological indication i.e. anxiety disorders, and / or autism. However, the work on that drug was abandoned in the preclinical stage, causing the complete closure of the development of the OXT agonists by the company [50-52].

From the information available to the authors, none of the leading pharmaceutical companies is continuing the work on oxytocin receptor agonists for the use in psychopharmacology. However, with an increasing number of clinical trials it is more and more clear that oxytocin in the form of nasal spray is effective against a variety of symptoms of mental illness, including schizophrenia. In the following part of the publication we are going to present and discuss the trials of oxytocin nasal spray in the treatment of psychosis. The first reports on the clinical use of oxytocin in the treatment of schizophrenia comes from the 70’s. They were published by Buyanov who postulated the significant clinical effect of intravenous oxytocin and glucose infusion at a dose of 10 to 15 IU or intramuscularly as a once a day dose of 20 - 25 IU. Describing his experience in a letter to the editor of the British Journal of Psychiatry he suggested that oxytocin is effective in exacerbation of schizophrenia and for preventing psychiatric hospitalization in patients with recurrent psychosis. To a lesser extent antipsychotic effect was observed in patients with symptoms of chronic schizophrenia [53].

The development of research on the central effects of intranasal oxytocin became significantly faster after the registration of that form of oxytocin by Novartis company. Although the intranasal form of the drug in its original indication (ie promoting lactation after birth) did not confirm its therapeutic effect in clinical studies [54], the introduction of intranasal form of oxytocin enabled the rapid development of research in behavioral neuroendocrinology and clinical psychoneuroendocrinology. However, there are more and more randomized, placebo-controlled proof- of-concept studies, which demonstrated a beneficial effect of oxytocin to psychopathology, cognition and social cognition in schizophrenic patients.

The first clinical studies on augmentation of antipsychotic therapy with oxytocin were short-term (2- and 3-week) and focused on a small research groups (N = 15,
N = 19) [55,55]. Feifel’s study demonstrated the efficacy of oxytocin to some psychopathological symptoms of schizophrenia [55], while Pedersen’s study demonstrated the efficacy of oxytocin to selected dimensions of social cognition and cognitive functioning in patients with schizophrenia[56].

As in the 70’s and 80’s of the twentieth century, oxytocin was studied for its beneficial and/or adverse effects on memory and learning [57], there is also a question whether intranasal oxytocin does not negatively affect cognitive functioning in patients with schizophrenia. However, in a small (N = 15, two weeks) study Feifel excluded amnesic effects of oxytocin, confirming its beneficial effect to verbal memory [55].

A clinical study by Modabbernia et al involved 40 patients with schizophrenia and lasted 8 weeks. Oxytocin was used as the augmentation of risperidone monotherapy [58]. The primary endpoint of this study was the difference in psychopathology as evaluated by PANSS between oxytocin and the placebo group at the end of the observation period. It has been shown that oxytocin was more effective than placebo in the overall severity of psychopathology, negative symptoms, positive symptoms and general psychopathology in PANSS evaluation [58].

However, in another study, which again involved a fairly small study group (N = 28), during a short follow-up period (3 weeks) the beneficial effects of oxytocin to positive symptoms, negative symptoms, or overall psychopathology as measured with PANSS in patients with schizophrenia of both sexes were not confirmed [25]. Surprisingly, the improvement in the overall severity of psychopathology was observed for placebo subgroups, and improvement of negative symptoms was observed in a separate subgroup of oxytocin and placebo groups of patients who were hospitalized compared to outpatients group. In this study, it was also observed that oxytocin improves smell identification, both in terms of the total score and the subscales of pleasant smell recognition in the measurement by the University of Pennsylvania Smell Identification Test (UPSIT) [25]. On the basis of this study it was confirmed that oxytocin improves the perception of the pleasant smell stimuli. It appeared to be parallel with the results of studies on healthy people, in the field of perception of different stimuli, in which oxytocin showed a greater effect in improving the recognition of pleasant stimuli (such as words and the facial expression) [25, 59], than in improving the recognition of the unpleasant stimuli.

**Conclusion**

The number of data confirming the dysregulation of the oxytocinergic pathway in schizophrenia is increasing. The development of the above branch of knowledge began to evolve alongside the mainstream of studies concerning gene polymorphisms for dopaminergic, glutamatergic and serotonergic systems. Both experimental studies and clinical trials have demonstrated an antipsychotic effect of oxytocin. The results of these trials regarding the role of the oxytocinergic system in schizophrenia seem to be encouraging – they confirmed the modulatory role of oxytocin for the mechanisms of social affiliation and social cooperation level. It seems unlikely that the only approved for marketing synthetic intranasal oxytocin (Syntocinon, Novartis)
will find the broad clinical application in psychiatry, due to the very short half-life of this substance. From the clinical point of view there is an urgent need to develop a selective oxytocin receptor ligands with a long half-life, because clinical studies have confirmed that these substances may be used in the treatment of a number of psychiatric disorders. Unfortunately, from the data available to the authors, none of the leading pharmaceutical companies is engaged in research in this field [49].

The use of of oxytocin receptor agonists seems to be the most reasonable in the case of psychiatric disorders in which the symptoms of social withdrawal, no need for social interaction or lack of satisfaction of such contacts are observed. Some schizophrenia researchers predict (not without support in the evidence based medicine), that the next decade of research on schizophrenia will be called “the oxytocin decade”. Studies concerning the role of the oxytocinergic system in the schizophrenia treatment may be of such importance that in some way alter the thinking of this disease.

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Schlüsselwörter: Schizophrenie, Oxytocin, soziale Kognition, Oxytocin-Rezeptor-Agonisten

Le modèle de l’ocytocine de la formation des symptômes psychotiques et les implications pour les recherches concernant le rôle du système ocytocinergique dans la schizophrénie

Résumé


Mots clés : schizophrénie, ocytocine, cognition sociale, antagonistes sélectifs des récepteurs de l’ocytocine

References


