

UNDERSTANDING THE IMPORTANCE OF OXYTOCIN IN DEPRESSION

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ABSTRACT

The current progress in the understanding of depression has lately shifted from the classical monoaminergic hypothesis to other mechanisms and molecules, which seem to be involved in depression, including the inflammation theory, immunological aspects, hypothalamic–pituitary–adrenal axis, oxidative stress status and lately oxytocin. Thus, the importance of oxytocin in psychiatry is increasing and many recent studies have been discussing the possible relevance of oxytocin in most of the psychiatric disorders, including depression. Furthermore, the latest studies

brought to attention the notion that oxytocin might be involved in many mechanisms of importance in depressive disorders. These include its solid connections both with neurotransmitters and the clinical markers relevant for depression, such as affected sleep and sexual functions, appetite loss, cognitive impairment or suicidal behavior. In this context, the present paper reviews the current knowledge on the connection between oxytocin and depression.

Keywords: Oxytocin, depression, neurotransmitters. Nobel Med 2017; 13(3): 5-11

DEPRESYONDA OKSİTOSİN'İN ANLAM VE ÖNEMİ

ÖZET

Depresyonu anlamada şu anki gelişmeler klasik monoaminergic hipotezden, enflamasyon teorisi, immunolojik bakış, hipotalamik–hipofiz–adrenal aks, oksidatif stres durumu ve en son olarak oksitosin gibi depresyona dahil gibi görünen mekanizma ve moleküllere kaymıştır. Bu nedenle oksitosinin psikiyatrideki önemi artarken, depresyonun da dahil olduğu birçok yakın zamanlı çalışma, çoğu psikiyatrik

hastalığın oksitosin ile olası alakasını incelemektedir. Daha ötesi son çalışmalar depresif hastalıkların önemli birçok mekanizmasında oksitosinin dahil olabileceğine dikkat çekmektedir. Bunlar hem nörotransmitterler, hem de depresyonla ilişkili klinik bulguları, örneğin uyku ve cinsel fonksiyonlarda bozulma, iştah kaybı, kognitif fonksiyonlarda bozulma, intihara eğilim gibi güçlü bağlantılar içerir. Bu çalışmada depresyon ve oksitosin arasındaki mevcut bilgi gözden geçirilmektedir.

Anahtar kelimeler: Oksitosin, depresyon, nörotransmitterler. Nobel Med 2017; 13(3): 5-11

INTRODUCTION

The classical view of oxytocin (OXT) as a hypothalamic neuropeptide, of importance in physiological birthing and lactation, is rapidly advancing now, as modern biological studies are confirming that OXT has also extra-hypothalamic cerebral sites of production and could be involved in many other central processes related to psychiatric conditions such as depression, autism, anxiety or schizophrenia.¹

So, how did OXT become an important target in psychiatry research? The extensive use of OXT in obstetrical settings and the particularly observed effects of OXT during maternity had led the research into further investigation of OXT, speculating extra-obstetrical uses. Thus, in different experimental settings, OXT was generally found to have a pro-social effect, positively modulating behaviors related to social interactions including trust, establishing relationships, partner choosing, empathy, affiliation, social cognition and stress modulation.² Furthermore, considering the impaired psychosocial functioning usually found in depression, connections between affective disorders and OXT were speculated.

Thus, studies on the relevance of OXT in psychiatric disorder are now rising, bringing more evidence that connect OXT to psychiatric processes and particularly to mood disorders. It has been suggested that the disruption of central OXT activity may have important consequences in mood modulation and direct or indirect impact in several psychiatric disorders, such as unipolar depression, bipolar disorder, anxiety, or autism spectrum disorder.¹

Currently, the knowledge on the OXT system relevance in depression is rather scarce, but there are still encouraging positive data provided by studies on human or animal models of depression and ongoing studies are trying to establish the place of OXT in depression.^{3,4}

Clinical Aspects For The Relation OXT-Depression

As previously mentioned, lately there is an increased interest in the possible connections between OXT and depression, including the vulnerability for some individuals to develop depression. For example, one study that analyzed the involvement of OXT receptor variability in stress resilience for people with AA OXT receptor genotype, found that low level of peripheral OXT is positively correlated with neuroticism score and dopamine transporter availability.⁵ These results suggest that the involvement of OXT in the way the organism reacts to stressful conditions may be explained by the correlations between OXT and the

dopaminergic system. Moreover, other studies support the idea that individuals carriers for the A allele of the OXT receptor are more likely to be socially impaired, when compared with G genotype individuals, who may be more resilient to stress.⁶ These studies confirm that the variability in OXT receptor may increase the risk for depression, by favoring a specific biological pattern of increased sensitivity and reactivity to stress.

It is well known that the diagnosis of depression is based exclusively on clinical criteria, particularly considering the fact that currently there is no biological diagnostic marker for this disorder, but also taking into account the importance of clinical symptoms in depression.^{7,8} Thus, we will analyze subsequently the relation between OXT and the most frequent clinical symptoms found in depression, such as affected sleep and sexual functions, appetite loss, cognitive impairment or suicidal behavior.

Regarding sleep disturbances, which is certainly an important clinical feature of depression, recent data showed that OXT might actually have a sleep inductor effect. The connection of OXT with sleep could be explained via the hypothalamic–pituitary–adrenal (HPA) axis, which is also known to be involved in depression. However, studies on animal models showed that OXT might have a dual mechanism of action, depending if there is a stress condition or a stress-free setting. In this manner, in stressful conditions, direct intracerebral administration of OXT and an OXT antagonist, into the lateral ventricle of rats, promotes wakefulness.⁹ Also, administration of exogenous OXT seems to modify the sleep pattern, by decreasing REM sleep and increasing high-frequency activity in the electroencephalogram, suggesting an overall augmentation of the arousal state.⁹ On the other hand, in a basal state, subcutaneous administration of OXT in high doses to rats will promote sleep, by decreasing the locomotor activity and rearing behavior.¹⁰ Thus, evidences of differential OXT implication in sleep, depending on the presence or absence of stress, are confirming the connection between OXT and the stress system, suggesting a possible implication of OXT in the sleep alterations found in depression.

In addition, the appetite loss accompanied by weight decrease is a very important clinical marker found in depression, recent evidences suggesting that leptin may also be involved in the process.¹¹ But it also seems that OXT of hypothalamic origin can be an anorexigenic hormone that could diminish food intake, increase energy consumption and lower the overall body weight.¹² Moreover, exogenous OXT produces a decrease in food intake, while the administration of an OXT antagonist is associated with increased food consumption.¹³

In fact, the level of OXT was investigated in anorexia nervosa and results from specific studies showed differential patterns of OXT secretion, depending on the presence or the absence of the food stimulus. Accordingly, a study published by Lawson *et al.* in 2011 found that during night time (e.g. fasting) the OXT level decreases in anorexic patients, while in the context of food intake there is a significant increase in the OXT level in patients with anorexia, when compared to healthy individuals.¹⁴ This differential way of action may be interpreted as a possible appetite regulator function of OXT.

Furthermore, genetic studies showed that specific nucleotide polymorphisms in the OXT receptor and OXT gene are associated with higher eating disorder intensity and increased severity of other psychiatric symptoms in patients with anorexia and bulimia.¹⁵ Also, other data showed that the level of endogenous OXT is directly correlated with the severity of anxiety and depression symptoms of an anorexic group.¹⁶

There are also recent evidences of significant correlations between OXT and leptin, an important hormone which is a very promising target in studies regarding obesity.¹² In this way, further studies need to analyze the possible connection between OXT, depression, appetite loss and leptin, considering that leptin could be an important connector between depression and anorexia.

Concerning sexual function, depressed patients demonstrate significant disturbances in every phase of their sexual response cycle, starting with arousal, plateau, orgasm and resolution, in both men and women.¹⁷ On the other hand, OXT is well known for exerting important roles in the reproductive behavior, including pair bonding and monogamy, while recent data also showed that OXT is directly involved in sexual function.^{18,19} Several reports regarding positive direct OXT impact on penile erection were provided by Melis *et al.*, together with other isolated positive case reports.^{18,20} Although data regarding OXT in sexual function exists, the role of OXT in the sexual function is not yet fully understood, and further studies clearly need to investigate the possible link between the sexual impairment in depression and OXT.

In addition, suicidal behavior is the most severe symptom of depression, and some groundbreaking studies, such as the one performed by the group of Lee *et al.* demonstrated for the first time important correlations between OXT levels and suicidal behavior, by using a specific suicidal scale.²¹

However, there are still controversies regarding the implications of OXT in the suicidal behavior. For instance, a study failed to find any correlations between people with affective disorders and suicide attempts in the last 12 months vs. affective disorders with no suicide attempts, in terms of plasma OXT concentrations, while some other research groups, such as the one of Jokinen *et al.*, reported a decreased level of OXT in the cerebrospinal fluid (CSF) of individuals who had a suicide attempt.²² Moreover, the same research group found that the intensity of suicidal planning measured by a specific subscale of Beck Suicide Intent Scale inversely correlated with OXT cerebrospinal fluid values.^{23,24}

In this fashion, considering the involvement of OXT in some critical behaviors that are usually impaired in depression, the disturbances in OXT activity could also account at least for some of the clinical symptoms seen in depressed patients. Moreover, besides being involved in the sexual functions, appetite, sleep and suicidality, OXT has also important functions in social behavior, emotion modulation, stress regulation and cognitive functioning. Overall, OXT is being labeled as an important prosocial hormone that modulates interpersonal relations and social bonding, trust, generosity, social cognition and emotional empathy. In addition, it is well known that depressed individuals have significant impairment exactly in this specific area, including social avoidance, decreased empathy and social performance, as well as decreased concentration and mind-reading.^{25,26}

Regarding cognition, an important evidence for the positive effects of OXT on cognition in depression was reported by Pincus *et al.* The experiment was designed on females with untreated depression, which received 40 UI of OXT during a test for identification of mood by the facial expressions. In this way, OXT increased neural activity within specific emotional circuits, such as cingulate and insula, as compared to the placebo in the depressed group, but also decreased the activity in healthy females.²⁷ Thus, although it has not been clearly established yet, OXT dysregulation might explain social and cognitive symptoms in depression.

The Relations Between OXT and the Main Neurotransmitters Implicated In Depression

In the present chapter we will also describe the main connections and related mechanisms of action that may exist between the main neurotransmitters implicated in depression and its connections with OXT, such as serotonin, noradrenaline, dopamine and GABA. Thus, we consider that from the biologic point of view it is quite relevant to analyze the relations between OXT and depression by studying also the connection

between OXT and several neurotransmitters for which there are evidences of clear imbalance in depression.

OXT and Serotonin

The relation between OXT system and serotonin is complex and has been highlighted by anatomical, clinical and animals studies. Thus, it is known that within the hypothalamus (e.g. near the magnocellular neurons that are producing and releasing OXT) there are projections of serotonergic fibers from the dorsal and medial raphe, while animal studies showed that near the raphe nuclei, where serotonin is produced, there are OXT receptors that seem to modulate the release of serotonin.²⁸

Even more, Emiliano *et al.* demonstrated an overlapping between OXT labeled neurons and SERT immunoreactivity fibers in many regions of the hypothalamus, by using immunofluorescent techniques. Also, the same research group found that the distribution of 5-HTT-labeled fibers follows the distribution of OT-labeled cells and this sustains a common neuroanatomical pathway between these two systems.²⁹

Moreover, the way that OXT is influenced by serotonin was investigated by Lee and his team, which reported that after the administration of fenfluramine, a serotonin agonist, an increase in OXT production was demonstrated (e.g. demonstrated by higher OXT plasma levels), as compared to the baseline group.³⁰ Also, another study published by Marazziti *et al.* on human subjects sustained the important and complex relations between serotonin and OXT, by exploring two parameters for the paroxetine binding on the platelet serotonin transporter (SERT) (e.g. Kd and Bmax) vs. plasma OXT level. In this way, they found positive correlations between Kd parameter and OXT, suggesting that the binding parameters on SERT may be one possible way of interaction between OXTic and the serotonergic systems.³¹

A more direct correlation was also investigated in a study focusing on mapping the cerebral 5-HT system, by using a specific antagonist of 5-HT1A receptors and the administration of either OXT or placebo. Their results showed that OXT administration increases binding potential in some key areas for serotonin production, but also in other regions of the brain important in modulation of emotions.³² Thus, the notion that OXT modulates serotonin activity in areas important for mood regulation, suggests once again a possible connection with some important mechanisms found in depression.

Still, a 2013 clinical study, which investigated the impact of administrating selective serotonin re-uptake

inhibitors (SSRI) in depressed patients on OXT levels, did not reported any significant modifications in OXT level after 12 weeks of effective SSRI treatment, when compared to baseline.³³ As follows, contrary to other studies that found significant correlations between OXT and serotonergic system, this report did not confirm this idea. However, the study had some important limitations, such as the absence of a healthy control group and did not evaluate the level of serotonin, as compared to the OXT level. In this context, a clear conclusion cannot be established. Still, these studies bring important evidences and confirming the hypothesis that OXT and serotonin are complexly linked, suggesting multiple ways of interaction that need to be further explored.

OXT and Noradrenaline

It is known that the importance of monoamines in depression is demonstrated not only by the biological studies, but also through long clinical practice that largely benefits from treatment with antidepressant agents, which acts through balancing noradrenaline, serotonin and dopamine neurotransmission.³⁴ Also, by advancing the monoaminergic hypothesis, we can speculate that other important factors (e.g. such as OXT) could have an increased relevance in the pathogenesis of depression, possible as a mediator influencing monoamine transmission.

In this way, in a study published by Onaka *et al.*, it was reported that noradrenaline was directly and dose-related influenced by the exogenous administration of OXT, directly into the hypothalamus.³⁵ Moreover, the administration in the same study of an OXT receptor antagonist resulted in a decreased noradrenaline release from the supraoptic nucleus, when a high-K⁺ solution or noxious stimuli were applied.³³ In addition, a study published in 2011 by Grewen *et al.* reported negative correlations between noradrenaline and OXT levels, as measured in peripheral plasma of early postpartum women.³⁶

Thus, these data could be explained by the important role of OXT as an anti-stress hormone and also by the fact that OXT is acting differentially, depending on the presence or the absence of stress. Thus, it seems that as in the case of OXT-serotonin relation, complex interactions between noradrenergic and OXT-ergic system also exist and they are worth further research.

OXT and Dopamine

Mesocorticolimbic dopamine activity is well known for pleasure seeking and represents a biological background in reward behaviour, affiliation, addiction, schizophrenia and depression.³⁷ The relation between OXT and dopamine is sustained by some reports that

connect dopamine activity with OXT. For example, it seems that the mesocorticolimbic and nigrostriatal dopamine pathways are activated by OXT, in order to accomplish some of its social functions.³⁸ It was also proven that depending on OXT genes variability, the dopamine system is highly influenced in how the organism is responding to stress, modulates mood and influences the attachment style.³⁹

In addition, there are other reports regarding some common pathways between dopamine and OXT. Thus, some studies described a specific OXT receptor variability, called OXT rs53576, in the striatum, near the area that produces dopamine and which could impact dopamine release.³⁸ Also, in the hypothalamus there is an expression of dopamine receptors in OXT neurons, suggesting a modulator role of dopamine on OXT activity.³⁹ Moreover, in different cerebral area, dopamine and OXT pathways converge, sustaining once again the link between these two systems.⁴⁰

OXT and GABA

GABA is an inhibitory neurotransmitter that is decreasing neuronal excitability, while the disruption of the limbic GABA transmission is fairly important in affective and anxiety disorders. Still, although it is not of primary importance in the etiopathogeny of depression, recent data are sustaining a connection between the GABA system and depression.⁴¹

Thus, the link between OXT and GABA was investigated by Harden *et al.* which showed that the administration of low concentration of an OXT receptor antagonist, Thr4,Gly7-OXT, is associated with GABA release in the dentate gyrus by the means of the action potential.⁴² Also, it was proven that some interneurons which synthesize GABA and are located in the dentate gyrus of hypothalamus are very responsive by rapid depolarization after the administration of OXT antagonist.⁴³

Furthermore, the activation of OXT receptors can decrease the release of GABA by triggering the Ca²⁺-dependent production of endocannabinoids, which are acting on specific presynaptic receptors (CB1).⁴³ In this way, all these studies are clearly showing the connection between OXT and GABA systems, while a connection with depression needs further exploration.

Mechanistical Aspects for the Correlations Between OXT and Depression

As mentioned above, the study of OXT in the context of depressive disorder could have important clinical implication not only in increasing the understanding of some psychiatric conditions, but also for further practical therapeutic purposes.

Thus, data regarding the impact of OXT in depression is relatively reduced. However, there are clearer evidences regarding these aspects from studies that investigated OXT in postpartum depression, where low levels of OXT were generally found to predispose to depression.⁴⁴ In addition, mixed data on a possible therapeutic role of OXT in postpartum depression exist, while some other therapeutic effects of OXT were reported in autism, anxiety or schizophrenia.⁴⁵⁻⁴⁸

However, the relationship between OXT and depression may be at least partially explained by changes in HPA function. In this way, a study published by Zetsche and his team, nocturnal OXT level and cortisol were measured in 12 depressed patients and compared to 12 age-matched healthy controls. They found a significant reduction of plasma OXT in depressed patients, when compared to the control group and these changes were accompanied by an increase in cortisol level.⁴⁹

Generally, OXT is considered an important HPA axis activity modulator with anti-stress and anxiolytic properties, while there are also of course clear evidences that disturbances in the HPA function appear in depression and anxiety.^{45,50} Thus, we can speculate that since in depression there is also an impaired HPA system, this could be somehow linked with OXT system.

Further evidences on HPA-OXT-depression, came from Purba and his team. They investigated the number of OXT PVN neurons in depressed patients (in postmortem studies) and reported an increase in OXT neurons, when compared to healthy individuals, concluding that this aspect was probably caused by the activation of the HPA axis which is commonly seen in depression.⁵¹

However, the OXT activity in depression is not necessarily linked with cortisol and HPA system, and there are suggestions for different pathways of action for OXT in depression other than stress system. In this way, a study done by Parker and his team found that the levels of OXT, but not cortisol, are decreased in depressed patients.⁵²

Also, a paper published by Keating *et al.* group did not show any changes in OXT and cortisol levels after efficient depression treatment with SSRI. Still, the study lacked a control group and was designed for a relatively short period of time (12 weeks), with not very conclusive results. However, this study is very important since it gives rise to some hypothesis that needs to be tested, including the idea that the clinical profile does not overlap at least in a certain time frame to the biological one, or the effective treatment

of clinical symptoms does not change automatically biological parameters, such as cortisol and OXT levels, or that some depressed patients do not have at all an impairment in stress system and OXT function.⁵³

In addition, Scantamburlo *et al.* group evaluated the levels of plasma OXT in 25 patients with major depressive disorder and tried to understand the degree of correlation with the symptomatology of this disease, as measured with the Hamilton scale for depression. They found that the patients which had a greater intensity of depression also had lower OXT levels, while the score of depression inversely correlated with the levels of OXT.²⁴ These results reinforce the idea of a significant link between OXT and depression and encouraging for further investigation of this connection.

Also, considering the increased awareness regarding the relevance of the oxidative stress in the affective disorders, as well as the fact that oxytocin was lately cited as a possible antioxidant, some correlations between these antioxidant effects and the implications of oxidative stress in depression could be speculated.⁵⁴⁻⁵⁶

Moreover, in some other studies, OXT was found to correlate with depression in different psychiatric disturbances, such as postpartum depression, fibromyalgia, or obsessive-compulsive disorder.^{44,57,58} OXT may also have antidepressant effect and some studies that investigated the effect of OXT on depression reported positive outcomes. Thus, in preclinical studies on animal models of depression, OXT showed an antidepressant effect, when compared the effect of OXT with imipramine, a classical antidepressant. Even more, the authors found similar or even better outcomes in cases of OXT group, as demonstrated by

reduced immobility duration and the escape failures, but also diminished latency to escape in the specific behavioral task used.⁵⁹

CONCLUSION

OXT has become an important target for research in most of the psychiatric disorders and this tendency has a growing background considering numerous evidences that are suggesting the involvement of OXT in at least some psychiatric disturbances. Clinical features relevant for depression seems to be also modulated by OXT including sleep, appetite, sex, emotion, cognition and social behavior. Furthermore, we demonstrated here important connections of OXT with different neurotransmitters that seem to be impaired in depression, sustaining once again a possible OXT-depression relation. However, as these evidences are generally sustaining indirect connections between OXT and depression, many questions remain to be answered. For instance, changes in OXT activity are the cause of depression or the result of it? Can OXT be a mediator for clinical symptoms of depression? Is OXT reaction just a response to a disruption of all these symptoms and what is the place of OXT in treatment of depression?

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