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THERAPEUTIC POTENTIAL OF NEUROPEPTIDE OXYTOCIN IN THE TREATMENT OF PSYCHIATRIC DISORDERS

TERAPIJSKI POTENCIJAL NEUROPEPTIDA OKSITOCINA U TRETMANU PSIHIJATRIJSKIH POREMEĆAJA

Dušanka Stanić[1], Bojan Batinić[1], Marin Jukić[1], Vesna Pešić[1]

[1] Katedra za fiziologiju, Farmaceutski fakultet, Univerzitet u Beogradu / Department of Physiology, Faculty of Pharmacy, University of Belgrade

Correspondence to:
Dušanka Stanić
Katedra za fiziologiju, Farmaceutski fakultet, Univerzitet u Beogradu/
Department of Physiology, Faculty of Pharmacy, University of Belgrade
Vojvode Stepe 450, 11 221 Beograd
Tel: +381 63 361 774
e-mail: dstanic@pharmacy.bg.ac.rs

Ključne reči

oksitocin, psihijatrijski poremećaji, dodatna terapija, osovina hipotalamus-hipofiza-nadbubrežna žlezda

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Sažetak

Poremećaji raspoloženja se smatraju jednim od najvećih zdravstvenih problema današnjice, zbog njihove visoke prevalence, hroničnog toka bolesti, kao i značajnog negativnog uticaja koji imaju na sam kvalitet života pojedinca. Postojeći tretmani ovih bolesti često nisu efikasni, ne obezbeđuju potpunu remisiju simptoma, niti mogu sprečiti pojavu relapsa. Ni jedan novi lek već dugo nije uveden u terapiju poremećaja raspoloženja, što jasno ukazuje na potrebu za pronalaženjem neke dodatne terapije navedenih poremećaja, koja će povećati stopu pozitivnog odgovora pacijenata na terapiju prvog izbora i omogućiti bolju kontrolu simptoma bolesti. Oksitocin je hormone peptidne strukture, uglavnom najbolje poznat po svojim efektima nakon traktilnost uterusailaktaciju. Danas je jako dobro poznato da su receptori za oksitocin široko rasprostranjeni i u mozgu, tačnije u regionima uključenim u regulaciju reproduktivnog i majčinskog ponašanja, učenja i pamćenja, kao i u delovima mozga koji učestvuju u regulaciji odgovora organizma na stress i kontroli anksioznosti. Navedena saznanja postavila su temelje značajno obimnijih istraživanja koja su podrazumevala ispitivanje uticaja oksitocina na centralni nervni sistem, pre svega na ponašanje.

Ovaj rad obuhvata dosadašnje znanje o uticaju oksitocina na aktivnost osovine hipotalamus-hipofiza-nadbubrežna žlezda, socijalno i emocionalno ponašanje, kao i o ulozi koju ovaj hormone ima u modulaciji ponašanja, kako iz studija na životinjama, tako i iz studija na humanoj populaciji. Takođe, rad pruža naučno potvrđene kliničke implikacije koje dovode u razmatranjeu potrebu oksitocina kao dodatne terapije u tretmanu velikog broja psihijatrijskih poremećaja koje karakteriše prisustvo socijalne i emocionalne disfunkcije, kao što su anksiozni i depresivni poremećaji, post-traumatski stresni sindrom, autizam, šizofrenija i zavisnost. Međutim, sve ove studije još uvek su na samom početku, i veliki broj pitanja i dalje zahteva odgovore kako bi tretman oksitocinom kod navedenih poremećaja bio ne samo efikasan, već i bezbedan.

INTRODUCTION

Mood disorders, in particular depression and anxiety disorders are among the most prevalent of all psychiatric conditions. According to the World Health Organisation, it is assumed that mood disorders affect about 20% of young population, and are becoming the leading cause of working disability worldwide (1). Because of their high prevalence, chronic course of illness, and significant negative impact on life quality, associated comorbidity and increased risk of suicide, these psychiatric disorders are considered as one of the biggest health problems nowadays (2). Additionally, conventional treatments are often ineffective, cannot ensure that patients reach full remission of symptoms nor prevent relapses(3). Also, a promising new drug has not been established in a therapy of mood disorders for decades(3, 4). All abovementioned clearly indicates the need for finding some additional therapy in the treatment of various psychiatric-conditions,in order to improve patient response to the first line therapy, and ensure better control of the symptoms.

Oxytocinis a nonapeptide hormone mostly synthesized in the paraventricular andsupraoptic nuclei of the hypothalamus(5). The best known effect of oxytocin on uterine con-

tractions during labour was accidentally found in 1906. by Dale, in his experiments on pregnant cats[6]. Shortly afterwards, a stimulating effect on lactation was described. Amino acid structure of oxytocin was revealed in early 50´s, enabling successful synthesis of this hormone[7]. The only one known receptor for oxytocin (OxtR) was cloned in 1992. byKimura et al[8]. This receptor is a member of G protein coupled receptors family. Specifically, it belongs to class I receptors (also known as rhodopsin-like receptors), and it is linked to phospholipase C and formation of inositol trisphosphate (IP_3) and diacylglycerol (DAG) [9]. At the periphery, the presence of oxytocin receptors has been confirmed in the uterus [10], ovary[11], mammary gland[12], but also in the testis[13], prostate [14], kidney [15], heart [16], thymus [17], pancreas [18] and adrenal gland [19]. These findings gave presumption that there are some other functions of oxytocin beside his well-known effects on lactation and during labour, and laid the groundwork for significantly larger body of research. These researches, among testing the effects of oxytocin on the periphery, involved investigation of oxytocin effects in the central nervous system, especially on behaviour.

Effects of oxytocin on central nervous system

Oxytocin receptorsare widely, and species and gender specifically distributed in the brain [20]. It is shown that brain regions containingOxtR include the brain stem, neocortex, hypothalamus, amygdalae, nucleus accumbens and hippocampus[21, 22, 23]. Those regions which are rich in OxtR are involved in regulation of reproduction, maternal behaviour, learning and memory, and building self-confidence. Also, since OxtR are identified in brain regions important in regulation of stress response and anxiety[24], it is postulated that oxytocin could act as some kind of a modulator of social and emotional behaviour in various primate species and humans[25]. Oxytocinergic neurons in the central nervous system interact with various neurotransmitter systems, including GABAergic, dopaminergic, serotoninergic and glutamatergic circuits[26]. For instance, oxytocin modulates the release of serotonin in the *raphe nucleus*, so it is postulated that anxiolytic effects of oxytocin could partly be a result of modulation of serotoninergic activity. This finding provides new possibilities for therapeutic strategies, especially in the treatment of major depressive disorder and autism[26].

Effects of oxytocin on social and emotional behaviour

Oxytocin is often considered as a "social hormone", since a large literature data indicate its capacity to moderate social behaviours in various species, including humans [25]. In studies investigating effects of oxytocin on behaviour it is shown that reaction of organism to stress stimuli is mitigated after oxytocin treatment[27]. Oxytocin participates in chronic stress adaptation mechanism[28], exhibits antinociceptive effect[29], improves social recognition [30] and regulates social fears[31]. A positive correlation between saliva oxytocin levels during pregnancy and early post-partal period and level of mother and child bonding is confirmed[32]. On the other hand, plasma oxytocin level is in negative correlation with the levels of depressive symptomatology[33]. Nakajima et al. [34] identified the population of OxtR positive interneurons in medial prefrontal cortex of mice that are involved in the regulation of social behaviour. The blockade of those interneurons in female animals leads to a loss of interest for males during active phase of the cycle. The studies on OxtR knockout mice showed increased aggressiveness and behavioural changes that may be linked to autism, such as appearance of repetitive behaviour[35].

Effects of oxytocin on the activity of the Hypothalamic-Pituitary-Adrenal axis

There is a significant body of evidence about oxytocin effects on the adrenal gland. The adrenal gland is the main effector organ of the Hypothalamic – Pituitary – Adrenal (HPA) axis, which is highly activated during physiological response of the organism to stress. Oxytocin is considered as some kind of growth factor or so-called "peripheral modulator" of the gland [20]. It is shown that in rodents, treatment with oxytocin increased number of chromaffin cells in adrenal medulla, and led to changes in volume of different zones of the adrenal cortex [36, 37]. Additionally, this treatment increased the amount of adrenaline (A), noradrenaline (NA), dopamine and serotonin in the gland [37]. Also, in the animal model of chronic stress/depression induced by three weeks corticosterone treatment, oxytocin exerted a protective effect on the adrenal gland structure and function. In particular, oxytocin prevented atrophy of the gland induced by chronic elevated glucocorticoid levels, and exhibit a positive modulation of *Slc6a2* and *Slc18a2* gene expression, the genesthatencode two main catecholamine transporters in the gland medulla, noradrenaline transporter (NAT) and vesicular monoamine transporter 2 (VMAT2)[38]. Additionally, in abovementioned animal model, oxytocin decreased basal plasma concentrations of A and NA[38]. Similarly, it was shown that central administration of oxytocin to female rats affected basal plasma concentrations of adrenocorticotrophic hormone (ACTH) and corticosterone and significantly decreased the response of those hormones after exposition of animals to acute stress stimuli[39].

Variations in OxtR gene and its role in modulation of behaviour

Beside the fact that the structure of oxytocin, as well as OxtR is phylogenetically well preserved, their genetic structure and spatial expression indicate variations which are species-specific[40].These variations are commonly seen as genetic polymorphism, and several studies investigated the relationship between allelic variations of OxtR and different psychiatric conditions [41] such as anxiety disorders, anxiety-related personality traits and responsiveness to stress. Also, several variants of OxtR are linked to increased probability of autism manifestation, with the results highly dependent on the ethnicity of the study population[42, 43]. Additionally, occurrence of negative symptomatology, such as anhedonia, antisocial behaviour, depression, high stress scores and lack of motivation can be connected with specific OxtRvariants[44, 45]. Besides genetic variations, epigenet-

ic regulation of OxtR gene is linked to the social anxiety disorder phenotype, increased cortisol response to stress and increased activation of amygdala[46]. The results of those studies unveiled the potential associations between a genetic predisposition and behavioural phenotypes, and gave additional support about oxytocin influence in the aetiology of socio-emotional dysfunctions [25].

Clinical implication for oxytocin in treatment of psychiatric disorders

The behavioural role of oxytocin was examined in a variety of species including rats, mice and prairie voles [47]. Studies on animal models were the basis for investigating the role of oxytocin in manifestations of mood disorders in humans, such as anxiety disorders, depression, PTSD, autism and schizophrenia,which all encompass social anxiety as a component[47].

Because of its peptide structure, oxytocin cannot cross the blood-brain barrier and enter the central nervous system. However, in order to exhibit effects on behaviour and social functioning, it is necessary that oxytocin reaches appropriate regions of the brain, and in that manner, intravenous and oral administration are considered ineffective. So far, intranasal administration has been the most common way of oxytocin delivery in humans [47]. Intranasally applied oxytocin promotes various aspects of social behaviours such as trust, social recognition, communication and attachment in healthy volunteers [48]. It still remains unclear how neuropeptides reach the central nervous system *via* the nasal route [49], but several studies reported that concentration of oxytocin in brain increased after intranasal administration[50, 51]. It could be that neuropeptides, such as oxytocin and vasopressin, pass the nasal epithelium and undergo retrograde transport trough the olfactory or trigeminal nerves, or reach subarachnoid space and diffuse from there into the brain [52] suggesting a direct nose-to-brain route. Also, it must not be ruled out that oxytocin applied intranasally exerts its effects via peripheral action, since OxtR are widely distributed through the body. It is suggested that in that way, the final effect of peripheral OxyR activation could be increased release of endogenously secreted oxytocin in the brain [53].

Numerous studies have examined the effects of intranasally applied oxytocin, as an additionaltreatment, in various psychiatric disorders affecting social functioning such as general and social anxiety disorder, depression, schizophrenia, autism and posttraumatic stress disorder. Oxytocin treatment inhibits the activity of neurons in the amygdala which are highly active in a response to social threats and fear [54]. Those neurons are connected to other brain regions associated with fear, such as cingulate cortex and medial prefrontal cortex. In that manner, oxytocin decreased activity of brain structures which were hyperactive in individuals with social anxiety disorder [55]. In addition of dampening activity of abovementioned pathways related to fear response, oxytocin heightens activity of brain regions associated with social and emotional behaviour, thus normalizing the activity of both pathways[56]. As an adjunct to exposure therapy, compared to placebo, oxytocin showed significant symptom reduction, improved positive evaluation of appearance and speech performance in individuals with social anxiety disorder [57]. Thus, oxytocin as an additional therapy may improve quality of life by reducing some of social anxiety disorder characteristics. Intranasally applied oxytocin reduced cortisol levels during stressful laboratory tasks that had a social-evaluative component[58], although no effects on basal cortisol levels in the absence of acute stressor was observed[59]. This finding leads to the conclusion that anxiolytic effect of exogenous oxytocin is amplified by a social cue, which is in accordance with the fact that under the stress-free conditions, the basal oxytocin activity is low and is increasing in the terms of social fear[60].

Depressive disorders are complex disorders and patients often experience impairments which disable them in everyday life functioning, such as reduced social behaviour and anxiety. Scantamburlo et al. [61] reported a significant negative correlation between plasma oxytocin levels and the severity of depressive and anxiety symptoms estimated with appropriate rating scales. Additional intranasal treatment with oxytocin to escitalopram for four weeks significantly reduced scores on Hamilton Depression Rating Scale in patients with treatment-resistant depression[62]. In mothers with postnatal depression (PND), treatment with oxytocin increased the quality of relationship with their babies, as relationship was rated more positive by mothers [63]. Also, after oxytocin administration PND mothers showed more protective behaviour regarding their baby in the presence of a stranger [64].

Repeated administration of oxytocin is shown to be a promising early preventive intervention for post-traumatic stress disorder (PTSD), owing to its reconsolidation blocking effects[25]. In particular, systemic oxytocin administration impaired reconsolidation of social fear memories after learned fear reactivation [65]. However, an important factor affecting the effectiveness of oxytocin administration is the timing of the initiation of the treatment with oxytocin relative to the cue presentation, as well as the nature of the threat itself (social vs. non-social) [66].

So far, treatment for schizophrenia is primarily used to control positive symptoms, leaving the negative symptoms such as asociality and affective flattening uncontrolled. Since the severity of these negative symptoms is strongly correlated with decline in social function and quality of life, there were some attempts to mitigate this negative symptomatology of schizophrenia [47]. Intranasally applied oxytocin as additional therapy to conservative antipsychotics showed improvement in negative symptoms in patients with schizophrenia and demonstrated an overall decrease in both negative and positive symptomatology scores [67, 68]. More precisely, those improvements consider increased high-level social functioning such as detection of deception and empathy, and enlarged ability to recognise other people emotions [69].

Another developmental disorder characterized with multiple social domains dysfunction is autism. People with autism exhibit decrease in social motivation and social relationship award with a difficulty in maintenance of social relationships, social reticence and lack of eye contact[70].

Also, recent studies support association between autism and schizophrenia as similarities in neurological, genetic, developmental and molecular substrate of these disorders are observed[47]. Administration of oxytocin in persons with autism increased eye gaze, enhanced feeling of trust, increased recognition of affective speech and increased scores on the Reading the Mind in the Eyes Test [71, 72].

It is proven that early life trauma has strong association with vulnerability for substance abuse and development of addiction later in life[73]. Recent studies linked these negative, stressful experiences in early life with changes in development of oxytocinergic system, so treatment with oxytocin could be beneficial and reduce drug-taking behaviour [73]. Those studies have proven the hypothesis that oxytocin could be a promising therapeutic agent for human addiction, especially for alcohol use disorders [74]. Preliminary trials have shown that intranasally applied oxytocin blocked withdrawal and reduced alcohol consumption in heavy drinkers, by the novel mechanism of diminishing established tolerance [74]. It is well known that oxytocin attenuates the reaction of the organism to stress such as heightened anxiety and activation of HPA axis. Those mechanisms underlie the phenomena that occur during substance abuse, withdrawal and abstinence [58, 75] (Cardoso et al., 2014; Koob, 2015). It is hypothesized that anxiolytic, antistress and inhibitory effects of oxytocin on established tolerance could be promising treatment in reducing negative reinforcement or so-called Koob's "dark side" of addiction observed during chronic substance abuse[74].

Another disorder which differs from the other abovementioned psychiatric disorders, but has social impairment as its marked component, is anorexia. As oxytocin is hormone that exhibit effects on food consumption, it is shown that treatment with oxytocin in patients with anorexia significantly decreased attentional bias for eating and negative body image stimuli[76]. This field requires further investigation and so far a relatively few studies regarding effects of oxytocin in patients with anorexia nervosa are published.

CONCLUSION

Numerous studies generally highlight neuropeptides, such as oxytocin, as a very interesting additional therapy for treatment of a large number of psychiatric disorders characterized by emotional and social dysfunction. However, those studies are still at their early beginning, and there are various issues that need to be solved in order to establish oxytocin as not only effective, but also a safe treatment option. At first, until now, oxytocin has not been reported to produce some serious side effects. Still, certain changes in the activity of cardiovascular, gastrointestinal and central nervous system, as well as changes in metabolism and anaphylactic reactions cannot be ruled out. Also, in order to establish standardized treatment protocol, and full effectiveness of treatment, adequate dosage, route of administration, treatment duration, interval of administration and best timing of starting the treatment with oxytocinneed to be optimized and defined for each disorder particularly.

In summary, current research provides evidence that make oxytocin highly attractive as a potential novel therapy for multiple psychiatric disorders such as anxiety, depression, PTSD, addiction and autism. Future implications will certainly include investigations regarding neurobiological mechanisms of action, as well as finding a reliable tool to access changes in patient's symptoms after treatment with oxytocin.

Abstract

Mood disorders are considered as one of the biggest health problems nowadays, because of their high prevalence, chronic course of illness and significant negative impact on life quality. Conventional treatments are often ineffective, cannot ensure full remission of symptoms nor prevent relapses. In the therapy of mood disorders a new drug has not been introduced for a long period of time, which clearly indicates the urge for finding some additional therapy that would improve patient response to the first line treatment, and ensure better control of the symptoms. Oxytocin is a nonapeptide hormone mostly known by its effects on uterine contractions and lactation. Today, it is well known that oxytocin receptors are widely distributed in the brain regions involved in regulation of reproduction, maternal behavior, learning and memory, as well as stress response and anxiety. Those findings laid the groundwork for significantly larger body of research that involved investigations of oxytocin effects in the central nervous system, especially on behaviour.

This paper summarizes "up to date" knowledge about oxytocin effects on the Hypothalamic-Pituitary-Adrenal axis activity, social and emotional behaviour, as well as its role in the modulation of behaviour from both, animal and human studies. It also provides scientifically proven clinical implications about considering oxytocin as additional therapy in the treatment of a large number of psychiatric disorders characterized by social and emotional dysfunction such as anxiety disorders, depression, post-traumatic stress syndrome, autism, schizophrenia and addiction. However those studies are still at their early beginning, and various issues need to be solved in order to establish oxytocin as effective and safe treatment option.

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