Role of Oxytocin in Psychiatric Pathology

Tomás Serón-Díaz[1], Juan Pablo Osorio-Munizaga[2]

Oxytocin is a neuropeptide. In mammals it has a significant role at different reproduction stages and in socialization behavior. In humans, its importance has been recognized in social regulation processes, such as social memory, affiliation, awareness and empathy. This Articles is aimed to make an updated review of the evidence about the role of oxytocin in psychiatric pathologies. A bibliographic search was made about this topic by using data bases, such as Medline/PubMed and SciELO. Results show evidence about the possible etiopathogenic role of oxytocin in various clinical scenarios. Additionally, research has looked for responses in this hormone in order to understand the various profiles of symptoms, such as emotional regulation, emotions recognition, awareness capability and response to stress, which could be part of potential therapeutical uses of oxytocin. Even though data are emerging and not too conclusive, oxytocin has become a primary focus of neurobiological/ therapeutical study in future psychiatric research.

Keywords: *oxytocin, socialization, affective regulation*

INTRODUCTION

Oxytocin is a primary neuropeptide in mammals' life. It regulates reproductive functions, uterine functions in labor, milk ejection and the maternal behavior[(1)]. Additionally, its relevance has been proved in socialization behavior, such as playing, grooming and sexual behavior in experimental models.

It has a primary role in human social regulation processes, such as response to stress, social anxiety, consolidation of social memory, affiliation and attachment, emotions recognition, awareness and empathy processes. All these areas may be disturbed in a certain degree in various diagnoses, such as autism, depression, schizophrenia and borderline personality disorder, among others[(2)]; therefore, homeostasis of the oxytocinergic system plays a primary role in these disorders[(3)].

This review is aimed to describe oxytocin role in the most significant psychiatric diagnosis from the evidence in experimental models till clinical findings leading future pharmacotherapeutics interventions.

Depression

It is described in depression, social dysfunctions, anxiety symptoms and deregulation as a response to stress. Oxytocin role[(4)] is added to

The authors declare that they have no conflicts of interest with respect to this article.
Accepted: 2021/03/06
Received: 2020/07/06

[1] Psychiatrist of Adults, Professor Instructor - Faculty of Medical Sciences - Universidad de Santiago de Chile.
[2] Adults Psychiatrist, Department of Psychiatry & Mental Health, Universidad de Chile – Sede Sur

monoaminergic hypothesis, hypothalamic-pituitary-adrenal axis, deficit in certain growth factors and proinflammatory disorders. Various studies describe increasing levels of plasmatic oxytocin in depressive patients and an increase of this hormone as a response before stress situations. Because of the aforementioned Cyranowski JM et al. analyzed the difference in regulation of the plasmatic release of oxytocin as a response to two specific tasks: one task led by imagery led to attachment bond (modified version of Ekman's Relived Emotions Task) for causing affective emotions and one aimed to cause a psychophysiological response regarding certain stressful situations (Speech Stress Task). These Authors found that depressive patients had higher levels of variability in plasmatic oxytocin measurements during execution of both tasks compared with the non-depressed control group[5]. After hour measurement of the hormone, depressed patients have been reported to have higher oxytocin levels that healthy subjects (especially at night), with no significant differences in the measurements of arginine-vasopressin and cortisol[4]. In the same line, a Japanese article made with adolescent population studied the serum levels of depressive patients with resistant depression, comparing them with non-resistant depressive patients and healthy control groups. The first group was found to have significantly higher levels of neuropeptide, which was correlated with depression in the family, activation with antidepressants and recurrent depression. However, no statistically correlation was found between the levels of serum oxytocin and severity of symptoms, measured by scales (CDRS-R and DSRS-C-J[6]. This oxytocin increase in depressive patients has not been consistently proved in other works. For instance, in the study of Ozsoy et al. which, in a sample of hospitalized depressive patients subject to antidepressive treatment or electroconvulsive therapy ECT, found low oxytocin levels, both before and after treatment. Additionally, a gender difference was observed. Depressive men do not differ from the control group regarding in the plasma oxytocin levels, while in women these levels are significantly lower compared with the control group[7]. On the other hand, a directly proportional correlation has been reported among oxytocin levels and more functional coping mechanisms and better perception of social support in depressive patients, which would improve psychosocial response to stress[8]. Regarding postpartum depression, no correlation has been found among this clinical picture and intrapartum exposure to synthetic oxytocin, after the evaluation made with the Edinburgh postnatal depression scale, from 8 to 12 weeks[9], although other works state its protecting role in the midterm[10].

Regarding use of oxytocin in mood regulation processes and response to stress, in studies of functional images in depressive women when exposed to certain facial expressions[11] intranasal oxytocin administration -in a single dose- has proved to increase activation of brain regions associated to emotions, such as the cingulate cortex and the insula. In an open study administration of intranasal oxytocin, in resistant outpatients, concomitant to 8 weeks, with 40 mg of Escitalopram has also been reported to significantly improve symptomatology, according to Hamilton´s Scale, after 4 weeks of treatment. Anxiety symptoms, functionality and quality of life (STAI-A State, CGI-S and Q-LES-Q)[12] improved as well. The information available still does not allow therapeutical use of oxytocin, but preliminary studies have positions oxytocin as a potentially significant component for understanding underlying depression mechanisms and its potential pharmacological use.

Schizophrenia

Schizophrenia is a pathology causing impairment, leading to significant functionality loss, mainly on social cognition. Antipsychotics have a better response on positive symptoms; however, negative, affective and cognitive symptoms still do not have an effective treatment. Plasma levels of this hormone have been reported to have an inverse correlation with severity of the symptoms, especially with cognitive and negative symptoms; however, in other research works, consistency of this statement has not been supported. Additionally, antipsychotic role in plasma levels of this neuropeptide[13] is not clear. A study relates the function of supraoptic/paraventricular oxytocinergic nuclei with the use of antipsychotics[14]. Oxytocinergic dysfunction has also been recognized as one of

the mechanisms involved in the metabolic syndrome of psychotic patients, as in the case of schizophrenia[15].

A study made in chronic schizophrenic patients who received intranasal oxytocin (40 UI) twice a day) for 3 weeks in concomitance to their antipsychotic treatment, reported a clinical recovery, both in the Positive and Negative Symptom Scale and in the Clinical Global Impression-Improvement Scale[16]. Oxytocin effect on emotional expressiveness of schizophrenic patients has been studied, apart from reliability on facial expressiveness compared with healthy controls. The study was made by using pictures with emotionally evoking expressions. Results proved a significant improvement in facial expressiveness as a response to images with emotional content but did not improve reliability[17]. Oxytocin and galantamine effectiveness have been compared in improvement of negative symptoms and on cognition, but there is no evidence of a significant improvement neither when using intranasal oxytocin nor with oral administration of galantamine, in any of the two areas evaluated, compared with the group who received a placebo[18].

A work performed with 32 schizophrenic patients who used antipsychotic drugs, assessed effectiveness of intranasal oxytocin as an increasing mechanism. The study had an interlocked design. One group self-injected oxytocin -every day- in a single dose (40 UI), for 4 months; the other group only had placebo. After one week of drug cleaning, the oxytocin/placebo injection was exchanged. By assessing positive and negative symptoms using PANSS patients were found not to get any improvement neither in negative symptoms nor on positive ones[19]. A meta-analysis performed in 2017, found no improvements in any dysfunction area of schizophrenic patients[20].

Borderline Personality Disorder

Patients with borderline personality disorders have well known difficulties in their attachment/connection relationships and in their interpersonal interactions. In this sense, an association of this disorder with oxytocin levels has been searched, thinking about the role it would have in social behavior and in affective regulation. Oxytocin has been reported to regulate response to affectional stimulus, apart from modulating emotional regulation, by means of its action on the amygdala, dorsolateral prefrontal cortex (DLPFC) and dorsolateral ventromedial cortex. Additionally, it acts on facial recognition of emotions, especially when there is a negative bias[21]. The importance of regulation of oxytocin genes of expression, genes of oxytocin receptors and regulator genes of the expression of this hormone in social behavior has also been stated. A polymorphism of oxytocin receptor gene with two social processes, which favor social interaction was associated: i.e. empathy and reactivity to stress[22]. A double blind/randomized/placebo controlled study analyzed attentional bias when looking at angry/happy faces. Infantile trauma record was assessed as well. Results reported that patients with borderline disorder had attentional preference to angry faces, which is directly correlated with their child abuse record. This response was eliminated with oxytocin administration[23]. Bertsch et al. evaluated threatening hypersensitivity before social stimulus; therefore, a randomized/double blind/placebo controlled study was made, where 26 UI of intranasal oxytocin were injected, 45 minutes before an fMRI was taken, and after that facial expressions images were displayed. Results proved that borderline patients have a faster fixation and have a preference for angry faces, with a lower response latency. This is directly related with the amygdalin activation level observed in the images. These findings were reverted when intranasal oxytocin was injected. Results of this experimental research could represent a new treatment approach for addressing patients with this personality disorder.[24].

Post-Traumatic Stress Disorder

High rates of people exposed to psychological trauma events have been described, which range from 70% to 90%. Additionally, PTSD life prevalence ranges between 7% to 8%. Therefore, it is quite relevant to develop strategies aimed to prevent complications derived from these traumatic situations. During the last few years preventive interventions have been developed, based on use of intranasal oxytocin, after a trauma experience, based on its neuroendocrine effects, by regulating the hypotha-

lamic-pituitary-adrenal axis and the autonomic nervous system. A controlled/randomized study investigated the effects of 120 ml of intranasal oxytocin. 3 doses were divided and used on people exposed to psychological trauma. Reduction of PTSD symptoms were evaluated 45 days after exposure. The group who received intranasal oxytocin obtained 9.32 points less in the Clinician-Administered PTSD Scale, compared with the control group who received a saline solution. These results are statistically significant[25]. In another controlled/randomized study performed on police officers, with/with no PTSD, the effects of a single dose (40 UI) of intranasal oxytocin was analyzed, regarding the subjective anxiety response and activation of the connections of the amygdala with the frontal cortex. Such response was measured by an fRMI. Two fMRI sessions were performed. During the first session, oxytocin was injected; for the second session, a saline solution was injected. Male subjects under study reported a lower functional connectivity between the right centromedial amygdala and the medial/ventromedial prefrontal cortex. This situation improved after oxytocin administration. In case of women, high connectivity was observed between the right basolateral amygdala and the right anterior cingulate cortex. This situation was reverted when this neuropeptide was injected. These findings were directly correlated with reported anxiety levels[26]. The effects of intranasal oxytocin in reducing PTSD symptoms in female population exposed to psycotrauma has been analyzed. Its results reported a reduction in measured symptoms, according to the Scale "Responses to Script-Driven Imagery", which evaluates three symptoms sets: avoidance, re-experimentation and dissociation. However, only for the item avoidance, this symptomatic improvement was statistically significant. This study has some limitations, as it is a small sample (35 women), apart from comorbility and use of psychopharmaceuticals[27]. Another group of police officers exposed to trauma was studied. By using fRMI, administration of 40 UI of intranasal oxytocin was found to improve response of the left anterior insula and right putamen, regarding response before social rewards, against the placebo. In this way, oxytocin administration was found to favor therapeutic alliance and social support impression[28].

Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a highly prevalent neurodevelopment disorder, whose main symptoms include social interaction/communication deficits, apart from restricted/repetitive behavior, which causes significant impairment in these people and their families quality of life. However, no pharmacotherapy has been found to improve these main symptoms. In this sense, as higher levels of this hormone would favor prosocial behavior, oxytocin has become a potential therapeutical target, especially for conduct/social regulation symptoms and social cognition. Possibly, this prosocial role is mediated by regulation histaminergic; however, these are only preliminary findings[29]. Plasmatic oxytocin levels and the differential expression in different brain areas of the oxytocin receptor account for social dysfunction variability, not only in ASD patients, but also in non-ASD siblings and healthy controls, with high hereditability, thus proving oxytocin role in social functioning, beyond this disease[30].

Basal plasma concentration of oxytocin may play a significant role in clinical response to intranasal oxytocin administration. High functioning ASD men have been reported to have a higher level of plasmatic oxytocin. Additionally, a higher level of basal oxytocin has been reported to be a predictor of better improvement rates in social performance, especially in ASD group. On the other hand, persistence of a high level of oxytocin, after its exogenous administration, was reported to be a predictor of a lower response to further oxytocin administration[3].1 In a randomized/double blind/placebo controlled/crossed study, including 20 high functioning adult ASD males who were injected with intranasal oxytocin (24 UI, twice a day) for 6 weeks, reported a significant reduction of social reciprocity symptoms. This test was evaluated with the Autism Diagnostic Observation Scale. This finding was correlated with an improvement in the right anterior cingulate cortex activity, and activity of the dorsomedial prefrontal cortex, analized with an fMRI[32].

In a group of male youngsters between 12 to 19 years old who received intranasal oxytocin (18 UI for youngsters between 12 to 15 years

old; 24 UI, between 16 to 19 years old), the administration of this substance in a single dose was reported to improve performance of the subjects after application of the Reading the Mind in the Eyes Task, widely used for studying emotions recognition[33]. An Australian study analyzed the effects of intranasal administration of oxytocin in youngsters between 12 to 18 years old, 18 or 24 UI (according to age) twice a day, for 8 weeks. Social functionality scales were applied, apart from reporting subjective observations of the caretakers on conduct aspects and on social cognition. Results did not account for a significant improvement in ratings of these scales, but the subjective perception by the caretakers turned out to be significantly better compared with the start of the study process[34]. In boys between 6 to 12 years, intranasal oxytocin administration (24 UI twice a day) for 4 weeks, reported improvements in Social Responsiveness Scale rate, with good tolerance. Basal levels of plasmatic oxytocin were a predictor for the response to this pharmacological intervention (those with a lower basal level of this hormone had better results[35]. Other meta-analysis found contradictory results regarding improvement of social cognition after oxytocin administration, thus suggesting that findings have been little consistent, but this could be due to main factors (age, sex, cognitive functioning level) and sample biases. The approach states if there is any social cognition inference, this would be differential, but not significant[36]. These findings seem to be incipient, but promissory and are aimed to find an effective therapy for social deficit in ASD patients; therefore, further/more standardized/ wider studies must be performed, aimed to get more significant results with clinical implications in the future.

CONCLUSION

Oxytocin role in social functioning and in links formation has posed an interesting neurobiological approach model regarding psychiatric pathology. That is why we have witnessed a neurofunctional correlation between structures associated to social behavior and oxytonergic regulation. Additionally, the potential pharmacological usefulness of oxytocin for various psychiatric conditions has been discussed; however, data available so far is not consistent enough to confirm its therapeutical role. Although these studies have proved certain clinical usefulness, the data are neither fully conclusive nor generalized. We still have to study some aspects, such as sexual dimorphism of oxytocin gene expression and its clinical influence, standardization of the necessary/safe dosage for treating certain psychiatric pathologies, safety and adverse effects in the long term, etc. However, a promissory area is opened for clinical research.

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Correspondence to:
Dr. Tomás Serón Díaz
Address: Community Mental Health Center, Santiago, Vicuña Mackenna Street 543, Santiago Downtown, Metropolitan Region
E-mail: tserond@gmail.com