

# Oxytocin in Prevention of Schizophrenia

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**Abstract** Hippocampal pathology plays a great role in the pathogenesis of schizophrenia. The hippocampus is susceptible to deleterious effects of stress. The link between chronic psychosocial stress and schizophrenia has been repeatedly described by different authors. Sustained psychosocial stress in combination with inherited predisposition can lead to excessively high cortisol levels and to hyperactivation of NMDA receptors. This can trigger delusions and worsen adult neurogenesis that is already insufficient. Subsequent impairment of glutamatergic transmission from the DG to CA3 region, hyperactivation of CA3 region and subsequent hyperactivity of ventral tegmental area (VTA), imbalance between pattern separation and pattern completion can bring to incorrect associations, hallucinations and false psychotic memories which would become salient due to the hyperactivation of dopaminergic system. Cognition, current state of the mind is strongly biased by past experience. Memorized and fixed psychotic experiences can irreversibly change individual's model of the world, mind and the way of reasoning. There are data suggesting that neurohormone oxytocin can be used in the treatment of schizophrenia. The aim of this paper was to investigate the biological mechanisms of therapeutic effects of oxytocin administration and to find out whether it can be used as a preventive agent. I have studied existing literature concerning biological effects of oxytocin. Briefly, oxytocin takes part in stress limiting mechanisms. This neurohormone dampens behavioral and physiological stress reactions. Importantly, it improves adult neurogenesis, glutamatergic transmission from the DG to CA3 region, activates GABA interneurons, increases BDNF levels and plays a substantial role in maturation of neurons during prenatal period and throughout life. In summary, oxytocin administration to patients with schizophrenia seems to be reasonable, because it fits for the most accepted theories of schizophrenia pathogenesis. And there is a possibility that it can be used as a preventive agent.

**Keywords** Schizophrenia, Hippocampus, Stress, GABA, Oxytocin, Neurodevelopment, Prevention

## 1. Introduction

Morphological research has found about 50 brain areas affected in schizophrenia. Over 1200 genetic studies were conducted to detect hereditary factors leading to this illness. And still, there is no full agreement on the etiology and pathogenesis of schizophrenia. There is agreement only on the complexity of the problem. Schizophrenia displays almost every pathological syndrome known in psychiatry. This complexity suggests that an approach from many angles may bring some valuable information.

Chronic, irreversible course of the illness, frequently observed poor results of the treatment with existing medications force a search of new drugs and new methods that could effectively stop the progress or even better - prevent the onset of the disease.

There are data suggesting that neurohormone oxytocin can be used in the treatment of schizophrenia. First suggestion was made in 1974.

Intravenous and intramuscular oxytocin injection has been reported to be able to stop psychotic symptoms and to cancel a necessity of hospitalization[92]. And several recent studies with administration of intranasal spray have also demonstrated positive effects (reduction of positive and negative symptoms)[100,101] and no significant side effects after 3 weeks of treatment[93]. However, the results of these trials were modest, perhaps, because they were conducted on chronic patients. Early intervention for example in patients with first episode could be more beneficial, because in this case psychotic perceptions and illogical associations would be still loose and reversible. Thinking is strongly biased by memory[103,109,110]. Ideas, illogical associations, hallucinations after being fixed in memory may irreversibly alter individual's model of the world, his mind and the way of reasoning. That is why more attention should be paid to prevention and early intervention.

The main aim of this article is to investigate the biological mechanisms of therapeutic effects of oxytocin administration and to find out whether it can be used as a preventive agent.

## 2. Functions of the Hippocampus

The twin studies have shown that if one identical twin has

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schizophrenia, then there is only a 30-50% chance that the other twin will have it as well. Probably, this fact suggests a substantial contribution of environmental factors including stress to the causation or triggering psychosis in predisposed individuals.

Abnormalities in the hippocampus and prefrontal cortex more frequently observed in schizophrenia and these areas are the most vulnerable to harmful effects of stress [120]. We will focus mainly on the hippocampus in schizophrenia, because this is an area where oxytocin possibly exerts its therapeutic effects.

The hippocampus plays an important role in learning and memory processes. It is a region where incoming sensory information converges with stored memories. Interaction of these two currents is an essential principle of cognition [103]. The hippocampus participates in perception [104,105], encoding, association, retrieval of information, novelty detection [2,27], in planning, imagination, probabilistic forecasting and other processes [106]. All sensory information passes through a trisynaptic pathway formed by the entorhinal cortex, dentate gyrus (DG), CA3 and CA1 regions.

The hippocampus also provides two important functions – pattern separation and pattern completion. Pattern separation is a process of differentiation of signals with similar but not identical features. It is mostly provided by the dentate gyrus.

Pattern completion is an opposing process when full representation is formed by completion of a partial cue. It is based on the retrieval of information from cortical memory storages via direct entorhinal – CA3 pathway bypassing the DG.

If a signal is novel or there is a novel combination of familiar signals i.e. there are no traces of this information in memory, then the signal would be associated with the context or other signals, encoded and memorized.

CA1 region provides a comparison of patterns or predictions formed in CA3 region with “sensory reality” i.e. with the inputs from the entorhinal cortex [1,2].

The unique and very important feature of the hippocampus is an ability to generate new neurons in the dentate gyrus throughout life, which is necessary for appropriate processes of learning and memory [113].

### 3. The Hippocampus in Schizophrenia

The hippocampal pathology in schizophrenia, first of all, includes reduced hippocampal volume that progresses with the course of illness. Volumetric reduction is seen as early as the first episode [3,4,5,6] and has been detected in healthy siblings [7]. In twin pairs discordant for schizophrenia the reduction is greater in psychotic twins. And non-psychotic twins have smaller volumes in comparison with individuals who do not have a family history of schizophrenia [8].

Basal perfusion of the hippocampus is increased indicating increased activity [9,10] which may underlie hallucinations [11,102].

However, patients perform poorer in tasks requiring

additional activation of the hippocampus i.e. tasks on conjunctive encoding (relational memory, episodic memory, verbal memory with temporal context, transitive inferring with overlapping patterns, word pair novelty etc.) [12,13,14,15,16].

Histological changes include alterations in synaptic plasticity proteins [17,18], in glutamatergic receptors [19,20] and reduced number of parvalbumin and somatostatin-positive interneurons [114]. Also a reduction of Ki-67, a marker of adult neurogenesis, has been found in the dentate gyrus suggesting that proliferation of new neurons is reduced in schizophrenia [21,22]. And plausibly this reduction is associated with schizophrenia risk genes DISC-1 and NRG-1 [23,24]. Hippocampal neurogenesis is necessary for pattern separation [26], encoding of novel information [113] and cognitive functions in whole, because the giant glutamatergic contacts between mossy fibers of the DG and pyramidal neurons are essential for cognitive processes [1,27]. Diminished glutamatergic transmission from the dentate gyrus to the CA3 region has been confirmed by Kolo meets and Uranova by detection of decreased number of mossy fiber terminals on the CA3 neurons [25]. Additionally, reduced gene expression coding for proteins involved in metabolism of granular cells [94] and reduced NR-1 mRNA in the DG have been found [95,96].

Pathological changes in oligodendroglia has also been reported [112,118,119]. Kolo meets and Uranova have found a correlation between oligodendroglial pathology in the CA3 region and increased reactivity of microglia [118].

### 4. Tamminga's Model of Hippocampal Dysfunction in Schizophrenia

Above stated data allowed Tamminga et al. to formulate a model according to which reduced neurogenesis in the DG results in the impairment of pattern separation and in the reduction of the glutamatergic DG-CA3 transmission. Subsequent lowering of long-term potentiation in the CA3 region, hyperactivity of the CA3 neurons and predominance of pattern completion over pattern separation generate inappropriate associations, misinterpretation of events, false or illogical memories and susceptibility to psychosis [28].

In addition, alterations in the interaction between incoming bottom-up information and stored top-down information may bring to delusions and hallucinations. Enhanced bottom-up processing may underlie delusions, whereas prevalence of top-down processing based on memory may underlie hallucinations [29].

The dynamics of symptoms is a characteristic feature of the disease. In the early phases delusions are the main symptoms, hallucinations appear later. This may represent pathological changes going on in the hippocampus. Predominance of bottom-up processing triggers delusions. This may be caused by stressful events, since stress and cortisol increase glutamate levels and enhance glutamatergic transmission. Further, chronic sustained stress reduces adult

neurogenesis and causes protective remodeling (contraction) of hippocampal dendrites. Reduced glutamatergic transmission from the DG, due to reduced adult neurogenesis, may be considered as weakened bottom-up processing of information. In this case predominant pattern completion, as a consequence of the CA3 region hyperactivity, i.e. predominant top-down processing based on memory would impose structure upon weak signals and it may bring to hallucinations[116]. Perhaps, that is why sensory isolation alleviates psychotic symptoms in schizophrenia[30].

## 5. Stress and Hippocampal Dysfunction

The link between chronic psychosocial stress and schizophrenia has been repeatedly described by different authors[35,36,37,38]. Anterior hippocampus is involved in regulation of psychological stress reactions[33,34]. It has been shown that neurogenesis is susceptible to harmful effects of glucocorticoids[31,32].

Smaller hippocampal volumes were found in individuals with low self-esteem and external locus of control - a propensity to ascribe life events to external uncontrollable factors independent of individual's actions. The hippocampus inhibits activity of HPA axis and diminishes cortisol secretion. Low self-esteem and smaller hippocampal sizes are associated with higher cortisol levels. It is considered that the origin of low self-esteem in humans with small hippocampal volumes lies in poor ability of individuals to call to mind reassuring events of success and social acceptance - the strategy that helps individuals with high self-esteem to maintain positive mood and self-concept[39].

Additionally, hippocampus is involved in probabilistic forecasting[41,42]. Hippocampectomized mice fail to elaborate conditioned reflexes to the stimuli with low (25% and 33%) probability of reinforcement[40]. Considering that positive and successful events usually happen rarely, it is logical to suppose that small hippocampus performs poorer in memorizing and recollection of such seldom events.

Low self-esteem and psychosocial stress can lead to further reduction of the hippocampus because prolonged excessively high cortisol levels and hyperactivation of NMDA receptors promote hippocampal atrophy, reduction of the adult neurogenesis and can bring to different psychiatric diseases[32,45].

Moreover, Lodge and Grace have demonstrated that psychological stress and subsequent hyperactivation of NMDA receptors of the anterior hippocampus can result in enhanced activity of dopamine neurons in VTA and consequent psychotic symptoms. The authors suppose that disrupted dopamine system in schizophrenia is a result of the hippocampal hyperactivity[38].

Mostly, deleterious effects of cortisol on the adult neurogenesis were ascribed to such diseases as PTSD, depression and anxiety disorder. But the data on reduced neurogenesis in the DG in schizophrenia add complementary

bonds between stress and schizophrenia. Moreover a study of Reif has shown decreased proliferation of neural stem cells in schizophrenia but not in depression[22].

Basal cortisol levels have been found higher in schizophrenia patients. And acute cortisol elevation just before the psychotic episode has been observed [43]. Hyperactivity of the HPA axis has been found in unmedicated first episode patients[108] and before the onset of the first psychotic episode[115]. And high cortisol levels can trigger or exacerbate psychotic symptoms in individuals with inherited predisposition (neural diathesis) to psychosis [107].

Neurogenesis is already insufficient in patients with schizophrenia, perhaps, due to decreased BDNF levels[46]. It is known that BDNF is necessary for neurogenesis and synaptic plasticity. Thus, high cortisol levels can deteriorate neurogenesis and trigger first and following psychotic episodes in predisposed people.

In this connection, probably, interventions aimed at inhibition of the HPA activity and at improvement of the adult neurogenesis in the DG can enhance pattern separation, improve glutamatergic transmission from the DG to the CA3 region, inhibit pattern completion and as a result can arrest psychosis or at least bring some relief.

The highest cortisol levels are observed in response to uncontrollable and unpredictable stress, in the situations of uncertainty[45]. Social interactions may be stressful because they are often uncontrollable, unpredictable and uncertain.

Although blunted cortisol release in response to social stress has been reported in first episode drug naïve patients [117], this observation does not cancel the importance of psychosocial stress in triggering or exacerbating psychotic symptoms but rather points on disintegration of the hippocampal regulation of the HPA activity from the very early phases of the illness[44].

Above stated data suggest that individuals with schizophrenia are vulnerable to deleterious effects of stress. Perhaps, this vulnerability is caused by insufficiency of stress limiting mechanisms. There is a growing body of evidence that neurohormone oxytocin is also involved in these mechanisms.

## 6. Oxytocinergic Dysfunction in Schizophrenia

There are data indicating oxytocinergic dysfunction in schizophrenia[47,48,49]. Very often the disease begins with social phobia, anxiety, inability to make and to keep friends.

Impaired ability to discriminate facial emotions and maintain appropriate levels of trust are robust deficits in persons with schizophrenia[62] and are closely linked to their social dysfunction[63]. Recent studies demonstrate that oxytocin ameliorates deficits in emotion discrimination [61,64,98] and reverses altered social behavior in animal models of schizophrenia[65]. In humans, oxytocin

diminishes both cortisol and behavioral responses to stress, promotes trust[60], and facilitates attachment and social affiliation[66]. In addition, oxytocin level during pregnancy is positively correlated with the strength of attachment between mother and her child[99].

Social anhedonia, autism of schizophrenic patients may be caused by oxytocinergic dysfunction and bring to decreased need for social interaction and to reduction of positive emotions related to social interactions[60].

Interestingly, the symptoms of phencyclidine (PCP) induced psychosis reduce after complete social and sensory isolation[67]. Possibly, psychotic effects of PCP are also mediated by reduction in oxytocin release, because administration of exogenous oxytocin abolishes the effects of PCP[55].

An association between low self-esteem and oxytocin receptors gene has also been found[53] as well as a significant correlation between schizophrenia and oxytocin and vasopressin genes[54].

As mentioned above individuals with low self-esteem also have small hippocampal volumes and elevated cortisol levels in response to psychosocial stress.

The hippocampus expresses a lot of oxytocin receptors and oxytocin secretion is regulated by the same hippocampal projections that regulate the HPA activity[56]. Oxytocin increases the adult neurogenesis[124] even under conditions of stress and glucocorticoid administration, i.e. oxytocin protects the hippocampus from harmful effects of stress-hormones[50]. Possibly, increased adult neurogenesis is caused by oxytocin induced increase in BDNF secretion [51]. Caldwell et al. have demonstrated that oxytocinergic dysfunction leads to disturbances in glutamatergic NMDA transmission[55], perhaps, due to diminished neurogenesis as neurogenesis is essential for effective glutamatergic transmission and appropriate pattern separation processes [52]. Thus, oxytocinergic dysfunction may disturb processes of pattern separation and pattern completion, alter interaction between top-down and bottom-up processing and bring to delusions and hallucinations.

## 7. Oxytocin and GABA

Oxytocin can activate hippocampal interneurons and inhibit excitation of pyramidal cells[70]. Hyperexcitability of hippocampal pyramidal neurons in schizophrenia may be supported by the pathology of GABAergic parvalbumin containing interneurons which normally inhibit excessive excitation and provide synchronous firing of hippocampal cells in gamma oscillations[69].

As mentioned above oxytocin increases BDNF levels and BDNF is also necessary for maturation, migration and functioning of GABA-interneurons[71-74]. CA3 region expresses a lot of BDNF receptors[75]. This growth factor participates in regulation of synaptic plasticity and the lack of BDNF leads to cognitive impairments[76].

Interestingly, BDNF blocking in mice brings to reduction

of habituation to aversive stimuli[77]. Whereas schizophrenic patients also demonstrate decreased hippocampal habituation to aversive fearful faces[78].

## 8. Oxytocin and Neurodevelopment

Pregnancy and labor complications are also linked with schizophrenia. Appropriate oxytocinergic function is necessary during prenatal period. In immature brain during prenatal period GABA is an excitatory transmitter. GABA signaling regulates the cell cycle and migration and provides formation of primitive network in early development, thus facilitates organization of neural units. Excitatory action of GABA in immature neurons is determined by higher chloride gradient. Neuronal chloride homeostasis is controlled by the activity of several chloride cotransporters. Developmental changes in two cation-chloride cotransporters: accumulating chloride NKCC1 and chloride extruder KCC2, play a pivotal role in the maturation of CNS. Decreased expression of NKCC1 and simultaneous increased expression of KCC2 in GABA neurons results in gradual shift from excitatory (depolarization) to inhibitory (hyperpolarization) action[79]. The activities of these transporters (NKCC1 and KCC2) are in turn regulated by a network of serine-threonine kinases that include OXSR1, STK39 and the WNK kinases WNK1, 3 and 4. Expression of these regulators is altered in schizophrenia[121].

The excitatory-inhibitory shift in rodents is urged during the delivery by maternal oxytocin. Oxytocin induces rapid reduction of NKCC1 and exerts inhibitory action of GABA. This inhibition preserves neurons from pernicious effects of hypoxia. It is supposed that newborn analgesia in humans is induced by fetal oxytocin[122]. Thus, oxytocin insufficiency in newborns may bring to hypoxic damage of neurons.

Interestingly, in the adult DG GABA is also excitatory mediator for the newborn neurons due to their high intracellular Cl<sup>-</sup> concentration[123]. Perhaps, oxytocin in the adult hippocampus also participates in maturation and survival of new neurons by facilitating reduction of NKCC1. Oxytocin insufficiency may result in excitotoxic damage of immature granule cells especially during stress. This is another plausible mechanism of oxytocin mediated improvement of adult hippocampal neurogenesis.

Notably, the volumes of the olfactory bulb (the second area where adult neurogenesis has been discovered) are also reduced in schizophrenia[125]. Neurogenesis, migration and maturation of interneurons in the olfactory bulb are also regulated by NKCC1[127]. Additionally, in the hippocampal formation, GAD25/GAD67 and NKCC1/KCC2 ratios are increased in patients with schizophrenia, reflecting a potentially immature GABA physiology[126].

Reduction of hippocampal and olfactory bulb volumes may be caused by the pathology of oxytocinergic function, because oxytocin improves neurogenesis and regulates maturation of newborn neurons by reducing the activity of NKCC1.

## 9. Oxytocin and Metabolic, Immune Impairments in Schizophrenia

Schizophrenia is also associated with immune, metabolic and cardiovascular pathology[97]. Although metabolic syndrome is mostly related to side effects of antipsychotic therapy, it has been found that first-episode, drug-naive patients with schizophrenia already have impaired fasting glucose tolerance and they are more insulin resistant and have higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects[80].

Polydipsia and changes in water-salt metabolism are also frequently observed metabolic abnormalities in schizophrenia[81]. Diminished oxytocin plasma levels were found in polydipsic hyponatremic schizophrenic patients that correlated with reduced anterior hippocampal volumes and facial emotion recognition impairments[82].

Increased level of IL-6 has been found in blood and CSF independent of medication with neuroleptics[83]. Study of Ellman et al. showed a direct correlation between structural brain changes among the offspring diagnosed with schizophrenia and increase in maternal levels of interleukin-8 (IL-8), one of the proinflammatory cytokines produced when fighting infection during pregnancy[85]. Thus state of immune system in pregnant women also can contribute to brain changes of their offspring, for cytokines can cross the placenta.

Activated lymphocytes, increased levels of proinflammatory cytokines may also be the result of diminished plasma and central oxytocin levels. Clodi et al. have found that oxytocin slows down acute inflammatory process, reducing the secretion of TNF- $\alpha$ , IL-6, and IL-8. Oxytocin treatment resulted in a transient or prolonged reduction in plasma ACTH, cortisol, procalcitonin, TNF- $\alpha$ , IL-1 receptor antagonist, IL-4, IL-6, macrophage inflammatory protein-1 $\alpha$ , macrophage inflammatory protein-1 $\beta$ , monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein 10, and VEGF[50]. So, oxytocin also provides an anti-inflammatory effect.

Markers of inflammation such as TNF- $\alpha$ , IL-6, C-reactive protein, fibrinogen and others are also implicated in the pathophysiology of metabolic syndrome. Obese adipose tissue secretes various inflammatory cytokines, such as IL-6 and TNF- $\alpha$ [88] and dysregulated production of these proinflammatory mediators over the anti-inflammatory adipokine is thought to be a central mechanism underlying adverse metabolic and cardiovascular consequences. Inflammation is the key process underlying atherogenesis and vulnerability of atherosclerotic plaque to rupture. Activation of inflammatory pathways in adipocytes impairs triglyceride storage and increases release of free fatty acids, an excess of which is known to induce insulin resistance in muscle and liver[89]. Thus, altered oxytocin function and consequent decrease in anti-inflammatory cytokines may cause insulin resistance. Additionally, central infusion of this neuropeptide decreases blood pressure[91].

Pathological changes in oligodendroglia mentioned above

may also be caused by oxytocinergic dysfunction. Oligodendroglia is sensitive to deleterious effects of microglial inflammatory cytokines such as calprotectin which can cause dendritic atrophy[86,87,111]. Perhaps oxytocinergic dysfunction underpins increased microglial activity.

Additionally, obesity, one of the components of metabolic syndrome, is also associated with central and peripheral oxytocin dysfunction. Oxytocin and oxytocin receptor-deficient mice develop late-onset obesity with normal food intake, suggesting that this hormone might exert a series of beneficial metabolic effects. This was recently confirmed by data showing that central oxytocin infusion causes weight loss in diet-induced obese mice. Deblon et al. observed a dose-dependent decrease in body weight gain, increased adipose tissue lipolysis and fatty acid  $\beta$ -oxidation, as well as reduced glucose intolerance and insulin resistance[90].

## 10. Clinical Implication

Altogether these data suggest that oxytocin may be used as a medication for schizophrenia.

Clozapine increases oxytocin levels. It is known that clozapine has low affinity to dopamine and serotonin receptors, but nevertheless it is one of the best antipsychotics. Increase of oxytocin release may be one of clozapine's therapeutic effects[68].

First suggestion that oxytocin could be used in the treatment of schizophrenia was made in 1974. Intravenous and intramuscular oxytocin injection has been reported to be able to stop psychotic symptoms and to cancel a necessity of hospitalization[92]. But permeability of blood-brain barrier for oxytocin is low. And several studies with administration of intranasal spray have demonstrated positive effects (reduction of positive and negative symptoms)[100,101] and no significant side effects after 3 weeks of treatment[93].

But all studies were conducted on chronic patients. Early intervention for example in patients with first episode could be more beneficial while psychotic perceptions and illogical associations are still loose and reversible. Thinking is strongly biased by memory[103,109,110] and ideas, illogical associations, hallucinations after being fixed in memory may irreversibly alter the individual's model of the world, his mind and the way of reasoning.

Considering that the earliest symptoms of the disease are social phobia, anxiety and inability to make and to keep friends and bearing in mind the ability of oxytocin to facilitate social affiliation, to diminish stress responses to psychosocial stress, it is quite logical to suppose a strong possibility that oxytocin administration to individuals at ultra high-risk of developing schizophrenia may arrest the onset and progression of the disease.

## 11. Conclusions

Hippocampal pathology plays a great role in the

pathogenesis of schizophrenia. The hippocampus is susceptible to deleterious effects of stress. Sustained psychosocial stress in combination with inherited predisposition (small hippocampal volumes, oxytocinergic dysfunction, pathology of COMT, NRG1 or DISC1 genes, insufficiency of BDNF, hyperreactivity of dopaminergic system) can lead to hyperactivation of NMDA receptors, trigger delusions and worsen adult neurogenesis that is already insufficient. Subsequent impairment of glutamatergic transmission from the DG to CA3 region, hyperactivation of CA3 region, imbalance between pattern separation and pattern completion can bring to incorrect associations, hallucinations and false psychotic memories which would become salient due to the hyperactivation of dopaminergic system.

The very early stages before the onset are characterized by social phobia, anxiety, inability to make and to keep friends. Perhaps, these symptoms suggest that oxytocinergic dysfunction is the first manifestation of the disease as oxytocin is responsible for prosocial behavior, reduces anxiety and dampens stress reactions and HPA activity in response to psychological stress. Moreover, oxytocin increases BDNF levels, improves neurogenesis, improves glutamatergic DG-CA3 transmission and activates GABA-interneurons, hence there is a great possibility that oxytocin can arrest psychosis. It was demonstrated in several studies. But it is important to start the treatment as early as possible, even before the onset, before the illogical associations, delusions and hallucinations did not become fixed and memorized. Cognition, current state of the mind is strongly biased by past experience. Memorized and fixed psychotic experiences can irreversibly change individual's model of the world, mind and the way of reasoning.

Additionally, there is evidence that oxytocin may improve metabolic, cardiovascular and immune impairments in schizophrenia. Pathological changes in oligodendroglia may be caused by hypersecretion of microglial proinflammatory cytokines. It is also may be a consequence of oxytocinergic dysfunction, as it has been reported that oxytocin decreases secretion of proinflammatory mediators.

It is not clear whether oxytocinergic dysfunction is a cause or a consequence of hippocampal dysfunction, but if there is vicious circle then it does not really matter. Oxytocinergic dysfunction fits almost for every schizophrenia theory, such as psychological theories, neural-diathesis stress model, glutamatergic, GABAergic, neurodevelopmental theories.

Surely, oxytocinergic dysfunction may include not only quantitative insufficiency, but also impairments of oxytocin receptors or genes. But studies on oxytocin administration in schizophrenia that have been conducted so far, have demonstrated beneficial results. Considering all above stated there is a great possibility that administration of oxytocin to individuals at ultra-high risk of developing schizophrenia may prevent the onset of the disease. Preventive measures are particularly important for developing countries like Uzbekistan. Here, modern atypical antipsychotics are unavailable for most of the patients. For example, olanzapine

costs about 200 \$ whereas disability pension is about 100\$ per month. Although, psychiatric help is free of charge, hospitals lack for atypical neuroleptics and subvention for medications is about 1\$ for each patient per day.

## 12. Directions for Future Investigation

1) At clinical level it would be useful to investigate whether oxytocin administration to individuals at ultra-high risk of developing schizophrenia or to first episode patients can prevent/stop the onset/progression of the disease.

2) At morphological level it would be useful to investigate hippocampal changes in oxytocin knocked-out mice. Reduction of hippocampal volume, decreased number of mossy fibers, decreased expression of Ki-67, NRG1 or DISC1, increased reactivity of microglia, increased calprotectin levels, pathological changes in oligodendroglia would confirm the existence of oxytocinergic dysfunction in schizophrenia. As far as I know there have been no studies investigating the influence of oxytocin on the secretion of microglial cytokines, particularly on calprotectin secretion.

3) Oxytocin improves neurogenesis. One of the plausible mechanisms is oxytocin induced reduction of NKCC1 (Cl- cotransporter). This reduction may prevent immature neurons from excitotoxic damage. Investigation of the influence of oxytocin on the expression of NKCC1 and KCC2 as well as on the activity of serine-threonine kinases (OXSR1, STK39 and the WNK kinases WNK1, 3 and 4) in immature granule cells may add some valuable information.

4) The olfactory bulb is also reduced in schizophrenia, perhaps, due to dysfunction of NKCC1 as a consequence of oxytocinergic dysfunction. Increase of olfactory bulb volumes after oxytocin administration would have proved this supposition.

5) Suppression of the adult neurogenesis has been reported in mood disorders. Antidepressants improve mood and increase neurogenesis. It is difficult to maintain a positive mood without hope and anticipation of a positive outcome. Negative events happen much more frequently. And maintenance of the positive mood means expectation of the outcome with low probability. One of the accepted functions of the adult neurogenesis is an acquisition of new memories. But novel information is information that has never been encountered before. In probabilistic terms it means that novel event has low probability of repetition. Thus, it is logical to suppose that neurogenesis is necessary for processing and encoding of events with low probability of occurrence. Hippocampctomized mice fail to elaborate reflexes on stimuli with low probability of reward. It would be interesting to investigate whether knocking down of adult neurogenesis brings to the same failure. This would have elucidated some of the behavioral impairments in individuals with small hippocampus and low self-esteem.

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