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OXYTOCIN: HOW DOES IT AFFECT SOCIAL BEHAVIOR?

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ABSTRACT

The neuropeptide oxytocin has had key roles throughout mammalian evolution in the regulation of complex social cognition and behaviors, such as attachment, parental care, pair-bonding, as well as social exploration and recognition. Recently, studies have begun to provide evidence that the function of this neuropeptide is impaired in mental disorders associated with social deficits. The fundamental ability to form attachment is indispensable for human social relationships. Impairments in social behaviour are associated with decreased quality of life and psychopathological states. In non-human mammals, the neuropeptide oxytocin (OXT) is key mediators of complex social behaviours, including attachment, social recognition and aggression. In particular, OXT reduces behavioural and neuroendocrine responses to social stress and seems both to enable animals to overcome their natural avoidance of proximity and to inhibit defensive behaviour, thereby, facilitating approach behaviour. Initial studies in humans suggest behavioural, neural, and endocrine effects of oxytocin, similar to that found in animal studies. This review focuses on advances made to date in the effort to understand the role of OXT in human social behaviour. First, the literature on OXT and its involvement in social stress and anxiety, social cognition, social approach, and aggression is reviewed. Second, we discuss clinical implications for mental disorders that are associated with social deficits (e.g. autism spectrum disorder, borderline personality disorder).

KEYWORDS: Neuropeptide, oxytocin, social behaviour, stress, anxiety, attachment, approach behavior

INTRODUCTION

Social interaction permeates the whole of human society and the fundamental ability to form attachment is indispensable for human social relationships. Impairments in social behaviour are associated with decreased quality of life and pathological states. In view of the ubiquity of abnormal social behaviour in mental disorders as noted, ''we are, by nature, a highly affiliative species craving social contact. When social experience becomes a source of anxiety rather than a source of comfort, we have lost something fundamental — whatever we call it''.[1] In non-human mammals, receptors for the neuropeptide oxytocin (OXT) is distributed in various brain regions associated with the central nervous control of stress and anxiety and with social behaviour, including parental care, pair-bonding, social memory, and social aggression.[2] Specifically, OXT seems both to enable animals to overcome their natural avoidance of proximity and to inhibit defensive behaviour, thereby facilitating approach behavior.[3-8]

Aside from its effects on social behaviour, OXT shows significant binding in the limbic system, including the amygdala.[9, 10] and decreases anxiety and the neuroendocrine response to stress in social interactions.[11-15] At a cellular level, recently showed that distinct populations of neurons in the amygdala are activated by OXT receptor stimulation, through which these peptides modulate the integration of excitatory information from the amygdala and cerebral cortex in opposite manners.[16] These results suggest that the endogenous balance between OXT receptor expression and activation may set distinct, individually tuned levels for the activation of the autonomic fear response. In general, centrally active AVP seems to be associated with increased vigilance, anxiety, arousal, and activation, while OXT has behavioural and neural effects associated with reduced anxiety, relaxation, growth, and restoration.[17] Thus, both peptide hormones are important in social stress and in social interaction, and in turn, a dysregulated metabolism may be associated with mental disorders of psychosocial relevance.

Much of the knowledge regarding the ability of OXT to regulate social interactions is based on data from animals using centrally administered agonists and antagonists or knockout mice. However, initial studies suggest similar social and stress-related effects of both neuropeptides in humans.[18,19] Besides the endogenous stimulation of OXT during breast-feeding and positive physical contact, leading to attenuated endocrine responses to stress in women, studies in humans have also been carried out with exogenous administration of OXT.[20-25]

Intravenous OXT infusion has also been shown to induce significant behavioural effects.[26] It seems that only a small part of the neuropeptide passes the blood–brain barrier, and possible side effects are more likely following intravenous infusion of neuropeptide. In particular, a potential clinical use is dependent on a more direct and secure pathway to the human brain. Fortunately, neuropharmacological research has shown that neuropeptide gain access to the human brain after intranasal administration, [27-29] providing a useful method for studying the central nervous effects of OXT in humans.[19]

This article reviews recent advances made to date in the endeavour to understand the role of OXT in human social behaviour. As the animal literature in this area is reviewed in detail by several other authors in this review article, we will focus on the existing findings from studies of healthy humans and patients. In this review, we emphasize the significance of OXT in stress responsiveness, anxiety, and prosocial behaviour.

OXYTOCIN AND HUMAN SOCIAL BEHAVIOR

Social stress and anxiety

In animal studies, OXT has been found to be released peripherally and within the brain in response to both physical and psychological stress and fearful situations.[30] Intracerebral OXT has been shown to inhibit the stress-induced activity of the hypothalamic-pituitary-adrenal (HPA) axis responsiveness,[31 32] the activity of the amygdale in the modulation of the autonomic fear response.[33] Numerous studies on the inhibitory influence of OXT on stress responsive neurohormonal systems focused on the endogenous stimulation of OXT during lactation in rodents. The suckling stimulus by the newborn was found to increase OXT release and decrease basal plasma levels of ACTH and cortisol.[34-39] In lactating women, the increase of OXT following breast-feeding is associated with dampened levels of ACTH and cortisol.[40-43] In addition, lactation in humans also appears to reduce responses to physical and psychosocial stress exposure. In lactating women, attenuated HPA axis responses can be observed if breast-feeding starts 30–60min before stress exposure, depending on the kind of stressor.[24,44] As no effect of stress has been found on OXT plasma levels, OXT does not seem to mediate the attenuation of cortisol stress responses at the adrenal level.[43] Thus, the inhibitory effect of OXT on HPA axis responsiveness points to a more central modulation and could, in fact, be localized in the paraventricular nucleus and in the septum, as demonstrated in rats. [38] Interestingly, breast-feeding mothers with increased plasma OXT in response to a speech stressor that immediately followed baby holding were found to have

lower blood pressure than mothers with a decrease in OXT after stress.[45] Furthermore, non-postpartum healthy women who showed increased plasma OXT levels in response to positive emotion and massage and who maintained OXT levels during negative emotion were less likely to report interpersonal problems associated with intrusiveness.[46] Maintaining OXT levels during sadness has also been associated with lower anxiety in close relationships. Recently, Ditzen et al. showed that women receiving standardized physical contact from their partner (neck and shoulder massage) before stress exposure exhibited significantly lower cortisol and heart rate responses to stress compared with women who received verbal social support or no social interaction from the partner.[47] Altogether, these results from human studies imply a direct protective effect of endogenous OXT stimulation. Within this context, however, it should be noted that there are a variety of confounding factors, in particular the release of other hormones (e.g. prolactin or opioids), which are difficult to control for endogenous stimulation paradigms such as lactation or physical contact. Moreover, plasma concentrations of OXT do not seem to reflect the central nervous availability of the OXT. [48] Thus, the specific effects of central OXT as an underlying biological mechanism for the reduction of stress and anxiety in humans have to be investigated using challenge procedure methodologies involving OXT administration in double-blind, placebo-controlled designs.

In a double-blind, placebo-controlled design, all participants were randomly assigned to receive intranasal OXT (24 IU) or placebo 50min before stress, and either social support from their best friend during the preparation period or no social support. Subjects who received both social support and intranasal OXT exhibited the lowest cortisol concentrations during stress exposure, whereas subjects who received no social support and placebo demonstrated the highest cortisol response.[49] Notably, there were corresponding results in psychological measures, indicating that subjects without social support and with placebo showed the expected decrease in calmness and increase in anxiety during stress. In contrast, participants who received either social support or OXT or both protective factors showed increasing calmness and decreasing anxiety scores during stress. Moreover, pre- and post-stress comparisons of anxiety showed an anxiolytic effect of OXT administration. Recent animal research indicates that central nervous OXT modulates the autonomic fear response via OXT receptors in the amygdala.[33] From these data, it may be concluded that OXT plays an important role as an underlying biological mechanism for the well-known stress-protective effects of positive social interaction.

Social approach behavior

Besides its modulating role in psychosocial stress, OXT is involved in the regulation of social approach behaviour, social affiliation, and attachment. A large body of evidence from animal studies has implicated OXT and AVP in mating, pair-bonding, and adult–infant attachment.[50] It is well known that pair-bonding in prairie voles, for example, is regulated by both OXT and AVP,[51] whereas maternal behavior in rats is modulated only by OXT.[52] In addition, aggressive behaviour seems to be modulated selectively by AVP.[53] In contrast to the long tradition of animal research, human studies have only just begun to gain insights into how OXT modulates social approach behaviour and affiliation including the associated cognitive processes. In a first study, OXT was found to increase the stress-reducing and anxiolytic effect of social support in a psychosocial laboratory stress protocol. Participants who had received OXT in combination with social support from their best friend showed significantly attenuated endocrine and behavioural stress responses compared with social support alone. [49] In another study on the effects of OXT on human memory, OXT selectively modulated implicit memory depending on the social relevance (reproduction-related vs. neutral) of semantic word stimuli.[54]

In humans, trust in other people is a prerequisite of social affiliation and social approach. Therefore, in the experiment it can be seen as a pivotal study addressing the role of OXT in human social approach behaviour. The authors showed that a single dose of 24 IU intranasal OXT caused a substantial increase in trust among humans, thereby, greatly increasing the benefits from social interactions in a trust game. More specifically, 45% of subjects in the OXT group showed the maximal trust level, whereas only 21% in the placebo group showed maximal trust. Most importantly, this study shows that the effect of OXT on trust was not due to a general increase in the readiness to bear risks. Rather, OXT specifically increases an individual's willingness to accept social risks within social interactions. These results concur with animal research suggesting an essential role for OXT as a biological basis of prosocial approach behaviour in humans.[55]

Taken together, the recent studies suggest that in humans too, OXT modulates social perception, social cognition, and social behaviour, thereby possibly promoting social approach and affiliation. Besides the stress-reducing and anxiolytic effects, OXT seems to be involved in social cognitive functions such as emotion recognition. Functional imaging studies support the idea that the anxiolytic effect of exogenously administered OXT is at least

in part due to a deactivation of amygdala-mediated arousal. Reduced emotional arousal during social encounters might also promote social approach and might therefore contribute to the positive effects of OXT on trust and social cognition. Clearly, alternative pathways will need to be investigated in future research, given the widespread distribution of OXT receptors in the brain and the distribution of the neural network underlying social cognition and emotion.[48, 56]

CONCLUSION

Over the last decades, animal models have achieved enormous insights into how oxytocin contributes to the regulation of social behaviour. We have reviewed a growing body of evidence from recent human studies indicating that the basic effects of OXT on social behaviour from animal research may also be applicable to human social interaction. Although the translation of behavioural and neurobiological findings from animal studies to humans generally bears the risk of drawing oversimplified parallels between rodents and humans. The findings to date are encouraging in terms of providing a better understanding of the neuroendocrine mechanisms of human social behaviour. Moreover, these translational findings suggest that OXT may play an important role in the etiology and treatment of a number of clinical disorders involving social deficits and disrupted attachment. With regard to the role of OXT in human social behaviour, the main findings can be summarized as follows: (i) OXT is associated with the regulation of the behavioural and endocrine stress response, that is OXT is released in response to socially relevant challenges and attenuates the endocrine and autonomic responses to stress; (ii) OXT is released in response to positive social interactions, such as social support or social proximity, thus, possibly representing a mediator for the well-known stress-protective effects of social support; (iii) The neural correlate for the anxiolytic effects of OXT has been suspected in limbic areas, in particular, in the amygdala; (iv) OXT has been found to attenuate amygdala reactivity to emotional and social stimuli and to reduce brainstem activity, which is associated with autonomic arousal and (v) OXT has been found to promote the interpretation of social signals, possibly representing an enhanced readiness to show social approach behaviour and empathy.

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