The possible role of oxytocin in neuropsychiatric disorders

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ABSTRACT

Oxytocin (OT) is a peptide hormone unique to mammals, typically involved in activities characteristic of this vertebrate class, such as labour and lactation. Evidence suggests a role of OT even in most complex activities, including child attachment, maternal care, couple bonding, emotional and social behaviors. Furthermore, it seems to contribute to the modulation of stress responses, learning, and memory processes, as well as to the connection of social signals with cognition, behaviors and reward. For this reason, for years there has been a debate on the possible contribution of the OT system in the pathophysiology of different neuropsychiatric disorders, including autism spectrum disorders, obsessive-compulsive disorder, depression, anxiety disorders, post-traumatic stress disorder, eating disorders, addiction, and schizophrenia. In this article, we describe the most relevant findings on OT system abnormalities in the aforementioned disorders, with a focus on possible therapeutic implications.

INTRODUCTION

Oxytocin (OT) is a neuropeptide hormone synthesized predominantly in the magnocellular neurons of the supraoptic (SON) and paraventricular (PVN) nucleus of the hypothalamus, whose axonal endings form a large portion of the posterior pituitary. Herein, OT is released into the bloodstream, reaching the target organs of its peripheral actions, such as the mammary gland and kidney. Actually, at the peripheral level OT receptors (OTR) are widespread in several sites, such as the gastrointestinal tract, heart, testes, uterus, corpus luteum, placenta, pancreas, thymus, and adipocytes, where contributing to the regulation of water balance, bone density and appetite.[1] Besides the posterior pituitary, OT is released locally within the SON and PVN, acting as self-modulators, as well as in the anterior pituitary via the hypothalamic-pituitary portal vascular system, acting as a regulatory factor of the anterior pituitary hormones, in particular prolactin, adrenocorticotropic hormone (ACTH) and gonadotropins.[1, 2] Furthermore, OT magnocellular axons also reach other brain regions, including the arcuate nucleus, the lateral septum, the medial amygdala nucleus and the median eminence.[1, 2] It is through the last innervations that OT seems to carry out its central functions, taking part in the regulation of stress responses, social behaviors, emotions, and cognition.[3] In particular, growing evidence highlights that OT may reduce stress response and social anxiety, improve parent and child social communication, and enhance positive social interactions, social support and trust. Furthermore, OT seems to be involved in emotional information processing, memory and learning, as well as in the interaction between social signals, cognition, emotions, and reward.[1-3]

Since several psychiatric disorders are characterized by deficits in emotions, cognition and social interactions/communication, and they are strongly influenced by social variables, it has been hypothesized that alterations of the OT system might contribute to their pathophysiology.[1, 2] Therefore, in this paper we examine the main evidence linking the OT system to the main neuropsychiatric disorders, particularly autism spectrum disorders (ASDs), obsessive-compulsive disorder (OCD), mood disorders, anxiety disorder, post-traumatic stress disorder (PTSD), addiction, eating disorders, and schizophrenia. A brief mention is also made on the potential use of the OT system as a new treatment target for these mental disorders.

AUTISM SPECTRUM DISORDERS

The term ASDs indicates a spectrum of psychological conditions characterized by an impairment in social cognition, interaction and communication, and repetitive behaviours, sometimes accompanied by deficits in language and cognitive abilities. Growing evidence reports that OT might be implicated in social skills, whose dysfunctional neural pathways have been proposed to underlie several aspects of ASDs.[1,2,4] Several data sources suggest that a link may exist between OT system alteration and ASDs pathophysiology. Firstly, it has been proposed that OT, which is oestrogen-dependent and is higher in women (especially during early development), may be a protective factor for the development of ASDs that show a higher prevalence in males.[1, 2, 4] Furthermore, animal models and linkage data from the genome screen in humans indicated that the OTRs gene variants and OT/OTRs genes single nucleotide polymorphisms (SNPs) might be risk factors for ASDs susceptibility.[1-4] More recently, the epigenetic regulation of OTRs gene has also been implicated in the ASDs onset.[1-3] In addition, OT knockout mice showed similar social deficits that are found in ASDs animal models, while OT therapy rescued social deficits and repetitive behaviour in both OT knockout and CD38 knockout mouse models.[3,4] In humans, an association has been found between decreased cerebrospinal fluid (CSF) and plasma OT levels and social behaviour deficits in patients with ASDs.[5] Moreover, the OT administration in ASDs subjects showed to be able to improve social behaviours, emotion recognition, and repetitive behaviours, as well as to increase the ability to remember spoken words and understand speech language.[6, 7] Additionally, intranasal OT administration has also been associated with improved partner interaction in adult patients with ASDs, and improved gaze and attention to faces.[4, 8] These clinical effects have been confirmed by some imaging data reporting how OT could improve the recognition of facial and social emotions.[2, 4, 8]

Hence, OT pharmacotherapy brings a promising treatment for repetitive and affiliative behaviours in patients with ASDs. However, a lot of work remains to be done in terms of possible routine use of OT in these patients, because long-term studies are a few and inconsistent.[4]

OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder is typically characterized by obsessions and/or compulsions. The possible involvement of the OT system in the OCD derives from both preclinical and clinical evidence. In animals, central OT microinjection produced a significant increase in grooming, sexual and aggressive behaviours that respectively can be considered the counterpart of cleaning compulsions and sexual and aggressive obsessions of OCD patients[2]. In humans, the evidence that pregnancy and the postpartum period, in which there is an increased release of OT, are characterized by an increased risk of developing OCD, in particular a subtype of OCD characterized by obsessions of contamination, further supports the hypothesis of a role of the OT system dysfunction in OCD pathophysiology.[2] The direct measurement of fluid OT levels in OCD patients showed inconsistent results. Indeed, while in some studies increased CSF or plasma OT levels were detected in adults with OCD when compared with healthy controls,[9, 10] other data noted no differences.[9] In addition, while some evidence revealed no correlation between CSF OT concentration and OCD symptoms,[2, 9] others described a negative correlation between OT levels and symptom severity, as well as positive relationships between OT levels and the fearful-avoidant and dismissing styles of romantic attachments, but only in male OCD patients.[9, 10]

Controversial results came from the attempts to administer OT to OCD patients. However, to date there is no evidence for the effectiveness of exogenous OT in the treatment of OCD, although the total number of patients studied is small[9].

MOOD DISORDERS

Major depressive disorder (MDD) and bipolar disorder (BD) represent the most common mood disorders. As the OT plays an important role in the modulation of the stress response, the possible connection between OT system abnormalities and stress-related mental disorders, in particular mood and anxiety disorders, has been investigated. Several studies measured the levels of OT and neurophysin 2 (its transporter protein) in the CSF and plasma in patients with MDD, and generally found no differences between patients with MDD and controls, as well as no correlation between plasma OT levels and measures of motor activity or neuropsychological testing results.[1, 9] By contrast, other studies showed reduced nocturnal plasma OT levels in patients with MDD compared with controls, and lower plasma levels of OT in women with MDD and fibromyalgia compared to that with fibromyalgia without MDD or healthy controls.[9] Furthermore, a negative correlation was found between OT levels and scores for depression and anxiety, and a positive correlation was described between OT levels and scores for happiness.[1, 9] In a more recent study, decreased serum OT levels were reported in inpatients with MDD or bipolar depression, compared with healthy controls.[11] In this study, OT levels were decreased both pre- and post-treatment with antidepressants or electroconvulsive therapy (ECT) and were unaffected by either treatment. Moreover, female patients showed significantly lower OT levels than the control subjects, whereas no differences were detected in men or between unipolar and bipolar depressed patients.[11]

The inconsistency of the results listed above would suggest a complex relationship between OT system and mood disorders, influenced by multiple factors in different patients. For example, it has been observed that anxiety comorbid with depression may be a modulator of OT effects in depression, since OT levels have been shown to correlate negatively with anxiety scores on the State-Trait Anxiety Inventory.[12] Similarly, a positive correlation of plasma OT levels with addictive and novelty-seeking temperament was observed, indicating a relationship between temperamental factors and OT levels which can confound study results.[13] Finally, depressed women involved in a laboratory protocol designed to stimulate and measure blood OT release in response to laboratory tasks, showed no change in OT levels during the Speech Stress tasks, but greater OT concentrations during the Affiliation-Focused Imagery Session, as well as greater variability in its pulsatile release as compared with healthy control subjects.[14]

Although some studies showed increased plasma OT levels after ECT, no significant effects on mood have been described following treatment with exogenous OT. However, it should be noted that few studies investigated this effect, and long-term, randomized, placebo-controlled studies on the OT administration in patients affected by mood disorders have not been conducted as yet.[9]

ANXIETY DISORDERS

Animal and human studies support a role of OT in regulating anxiety behaviours.[3] In particular, the increased levels of OT during pregnancy and breast suckling showed to decrease cortisol level and anxiety response, to be associated with positive mood state, and to be protective for anxiety disorders, including panic disorder.[3] Some MRI studies on healthy humans with no history of psychiatric disorders suggested that fear stimuli activate the amygdala with an increase in anxiety behaviour, while OT administration decreased amygdala activation with an anxiolytic effect.[1, 3] Similarly, intranasal administration of OT improved symptoms of social impairments in patients with social anxiety disorder (SAD).[15] This anxiolytic effect of OT may be because of the projections of a large number of PVN OT neurons to different limbic brain regions, including medial preoptic area, olfactory bulb, anterior hypothalamus, substantia nigra, and amygdala. In particular, dysfunctions of the amygdala, which is implicated in the biological response to danger signals in social interaction, have been detected in both depression and anxiety disorders.[3] Moreover, a downregulation of OTRs has been related to the pathophysiology of SAD, which might explain the cognitive misappraisals typical of the subjects affected by this condition.[3] However, no significant differences in OT levels were found in SAD patients compared with healthy controls, and SAD patients with higher OT levels showed higher severity of social anxiety symptoms and dissatisfaction with social relationships.[2]

POST-TRAUMATIC STRESS DISORDER

The first evidence on a potential role of the OT system in PTSD pathophysiology derived from animal experiments, showing that exogenous OT administration modulated anxiety and fear responses and mitigated the activation of the HPA axis and sympathetic system.[16] Subsequently, several studies in humans reported a significant relationship between reduced OT levels and traumatic experiences and/or PTSD following early severe and recurrent abuse during childhood, while OT levels were increased in children exposed to minor traumas who lived in safe environments.[16] Increased OT levels were detected also in women exposed to traumatic/stressful situations, while inconsistent results were present in men.[16] Such differences could be explained considering that oestrogen influences OT release and OTRs expression, and that basically women have higher OT levels than men.[17] A small number of studies directly evaluated plasma OT levels in patients with PTSD. Some reports revealed a reduction in OT levels in subjects exposed to major trauma who have developed PTSD, although there are no conclusive results.[16] Consistently, one of our recent studies showed the presence of decreased plasma OT levels in outpatients with PTSD of both sexes as compared with healthy control subjects, hence supporting the possible involvement of OT in the pathophysiology of some aspects of PTSD (unpublished data). However, given the complexity of PTSD clinical picture, future investigations are necessary to better deepen the role and level of oxytocin in PTSD. In addition, genetic association studies showed that some OTRs gene polymorphisms might be related to increased risk of developing PTSD.[16]

As regards the administration of exogenous OT in subjects exposed to trauma experiences or suffering from PTSD, to date there are inconclusive or opposite results, probably due to the possible interference of various factors (sex, context, acute or chronic trauma).[16]

ADDICTION

All abuse drugs act by enhancing the brain reward mechanisms: a crucial drug-sensitive component of this circuit is represented by the mesolimbic dopaminergic system that is under the modulatory control of several neurotransmitters and hormones.[1, 2] Some evidence suggested that OT is connected to the dopaminergic system while modulating dopamine in the reward system; therefore it might be implicated in the neural events leading to drug tolerance and addiction.[8] Furthermore, it has been hypothesized that early childhood negative experiences can influence the development of the OT system increasing the susceptibility to such processes.[8] Addiction is considered to be also a form of dysfunctional learning, and since studies showed that OT inhibits learning and memory consolidation, it might be helpful in improving drug addiction.[18]

In animal studies, OT appeared to inhibit the morphine tolerance onset and to attenuate the severity of symptoms of morphine withdrawal.[2,8,18] After OT administration, rats showed a reduction of intravenous self-administration of heroin. Furthermore, OT showed to attenuate the cocaine-induced hyperactivity and to inhibit the cocaine tolerance development, facilitating the development of behavioural sensitization.[2, 8, 18] The same OT tolerance reducing effect was observed in studies conducted using alcohol as a drug of abuse.[2, 8, 18] However, while acute alcohol administration inhibited OT secretions, its chronic use stimulated it. In addition, some reports suggested that OT might also be involved in the cognitive dysfunctions observed in alcoholics[2]. Finally, OT systemic administration was shown to reduce methamphetamine-induced expression of the Fos protein in the nucleus accumbens, while intracerebroventricular administration of OT revealed to be able to prevent relapses of methamphetamine-based drugs caused by stress.[8, 18]

There are relatively few human studies that have examined the OT effects in subjects with alcohol and drug dependence. The potential use of OT as a treatment for alcohol use disorder was highlighted by a recent small clinical trial in alcohol-dependent subjects, in which all subjects underwent alcohol detox with lorazepam administration and were simultaneously randomized to receive intranasal OT or placebo during the withdrawal period.[19] Subjects randomized to receive OT had significantly fewer alcohol withdrawal symptoms and required less lorazepam triggered by withdrawal symptoms than the placebo group. Furthermore, the OT administration has been shown to reduce stress-induced craving and anxiety in cannabis-addicted individuals. In addition, cocaine-dependent patients exhibited a significant positive relationship between anger and cue-induced craving that was absent after OT administration.[19]

In conclusion the literature suggests that as OT is involved in the mechanisms of reward, underlying, it might be useful in treating addictions. In a recent study, intranasal OT showed to reduce fMRI amygdala response to cocaine only in men with a history of childhood trauma, while women with a history of childhood trauma showed an enhanced amygdala response to cocaine, and cocaine-dependent subjects with no history of childhood trauma exhibited no effect of OT on amygdala response.[20] Therefore, in humans the OT effects on addiction disorders seem to be modulated by gender and childhood trauma.[20]

EATING DISORDERS

Eating disorders (EDs) are characterized by several neuroendocrine dysfunctions, including OT system alterations. In particular, the serum activity of prolylendopeptidase (PEP), an enzyme that cleaves OT, was found reduced in both bulimic and anorexic patients.[1, 2] However, CSF OT levels were found lowered only in the patients with anorexia nervosa. It was also reported that these abnormalities tend to normalize after weight regain, so they are interpreted as secondary to malnutrition and fluid balance abnormalities. Furthermore, in both anorexia and bulimia nervosa autoantibodies against OT were detected, suggesting also that the immune dysfunction may be involved.[1, 2]

In addition, acute intranasal OT administration has been associated with a reduction in caloric intake in normal weight and obese individuals. These effects suggested that OT may improve dysfunctional eating behaviour in the therapeutic setting.[21] However, to date there are no clear results on the effect of exogenous OT administration in eating disorders, neither with regard the social cognition

and the support for food therapy, nor with regard the body image distortions and perception of interoceptive signals, such as affective touch and cardiac awareness.[22]

SCHIZOPHRENIA

Schizophrenia is a chronic neuropsychiatric disorder characterized by complex symptoms, mainly divided into negative, positive, and cognitive symptoms. Little is known on the relationship between the OT system and schizophrenia, but OT appears to be an important mediator that positively influences the symptoms associated with schizophrenia. Recent studies suggested that the SNPs of the OT and OTRs genes are linked with symptom severity in patients with schizophrenia.[3, 8] In particular, an OT gene polymorphism (rs2740204) showed to be involved in the negative symptoms of schizophrenia, and it was linked to clozapine response to treatment.[23] Furthermore, fMRI studies revealed that dysregulation of the OT system is associated with the social and cognitive deficits in schizophrenia,[24] while the exogenous OT infusion improved social cogitation and social interaction in schizophrenia.[25] Clinical studies also suggested that intranasal administration of OT may be a potential candidate in schizophrenia treatment, as it was found to improve social behaviour and cognitive dysfunctions in schizophrenic patients.[3] Similarly, a group of schizophrenic patients receiving intranasal OT showed improved verbal memory and positive and negative syndrome scale (PANSS) scores.[8] Briefly, these findings suggest that a disrupted OT system might be an underlying mechanism of negative, positive and cognitive symptoms of schizophrenia. In conclusion, it leads to hope that OT might be used as potential therapy to rescue the symptoms domains of schizophrenia.

CONCLUSION

In recent years, the OT system attracted great interest in several research lines, particularly in neuropsychiatric field, given the evidence that OT plays an important role in the regulation of several mental functions, including the modulation of social bonds, stress responses, emotions and cognition. For this reason, it has been hypothesized that dysfunctions of the OT system may be involved in the pathophysiology of different neuropsychiatric disorders. Several preclinical and clinical studies reported body fluid OT levels alterations and associations of OT/OTRs genes variants/polymorphisms in a wide range of psychopathological conditions.[1, 3, 4, 9, 10, 20, 21] In addition, some evidence suggested the potential use of exogenous OT as a new treatment for certain psychiatric disorders, especially ASD and PTSD.[1, 3, 4, 9] However, the available studies are few, carried out in small samples, and with inconsistent or opposite results, even because the reliability of plasma OT concentrations as peripheral markers of central OT levels is still debated.[1, 3, 4, 9, 10, 20, 21] In conclusion, if supported by further data, it can be hypothesized that OT dysfunctions may contribute to the development of psychopathology, opening new horizons for new therapeutic interventions.[1, 3, 4, 9, 10, 20, 21]

CONFLICT OF INTEREST STATEMENT

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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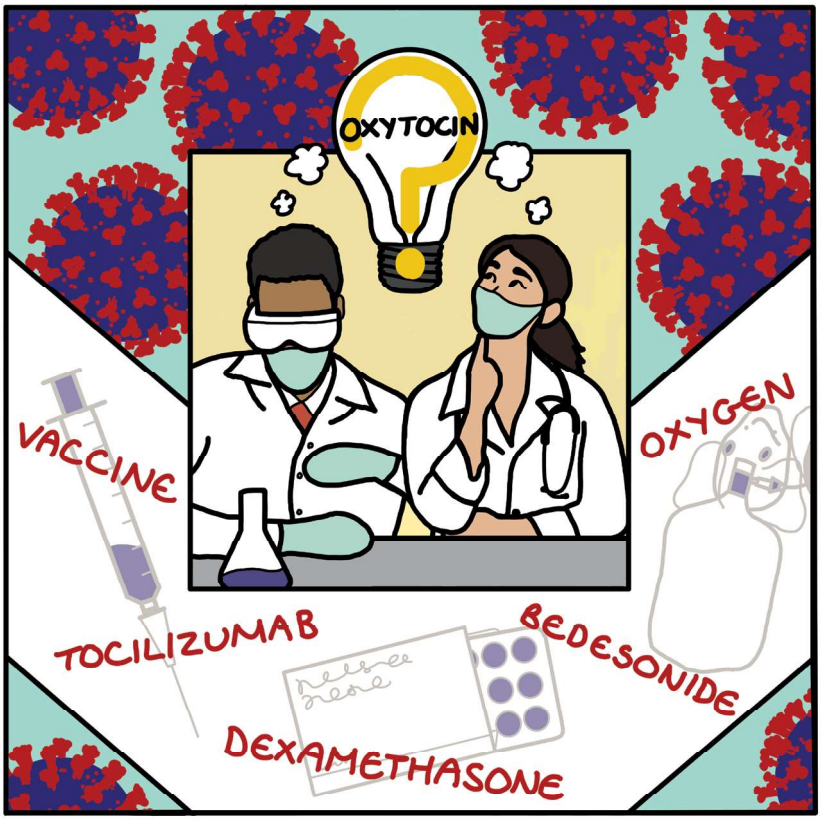

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