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Review Article

Oxytocin: A Potential Novel Therapeutic Agent in Treatment of Autism

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Abstract

Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by varying deficits in social interactions, communication, and learning, as well as stereotypic behaviors. Despite the significant increasing rates of ASD during the last two decades, there are few clues for its exact pathogenesis, delaying early detection and effective intervention. Thus, identifying causes and treatments is imperative. So far, there are no known efficacious treatments for the core social symptoms, although effects on repetitive behaviors are indicated with some data. During the past decade oxytocin (OT) research has shown a major upsurge. The beneficial roles of OT on social functioning raise the question regarding its potential usefulness in ASD management. If clinical application of OT in the treatment of ASD proves successful then it may introduce a new hope for afflicted individuals and their families. Fortunately pioneering clinical studies support this notion; however, more research should go on to resolve issues concerning clear mechanisms by which OT modulates social behavior before its real introduction for clinical application. Also probable adverse affects must be thoroughly investigated to ensure safe treatment outcomes.

Key words: Autism, oxytocin, social behavior, mind reading, eye contact.

Introduction

Autism Spectrum Disorders (ASD) are pervasive neurodevelopmental disorders that include autistic disorder, Asperger's disorder, and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) [1]. ASD are characterized by variable deficits in communication and social skills, a wide range of behavioral and learning problems and stereotypic behaviors. ASD manifest during early childhood and at least 30% of cases present with sudden clinical regression of development around 3 years of age often after acute episodes, such as a viral infection or following a vaccination [2]. Over the last 20 years, there has been an impressive increase in ASD prevalence of about 15% per year. A recent report from the US Centers for Disease Control estimated that 1/88 children may be affected by ASD [3]. In the majority of cases, however, the cause of ASD is unknown in spite of the apparent increase in ASD prevalence. Unfortunately there is currently no known 'cure' for autism. Management relies upon ameliorating the core behavioral deficits in autistic children by early intensive behavioral and educational interventional therapy.

Interestingly the popularity of oxytocin (OT) has grown exponentially during the past decade, and so has the number of OT trials in healthy and clinical groups. OT is labeled the 'love hormone' and widely advertised as a wonder drug to enhance the individual's social skills on the job and at home, and to cure or alleviate more serious illnesses such as depression, post-traumatic stress and other psychiatric syndromes. After the initial excitement about positive effects on trust, it soon became clear that OT might be anxiolytic and facilitate prosocial behavior [4]. Since 20 years clinical trials have involved patients with depression, social anxiety, schizophrenia, obsessive-compulsive problems, borderline personality disorder and post-traumatic stress disorder. The positive influence of OT on social behavior raises the issue whether this hormone is possibly useful for ASD therapy. Clinical application of OT in the treatment of this disorder can provide some recourse to afflicted individuals and their families. This review discusses the potential of

oxytocin use as a novel therapeutic tool in managing autism.

Oxytocin

OT is mainly synthesized in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus that project to the posterior pituitary. From the pituitary, it is released into the bloodstream to act as a hormone and influence bodily functions. In addition, neurons in the paraventricular nuclei project to various limbic, mid- and hindbrain structures (for example, hippocampus, amygdala and nucleus accumbens) containing a plenitude of OT receptors. Within the brain, OT can act both as a neurotransmitter and as a neuromodulator [5].

Animal studies have shown that OT is involved in lactation and the onset of maternal behavior [6]. Recent research also suggests an important role of OT in human caregiving [7]. Higher maternal OT levels across pregnancy predict higher quality of postpartum maternal behavior [8]. In pregnant women, lower plasma OT levels in mid-gestation are predictive of postnatal depression [9]. More generally, depressive symptomatology has been found related to lower plasma OT levels [10]. Similarly, in patients with schizophrenia, plasma OT levels were found to be lower than in non-clinical subjects, and they correlated negatively with psychotic symptoms [11].

Intranasal OT administration

Early behavioral experiments with intravenous administration of large quantities of OT were short-lived because of disappointing results presumably because the blood-brain barrier might have been difficult to pass for OT injected into the veins [12]. Intranasal OT administration seems to circumvent this blood-brain barrier as it leads to replicable changes in brain functioning [13, 14], perception [15] and behavior [16]. Many studies suggest that intranasal OT may be quite effective, for use in clinical settings [4, 17, 18]. Intranasal administration of OT is simple to use. The nasal mucosa provides a direct connection with the central nervous system, and several absorption

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routes from the nasal cavity to the central nervous system have been suggested [19]. These include the transfer of OT through the olfactory epithelium into the systemic circulation, through oral mucosa (after swallowing), through the olfactory bulb pathways directly into the cerebrospinal fluid and brain, through the trigeminal nerve that innervates the respiratory and olfactory epithelium and enters the brain stem and the pons, and through the paravascular spaces that connect into the interstitial spaces of the brain parenchyma [19]. The feedforward mechanism of the oxytonergic system, leading to an increased production of OT with higher OT levels, may have an important role in the explanation of the persistently high levels after intranasal administration. Treatment with exogenous OT may stimulate a 'feedforward' release of the endogenous peptide [4].

Potential of oxytocin in therapy of autism

Recent worldwide epidemiological studies have shown that at least 1 in every 88 people has some form of autism spectrum disorder (ASD) [3, 20]. However, there is no established pharmacological treatment for social dysfunction, the core feature of ASD. Thus, identifying the cause and treatment is a necessity of utmost importance. Although an intensive search for the biological markers of ASD has provided some major advances in the understanding of genetic, neurobiological, and developmental underpinnings, many aspects of the disease spectrum are still poorly understood.

In the past decade, research from various fields has revealed that OT plays an important role in social interactions that goes far beyond the previously documented effects in female reproduction [21, 22]. Humans exposed to OT make more eye contact, feel increased in-group trust, and are better able to infer emotions from other peoples' facial expressions [23-26]. The beneficial roles of OT on social functioning strongly suggest its possible use for ASD therapy. Although pioneering clinical studies support this notion, much remains to be learned about the mechanisms by which OT modulates social behavior before it is ready for clinical use [27-29]. Specifically, little is known about the mechanistic effects of OT on

social brain circuits, which are at the core of the observed behavioral changes.

Evidence for a neuromodulatory role of oxytocin in human social cognition and behavior

Current perspectives on the neuromodulatory effects of OT in the domain of human social cognition and behavior emphasize its potency as a facilitator of sociality. The basis of this prevailing view has progressed from animal research documenting a pivotal role of OT in promoting social bonding and attachment [6, 30, 31] and controlling fear and stress responses [32-34] to pharmacological challenge studies in healthy humans, which demonstrated beneficial effects of intranasal single-dose (24-48 IU) administration of OT on behavioral responses in various social-economic and social-cognitive tasks. These tasks have addressed, for instance, interpersonal trust and cooperation [35, 36], generosity [37], social recognition memory [38-40], social reinforcement learning and emotional empathy [41], assessments of facial attractiveness and trustworthiness [42], and self-perception [43].

However, recent studies contrast with the notion that OT exerts uniformly positive effects on human social cognition and behavior in showing that the peptide can also promote envy and gloating [44], ethnocentrism (including prejudice, xenophobia, and racial bias) [36], and outgroup derogation [45]. In addition, OT has been implicated in impeded trust and cooperation as well as in negatively biased recollections of maternal care and closeness in insecurely or anxiously attached individuals [23, 46].

In an attempt to reconcile these conflicting findings, it has been hypothesized that the effects of OT on human social cognition and behavior result from reduced anxiety and/or reflect increased perceptual salience of social cues [23]. The anxiolytic action of the peptide has indeed been shown as decreased endocrine and subjective responses to social stress [47] or as reduced negative cognitive self-appraisal in individuals scoring high in trait anxiety [48], whereas the social salience hypothesis has gained considerable support from studies showing increased eye contact [38] and

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improved “mind reading” from facial gestures [49] following administration of OT. Whether these mechanisms ultimately yield positive or negative social outcomes may vary as a function of context and/or person-specific features [23]. An alternative concept argues that emotional valence may be the dominant factor guiding the effects of OT on human social cognition and behavior, with OT promoting social approach to positive cues and inhibiting social withdrawal from negative ones [50].

However, the neuromodulatory role of OT is not only extensively studied in healthy humans with the purpose of unraveling the psychobiological substrates of its social effects—based on a rapidly growing number of baseline plasma-level studies and treatment trials in clinical populations—it is also beginning to emerge as a target for adjunctive therapy of social-behavioral dysfunction in several mental disorders [51], including ASD [27, 28, 29, 52], borderline personality disorder [53], schizophrenia [54–56], and social phobia [57, 58]. This clinical translation, if proven to be feasible, would substantially extend and make innovations in current treatments of these disorders.

Oxytocin and autistic social dysfunction

Considering the sexually dimorphic feature and prosocial effects of OT, it has been suggested that this neuropeptide can contribute to the pathophysiology of ASD, a sexually dimorphic neurodevelopmental disorder with social deficits as a core feature [59]. Indeed, a lower-than-normal plasma OT level exists in ASD subjects [60], so it could be a candidate therapeutic agent for the symptoms of ASD [20]. Several pioneering studies have suggested improvements in autistic behavioral and cognitive characteristics following administration of OT. Intravenous infusion OT treatment decreases the observed severity of repetitive behavior in ASD [52]. Further, it improves the ability to accurately assign emotional significance to speech intonation in the speech comprehension task [27]. Oxytocin makes patients with autism more sociable by making them more aware of the social nature of interactions and by supporting them to overcome their reluctance to look faces in the eyes [28].

Guastella et al. (2010) reported that male youths with ASD who received intranasal administration of OT showed significantly better performance on the “Reading the Mind in the Eyes” task, a widely used test of emotion recognition [29]. Also intranasal administration of OT in ASD individuals has been demonstrated to potentiate social interactions and enhance feelings of trust together with elevating plasma levels of OT [28]. The above findings, together with recent case reports showing improvements in autistic symptoms [60, 61] suggest that OT could be used to treat the currently untreatable autistic social dysfunction [62]. Clinical application of OT in the treatment of ASD could provide a long-awaited and effective treatment option for autistic patients. It is expected that OT treatment cannot only correct the behavioral phenotype but also the neural-level intermediate phenotype. It is even possible that OT may have favorable gene-level effects, such as epigenetic modulation of oxytocin receptor gene [63].

However, further large-scale studies or long-term trials are needed to explore the neural tools by which OT improves autistic behavior as these mechanisms are still unclear. It is also imperative that future studies aim to unravel the potential social side effects and “contraindications” of OT as a treatment, as subject-specific biological and psychological characteristics as well as contextual factors may critically determine its efficiency.

Conclusions

Autism is a lifelong neurodevelopmental disorder. The core symptoms of autism include impairments in social interaction and communication, as well as the presence of restricted and repetitive behaviors. The prevalence of ASD is as high as 1 in 88 individuals and constitutes a heavy burden to society. OT research during the past decade is achieving a progressive improvement. OT system is evolutionarily highly conserved in the mammalian brain and overlapping regions such as the amygdala, striatum, hypothalamus, and medial frontal cortex have been indicated as shared neural effector sites in both humans and animals [64–66]. Several different levels of evidence from animal models,

genetic and human nonclinical and clinical studies support an association of OT with a wide range of social emotional behaviors from animal affiliation and bonding to human social perception, trust, and ethnocentrism. Accumulated evidence further supports the involvement of OT in the pathophysiology of disorders with pronounced social deficits including social anxiety disorder, borderline personality disorder, schizophrenia, and ASD. Successful clinical utilization of OT in the treatment of ASD could provide a strong new hope for affected patients and may better re-shape their lives. The steadily increasing body of evidence proposing the potential use of oxytocin in ASD should be supported by extensive research investigating the exact mechanistic effects of OT on social brain circuits, which are at the core of the observed behavioral changes. Meanwhile, the possible “other face” side effects of the drug should be carefully studied to set clear vision of its probable contraindications.

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