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Oxytocin and social functioning

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Social anxiety is a form of anxiety characterized by continuous fear of one or more social or performance situations. Although multiple treatment modalities (cognitive behavioral therapy, selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors, benzodiazepines) exist for social anxiety, they are effective for only 60% to 70% of patients. Thus, researchers have looked for other candidates for social anxiety treatment. Our review focuses on the peptide oxytocin as a potential therapeutic option for individuals with social anxiety. Animal research both in nonprimates and primates supports oxytocin's role in facilitation of prosocial behaviors and its anxiolytic effects. Human studies indicate significant associations between social anxiety and oxytocin receptor gene alleles, as well as social anxiety and oxytocin plasma levels. In addition, intranasal administration of oxytocin in humans has favorable effects on social anxiety symptomology. Other disorders, including autism, schizophrenia, and anorexia, have components of social anxiety in their pathophysiology. The therapeutic role of oxytocin for social dysfunction in these disorders is discussed.

Introduction

Over the past decade, research has investigated impairments in processing of social information in a broad range of illnesses, including autism, schizophrenia, anorexia, and social anxiety disorder.[1-3] Difficulty in social stimuli processing is often evaluated over multiple dimensions and is disease-specific, for instance evaluation of social communication in autism or social fear in social anxiety disorder.[3,4] This review specifically discusses the role of oxytocin in social anxiety. Although disorders that contain an aspect of social anxiety differ greatly in symptomatology and etiology, it is important to recognize where similarities exist in the development and functioning of brain regions specific to processing of social stimuli. Thus, treatment beneficial to social anxiety disorder could also be useful for other disorders with social processing dysfunction.

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) defines social anxiety disorder as a "persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others."[5] Social anxiety occurs on a wide spectrum ranging from mild

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adaptive fear to a maladaptive disorder, severely impacting an individual's life. Social anxiety symptomology can exist alone or as a comorbidity with other psychiatric disorders, including, most commonly, eating disorders, major depression, schizophrenia, and other anxiety disorders (generalized anxiety disorder, panic disorder).[6,7] However, the connection between symptom and comorbidity is often unclear; a comorbidity can result from the same disease process as the disorder itself. To add to the complexity, the causes of social anxiety are multifactorial, involving genetics, neurobiology, the fetal environment, and the postnatal environment.[8]

Multiple neurological pathways, neurotransmitters, and brain regions, including the amygdala and anterior cingulate, have been studied in regard to social anxiety, but many remain unknown.[9] Current treatment focuses on cognitive behavioral therapy as a first-line treatment and on medications, such as selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs), as a second-line treatment. Occasionally benzodiazepines are used for short-term relief; less commonly, β-blockers are used in order to control the sympathetic nervous system.[8,10] Despite multiple treatment options, treatment is ineffective for 30% to 40% of patients with social anxiety disorder.[11] A necessity for more effective treatments exists not only for social anxiety disorder but other disorders with a social impairment component, such as schizophrenia and autism. This need has led researchers to explore other potential mechanisms involved with social anxiety.

Oxytocin is a neuropeptide synthesized primarily in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus.[12] Oxytocin plays a key role in social cognition, in social behaviors, and in fear conditioning, which are important in social anxiety as well as in other disorders with impaired social functioning. A plethora of studies have uncovered a role for oxytocin in intimacy, social recognition, pair bonding, and anxiety, among others.[13] Oxytocin acts centrally within the brain to control behavior, as opposed to its well-known peripheral role in parturition and lactation.[13] Oxytocin receptors are distributed throughout the brain, including within the amygdala, ventromedial hypothalamus, brain stem, and nucleus accumbens.[14] This review will focus on oxytocin's central role on social anxiety and social processing as a potential target for the treatment of social anxiety and other disorders with dysfunction in social processing.

Animal studies and social anxiety

Animal research investigating oxytocin's role in basic behavioral processes has set the foundation for investigation of oxytocin in human illnesses, including autism, schizophrenia, and anxiety disorders. Animal models of social anxiety–related behaviors are vital for understanding the implications of oxytocin in human social processing and social anxiety. The following sections examine nonprimate and nonhuman primate studies for social behavior and also anxiety components of social anxiety.

Social behavior

Animal studies have examined the role of oxytocin in a variety of mammals, including sheep, mice, and rats.[15] Prairie voles have been of particular interest in oxytocin animal research because they demonstrate selective social preference in order to survive and reproduce in their habitats.[16,17] Early animal studies demonstrated oxytocin's ability to induce the prosocial behavior of bonding, both maternal bonding with offspring and pair bonding.[18-20] In voles, pair bonding is measured by time spent in proximity of a partner versus a stranger, in which more time spent with a partner indicates pair-bond formation.[21,22] Pair bonding can be induced in female voles via intracerebroventricular oxytocin injection, or prevented by an oxytocin receptor antagonist in the nucleus accumbens and prefrontal cortex.[20,23] Maternal/infant bonding has also been demonstrated in voles.[24] Individuals with social anxiety disorder, as well as other disorders such as autism, can struggle with forming and maintaining interpersonal relationships. Oxytocin has the potential to facilitate human "bonding" and should be considered in future studies investigating its effects on relationships in people with social anxiety or autism.

Another aspect of social behavior is social memory, the ability to recognize and differentiate between individuals.[25] Central oxytocin administration enhances social memory in male rats,[26,27] whereas an oxytocin receptor antagonist blocks social memory in female and male rats.[26-28] Oxytocin affects social memory in multiple brain regions, including the olfactory bulb, lateral septum, ventral hippocampus, and amygdala, in nonhuman primates.[29-34] These and other studies suggest the potential of oxytocin to also promote prosocial behav-

iors and enhance social cognition in humans. However, social behavior in humans is distinctively different and more complex than that of nonprimates like voles and rats, which will be discussed below.

Anxiety

Animal research has demonstrated relationships between oxytocin's role in anxiety and social behaviors; for instance, under stress, oxytocin causes rodents to approach and maintain closeness with familiar rodents.[35-37] Systemic pretreatment with oxytocin before a stressor (flooded cage) led to a longer amount of time spent with other prairie voles after the event.[38] This finding suggests that oxytocin can change stress neural connectivity and promote social cohesion after a stressor that usually would cause dispersal.[38] This relationship is not surprising given oxytocin's involvement in brain regions such as the amygdala and paraventricular nucleus of the hypothalamus where oxytocin modulates fear and stress responses.[39-42] Specifically, anxiety-provoking stimuli activate the oxytocin system by increasing oxytocin neuronal activity, oxytocin gene expression in the paraventricular and supraoptic nuclei of the hypothalamus, and central and peripheral release of oxytocin.[43-48]

The acute and chronic anxiolytic effects of oxytocin have been demonstrated in a number of rodent studies.[49] One method of evaluation used is the elevated plus maze (EPM). More time spent in open space indicates a successful anxiolytic response for the EPM. Central amygdala, prelimbic cortex, and intracerebroventricular administration of oxytocin has demonstrated acute anxiolytic effects in rodents in the EPM test,[50-53] whereas administration of oxytocin receptor antagonist induced anxiogenic effects. Similar effects were shown when chronic anxiolysis was evaluated.[54,55] Oxytocin's involvement in anxiety-modulating regions of the brain and rodent studies demonstrate its anxiolytic effects and support the potential for using oxytocin in treatment of anxiety disorders. *Figure 1* illustrates the human implications of nonprimate animal studies on social functioning and anxiety.

Nonhuman primate studies

Rodent studies have provided insight into the central effects of oxytocin. However, rodents display distinctively different social behaviors than that of humans,

and this has led animal researchers to use nonhuman primate models of human social behavior. The rhesus macaque has been a central focus of nonhuman primate research because of its complex "human-like" social behaviors, including social imitation, perceptional understanding, and prosocial behaviors.[56] Similar to humans, the macaque primarily uses audition and vision for social communication. Oxytocin receptors reside in areas of the brain involved with auditory and sensory stimuli processing of the macaque. These include the superior colliculus, trapezoid body, ventromedial hypothalamus, nucleus basalis of Meynert, and the pedunclopontine tegmental nucleus in the rhesus macaque.[57]

Rhesus macaques have been studied in several social domains including social development, prosocial choices, and social attention . Oxytocin expression may depend on the presence of a maternal figure in the early stages of life and influence later prosocial behavior development. Macaques reared by mothers have significantly higher baseline oxytocin cerebrospinal fluid levels at 18, 24, and 36 months of age than those raised without a mother.[58] Mother-reared macaques also spend more time sitting in close contact and allogrooming (prosocial behaviors), with a significant correlation between these social behaviors and cerebrospinal fluid
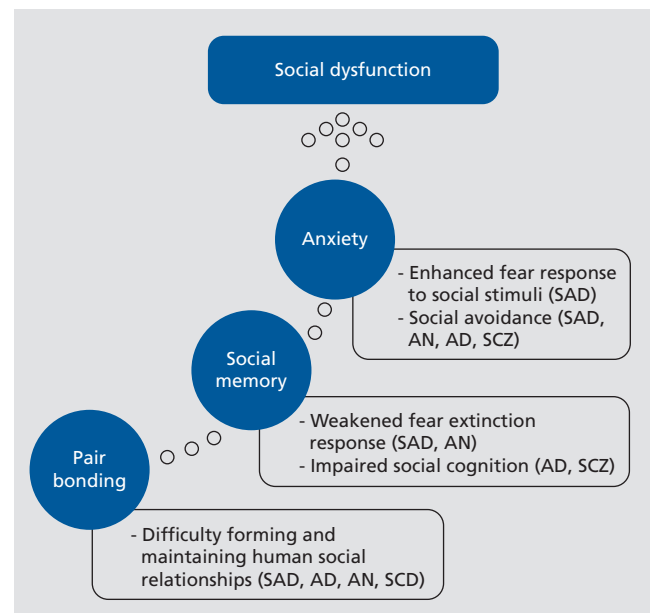

Figure 1. Human implications of nonprimate oxytocin studies on social functioning and anxiety. AD, anxiety disorder; AN, anorexia nervosa; SAD, social anxiety disorder; SCZ, schizophrenia.

oxytocin levels.[58] Prosocial behaviors have also been studied in adult rhesus macaques. Macaques increase the number of prosocial choices related to "social donation" after 2 hours of oxytocin inhalation. The macaque administered oxytocin made more prosocial choices (providing a juice box to another macaque) than the macaque that did not receive oxytocin.[59] These studies support that overall, oxytocin enhances macaque prosocial behavior.[56-59]

The effects of intranasal oxytocin on gaze patterns and social vigilance in rhesus macaques has been investigated as a component of social attention.[60] After oxytocin administration, macaques shifted their gaze patterns; they increased the amount of time spent gazing at eyes and faces of macaque images. In addition, they decreased species-typical social vigilance for images of emotional, dominant, and unfamiliar macaque faces in images. Similar responses were observed to images of negative faces after oxytocin administration, and in addition, there was no observed change in response to neutral faces.[61] A possible explanation is that oxytocin reduces activity in brain regions that involve attention and arousal, including the amygdala, which regulates vigilance, properties of faces, and emotional expression.[60]

Decreased social vigilance can lead to prosocial behavior. These findings are especially relevant to disorders with social-processing dysfunction. Decreased eye contact is a common symptom of multiple psychiatric disorders, including autism and social anxiety disorder.[62,63] Increased attention to social situations perceived as threatening is a component of social anxiety disorder.[64] Oxytocin is a candidate for both enhancing eye contact and helping to alleviate social vigilance in social anxiety disorder, without affecting social situations viewed as neutral or nonthreatening.

Anxiety has also been investigated in nonhuman primates. Multiple studies support that administration of oxytocin in rhesus macaques decreases cortisol, a glucocorticoid released in response to stress.[65] Oxytocin both increases prosocial behaviors and decreases salivary cortisol in macaque infants.[66] In addition, mother-reared macaques have decreased plasma cortisol when introduced to a new cage with a companion compared with non–mother-reared macaques.[58] As mentioned previously, the mother-reared macaques have increased oxytocin expression. No significant difference between the two groups was found when the macaques were put in a novel cage without a companion. These results indi-cate an anxiolytic effect in the presence of a companion, relating also to the social effects of oxytocin.

Human studies and social anxiety

The facilitation of prosocial behaviors and anxiolytic effects of oxytocin observed in animal research has led scientists to investigate oxytocin's role in human psychiatric conditions, such as social anxiety disorder, schizophrenia, and autism. The anxiolytic effects of oxytocin are supported by research demonstrating diminished negative self-judgment during a social task and decreased anxiety in response to social rejection.[67,68] Functional magnetic resonance imaging studies implicate underlying anxiolytic neurocircuitry, as decreased fear-associated amygdala activity was observed in response to threatening faces in individuals with generalized social anxiety disorder.[69] Research has been conducted at the molecular level, examining oxytocin genes and plasma levels, and at the clinical level, evaluating the effectiveness of intranasal oxytocin as a potential treatment for social anxiety disorder and other disorders with social dysfunction (*Figure 2*). The impact of oxytocin on social impairment in multiple psychiatric disorders is discussed below.

Genetic and biochemical studies

Genetic variations in the oxytocin receptor gene have been implicated in several psychiatric disorders, including depression, mood disorders, and autism spectrum disorders.[70,71] The polymorphism (rs53576) of the oxytocin receptor gene is located on the third intron in three forms: GG, AA, and AG.[72] In past studies, the G allele was found to be connected with prosocial traits like empathy, trust, and optimism; whereas the A allele was associated with sensitivity to stress, less optimism, less social skills, and lower self-esteem.[73,74] Oxytocin receptor gene methylation occurs in individuals with social anxiety disorder, including hypomethylation at CpG chromosome 3:8809437, which is associated with higher scores on the Social Phobia Scale and Social Interaction Anxiety Scale and a greater degree of amygdala responsiveness to social phobia–related words.[75] It is unclear whether the hypomethylation is a cause or result of social anxiety disorder.

Oxytocin plasma levels have also been analyzed in individuals with social anxiety disorder, although

results have not been consistent. In one study, plasma oxytocin levels showed a positive correlation with social anxiety symptom severity.[76] However, another study did not fully support these results. In individuals in close relationships, they found a positive correlation between oxytocin levels and anxiety but not oxytocin levels and avoidance scale scores.[77] Human genetic and biochemical research on the role of oxytocin in social anxiety disorder and other social functioning disorders is still being explored. The studies above suggest an association, but at this time there are no conclusive results.

Intranasal oxytocin studies

Social anxiety disorder

Oxytocin is a 9-amino-acid peptide that is unable to cross the blood brain barrier and enter the central ner-

vous system.[13] Intranasal administration has been the primary means of oxytocin delivery in humans thus far. Numerous studies have examined the effects of intranasally administered oxytocin on social anxiety symptoms and as an adjunct treatment for social anxiety disorder.

The amygdala has been a specific focus of human oxytocin research because of its hyperactivity in response to social threats and fear.[78,79] Oxytocin inhibits neurons in the amygdala that connect to other brain regions associated with fear, including the anterior cingulate cortex (ACC) and the medial prefrontal cortex (MPC).[80,81] Oxytocin reduces increased activation of the ACC and MPC in individuals with social anxiety disorder in response to sad faces.[81] Intranasal oxytocin has also been shown to enhance functional connectivity between the amygdala and the bilateral insula and middle cingulate/dorsal cingulate gyrus in individuals with social anxiety disorder when shown fearful faces.
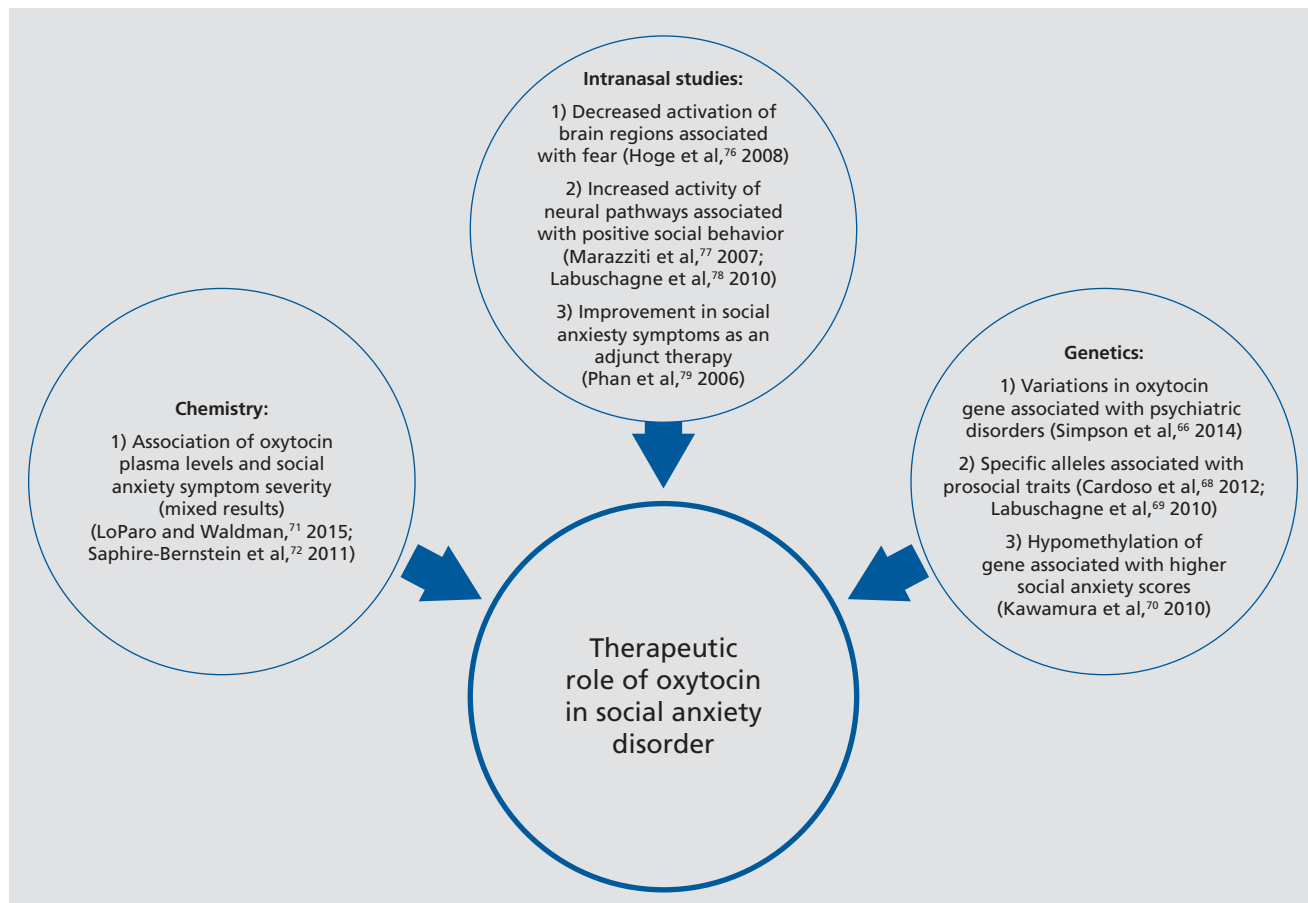

Figure 2. Studies supporting the therapeutic role of oxytocin in social anxiety disorder.

These pathways are associated with social/emotional behavior and suggest that oxytocin heightens activity in these regions and dampens activity of pathways related to fear response, thus "normalizing" both pathways.[82] A negative correlation has been described between connectivity of the amygdala-anterior cingulate/prefrontal cortex pathway with social anxiety severity at rest. Oxytocin also increases activity in the underactive rostral anterior cingulate cortex/medial frontal cortex pathway in individuals with social anxiety.[83]

Oxytocin has also been studied as an adjunct to other therapies for social anxiety. In a randomized placebo-controlled study, individuals with social anxiety disorder were administered intranasal oxytocin as an adjunct to exposure therapy.[84] Statistically significant improvement in positive evaluation of appearance and speech performance was demonstrated compared with placebo. However, both the placebo and oxytocin groups showed significant symptom reduction and improvement in life impairment scores, indicating a significant placebo effect. Thus, oxytocin as an adjunct may enhance improvement of some characteristics of social anxiety disorder but not others.

Other disorders: schizophrenia, autism, and anorexia

Although the focus has been on social anxiety, it is important to consider the effects of intranasal oxytocin on other disorders with impairments in social function, including schizophrenia and autism. Anorexia will also be discussed briefly because of a high comorbidity with social anxiety disorder (the lifetime prevalence has been reported as 33.9%).[85]

Schizophrenia treatment primarily addresses the positive symptoms of the disease but not the negative symptoms, such as asociality and affective flattening. The severity of these negative symptoms is strongly correlated with decline in social function and quality of life, and attempts to diminish this decline have been largely unsuccessful.[86] Oxytocin is a potential candidate for the treatment of these negative symptoms. Intranasally administered oxytocin in patients with schizophrenia has demonstrated an overall decrease both in negative and positive symptomology scores.[87] Six published clinical trials have reported improvement in negative symptoms with intranasal oxytocin added as an adjunct treatment to atypical antipsychotic medication.[88] Specific improvements in social functioning in patients with schizophrenia include increased ability to recognize emotions and improvements in high-level social functioning, such as detection of sarcasm, detection of deception, and empathy.[89,90] Individuals with autism also have dysfunction across multiple social domains. They show decreased social motivation, social aloofness, diminished eye contact, decreased social relationship reward, and difficulty maintaining social relationships.[91] Multiple studies support the conclusion that administration of intranasal oxytocin in individuals with autism increases eye gaze, enhances feelings of trust, increases recognition of affective speech, and increases scores on the Reading the Mind in the Eyes Test.[92-94] Research supports a strong association between autism and schizophrenia,[95] and studies are currently investigating the neurological, genetic, developmental, and molecular similarities between these illnesses. Oxytocin and other novel treatments beneficial to one should thus also be considered in the other.

Anorexia differs greatly from schizophrenia and autism, but one commonality is that social impairment can be a marked component of the disorder.[6] Oxytocin clinical trials have had mixed results in improvement of anorexia symptoms, and relatively few specific social dysfunction symptoms have been studied.[96-98] One study found that oxytocin significantly decreased attention toward "eating" stimuli and "negative body image" stimuli in patients with anorexia. Specific to social dysfunction, these results were most apparent in anorexics with higher levels of autistic-specific traits, indicating that the potential benefit of oxytocin in anorexics could be most effective in those with concurrent social difficulties.[94] It remains unclear whether oxytocin plasma levels are reduced in anorexia nervosa at baseline. Some studies have indicated lower levels of oxytocin; however, others have shown increases in plasma oxytocin after eating.[99] Future research implications include investigation of the role of oxytocin in anorexics with specific symptoms related to social dysfunction.

Clinical implications for oxytocin in social anxiety treatment/discussion

Researchers investigating the neural impact of oxytocin have primarily used the intranasal route of administration. Because oxytocin is unable to cross the blood-brain barrier, intravenous and oral administration of oxytocin are ineffective.[99] Although intranasal

administration provides some degree of central access, the bioavailability of exogenous oxytocin in the central nervous system is limited for a number of reasons. First, oxytocin, like any other peptide, will scarcely pass the blood-brain barrier and will be subject to degradation in the living organism. Second, upon intranasal administration, oxytocin can be absorbed through the nasal mucosa in multiple compartments, each of which varies in their absorption capacity and influences the amount of oxytocin that reaches the cerebrospinal fluid versus systemic circulation.[100] Thus, the prosocial behaviors or anxiolysis after oxytocin administration could result from multiple pathways: a direct pathway through the olfactory bulb to the cerebrospinal fluid, an indirect peripheral pathway that through a possible feed-forward mechanism influences central nervous system release of endogenous oxytocin, or other routes, such as through the oral mucosa and through a gastroenteric route.[101,102] Intranasal oxytocin bioavailability is likely to vary widely because of multiple factors.

Despite these factors, intranasal administration of oxytocin has yielded positive results in improvement of social dysfunction across multiple psychiatric disorders. Until other methods of delivery are developed, these results warrant continuation of intranasal oxytocin research in social anxiety disorder. Currently, researchers are attempting to create small-molecule oxytocin-receptor activators that hold promise for exposing the brain to high levels of oxytocin after oral administration. Important to advancement of these future analogs

and intranasal oxytocin is evidence of target engagement. Additional studies can investigate the relationship between specific regional receptor binding in the brain and therapeutic outcome at controlled dosages of intranasal oxytocin.[103] Future research may also include investigation of other neurotransmitters and neuropeptides implicated in social dysfunction pathophysiology. Multiple such molecules have been suggested to be involved in the pathophysiology of social anxiety. Of particular importance is the neuropeptide vasopressin. Research also supports the role of vasopressin—closely related to oxytocin—in maintaining social relationships and pair bonding.[104] One consideration for future investigation of social functioning is whether social dysfunction in psychiatric disorders results from an imbalance in oxytocin and vasopressin neural activity.

In summary, research provides evidence for the role of oxytocin in the pathophysiology of social dysfunction across the span of multiple psychiatric disorders through its impact on social vigilance, positive social evaluation, prosocial behaviors, and anxiolytic effects. Future implications include research supporting oxytocin target engagement, dose relationship of oxytocin with therapeutic effects, and consideration of other neural peptides and neurotransmitters in social functioning pathophysiology. ❏

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La oxitocina y el funcionamiento social

La ansiedad social es una forma de ansiedad caracterizada por un temor continuo de una o varias situaciones sociales o de rendimiento. Aunque para la ansiedad social existen diversas modalidades terapéuticas (terapia cognitivo conductual, inhibidores selectivos de la recaptura de serotonina, inhibidores selectivos de la recaptura de serotonina y noradrenalina, y benzodiacepinas), ellas resultan efectivas en no más del 60% a 70% de los pacientes. Debido a esto, los investigadores han buscado otras opciones de terapia para la ansiedad social. Esta revisión se enfoca en el péptido oxitocina como una potencial opción terapéutica para sujetos con ansiedad social. La investigación animal tanto de primates como de no primates da soporte al papel de la oxitocina en la facilitación de las conductas pro-sociales y sus efectos ansiolíticos. Los estudios en humanos muestran asociaciones significativas entre la ansiedad social y los alelos del gen del receptor de oxitocina, como también de la ansiedad social y los niveles plasmáticos de oxitocina. Además, la administración de oxitocina intranasal en humanos tiene efectos favorables para la sintomatología de la ansiedad social. Otras patologías, incluyendo el autismo, la esquizofrenia y la anorexia tienen componentes de la ansiedad social en sus fisiopatologías. En este artículo se discute el papel terapéutico de la oxitocina para la disfunción social en estas patologías.

Ocytocine et fonctionnement social

L'anxiété sociale est une forme d'anxiété caractérisée par la peur permanente d'une ou plusieurs situations sociales ou de performance. De nombreuses modalités de traitement existent pour l'anxiété sociale, (thérapie cognitive comportementale, inhibiteurs sélectifs de la recapture de la sérotonine, inhibiteurs sélectifs de la recapture de la noradrénaline, benzodiazépines), mais elles ne sont efficaces que pour 60 à 70 % des patients. Des chercheurs ont donc examiné d'autres possibilités de traitement de l'anxiété sociale. Cet article s'intéresse au peptide ocytocine comme traitement éventuel des personnes atteintes d'anxiété sociale. La recherche chez les animaux, à la fois chez les primates et les non-primates, confirme que l'ocytocine facilite les comportements pro-sociaux et a des effets anxiolytiques. D'après des études chez l'homme, il existe des associations significatives entre l'anxiété sociale et les allèles du gène du récepteur de l'ocytocine ainsi qu'entre l'anxiété sociale et les concentrations plasmatiques d'ocytocine. De plus, l'administration intranasale d'ocytocine chez l'homme a des effets bénéfiques sur les symptômes de l'anxiété sociale. Nous analysons ensuite le rôle thérapeutique de l'ocytocine sur le dysfonctionnement social dans l'autisme, la schizophrénie et l'anorexie, des troubles dont la physiopathologie présente une composante d'anxiété sociale.