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CHAPTER 28

Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans

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Abstract: 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 neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) are 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. AVP has primarily been implicated in male-typical social behaviours, including aggression and pair-bond formation, and mediates anxiogenic effects. Initial studies in humans suggest behavioural, neural, and endocrine effects of both neuropeptides, similar to those found in animal studies. This review focuses on advances made to date in the effort to understand the role of OXT and AVP in human social behaviour. First, the literature on OXT and AVP and their 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). Finally, a model of the interactions of anxiety and stress, social approach behaviour, and the oxytocinergic system is presented, which integrates the novel approach of a psychobiological therapy in psychopathological states.

Keywords: neuropeptides; oxytocin; arginine vasopressin; social behaviour; stress; anxiety; attachment; approach behaviour

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, Insel (2002) 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" (p. 3). In non-human mammals, receptors for the neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) are distributed in various brain regions (Landgraf and Neumann, 2004) associated with the central nervous control of stress and anxiety and with social behaviour, including parental care, pair-bonding, social memory, and social aggression. Specifically, OXT seems both to enable animals to

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overcome their natural avoidance of proximity and to inhibit defensive behaviour, thereby facilitating approach behaviour (Carter and Altemus, 1997; Pedersen, 1997; Carter, 1998; Uvnas-Moberg, 1998; Insel and Young, 2001; Young et al., 2002). AVP has primarily been implicated in male-typical social behaviours, including aggression, pair-bond formation, scent marking, and courtship (Carter, 1998; Young and Wang, 2004; Lim and Young, 2006).

Aside from its effects on social behaviour, OXT shows significant binding in the limbic system, including the amygdala (Landgraf and Neumann, 2004; Huber et al., 2005) and decreases anxiety and the neuroendocrine response to stress in social interactions (Windle et al., 1997a, 2004; Neumann et al., 2000a; Bale et al., 2001; Carter et al., 2001; Parker et al., 2005). In contrast, AVP seems to play an anxiogenic role, with elevated AVP expression in the hypothalamic paraventricular nucleus being associated with increased behavioural and neuroendocrine anxiety levels (Murgatroyd et al., 2004). In addition, Ferris et al. (2006) recently showed that the orally active AVP V1a receptor antagonist SRX251 selectively blocks aggressive behaviour in hamsters. At a cellular level, Huber et al. (2005) recently showed that distinct populations of neurons in the amygdala are activated by OXT and AVP receptor stimulation, through which these peptides modulate the integration of excitatory information from the amygdala and cerebral cortex in opposite manners. These results suggest that the endogenous balance between OXT and AVP 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 (Carter, 2007). 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 and AVP 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 (for review, see Bartz and Hollander, 2006; Heinrichs and Gaab, 2007). Besides the endogenous stimulation of OXT during breast-feeding and positive physical contact, leading to attenuated endocrine responses to stress in women (Altemus et al., 1995; Turner et al., 1999; Heinrichs, 2000; Light et al., 2000; Heinrichs et al., 2001, 2002; Ditzen et al., 2007), studies in humans have also been carried out with exogenous administration of OXT and AVP. Although intravenous OXT infusion has been shown to induce significant behavioural effects (Hollander et al., 2003, 2007), 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 neuropeptides. 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 neuropeptides gain access to the human brain after intranasal administration (Pietrowsky et al., 1996; Born et al., 1998, 2002; Heinrichs, 2000), providing a useful method for studying the central nervous effects of OXT and AVP in humans (Heinrichs and Gaab, 2007).

This article reviews recent advances made to date in the endeavour to understand the role of OXT and AVP in human social behaviour. As the animal literature in this area is reviewed in detail by several other authors in this issue, we will focus on the existing findings from studies of healthy humans and patients. In the first part of this review, we examine the significance of OXT in stress responsiveness, anxiety, and prosocial behaviour. In the second part, we address the role of AVP in social behaviour. Finally, we conclude by outlining the clinical implications for mental disorders that are associated with social deficits and present a model of the interactions of anxiety and stress, social approach behaviour, and the oxytocinergic system.

Effects of oxytocin on human social behaviour

Oxytocin, 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 (Neumann et al., 2000a, b). Intracerebral OXT has been shown to inhibit the stress-induced activity of the hypothalamic-pituitary-adrenal (HPA) axis responsiveness (Neumann, 2002; Parker et al., 2005) and the activity of the amygdala in the modulation of the autonomic fear response (Huber et al., 2005). 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 (Uvnas-Moberg, 1994; Carter and Altemus, 1997; Windle et al., 1997b; Uvnas-Moberg et al., 1999; Neumann et al., 2000b; Carter et al., 2001).

In lactating women, the increase of OXT following breast-feeding is associated with dampened levels of ACTH and cortisol (Chiodera et al., 1991; Amico et al., 1994; Nissen et al., 1996; Heinrichs et al., 2002). 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 30–60 min before stress exposure, depending on the kind of stressor (Altemus et al., 1995, 2001; Heinrichs et al., 2001). 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 (Heinrichs et al., 2002). 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 (Neumann et al., 2000a, b). 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 (Light et al., 2000). 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 (Turner et al., 1999). Maintaining OXT levels during sadness has also been associated with lower anxiety in close relationships. Recently, Ditzen et al. (2007) 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. 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 opioid peptides), which are difficult to control for in 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 neuropeptide (Landgraf and Neumann, 2004). 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 an initial study, we were interested in investigating the interactive effects of an altered availability of central nervous OXT and social support in a standardized psychosocial stress protocol (Heinrichs et al., 2003). In a double-blind, placebo-controlled design, all participants were randomly assigned to receive intranasal OXT (24 IU) or placebo 50 min 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 (Heinrichs et al., 2003). 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. 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.

Recent animal research indicates that central nervous OXT modulates the autonomic fear response via OXT receptors in the amygdala (Huber et al., 2005). In an initial functional magnetic resonance imaging (fMRI) study in humans, Kirsch et al. (2005) imaged amygdala activation through fear-inducing visual stimuli in healthy men after double-blind, placebo-controlled crossover substance administration. The authors found that 27 IU intranasal OXT markedly reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioural manifestations of fear. Most recently, we extended these results by measuring neural responses to social cues with different emotional valences: emotional faces with fearful, angry and happy expressions (Domes et al., 2007a). In an fMRI study using a double-blind, placebo-controlled within-subject design, we found that a single dose of 24 IU OXT reduced right-sided amygdala responses to all three face categories even when the emotional content of the presented face was not evaluated explicitly. In addition, exploratory whole brain analysis revealed modulatory effects in prefrontal and temporal areas, as well as in the brainstem (Domes et al., 2007a). In conclusion, these initial neuroimaging studies suggest a modulatory role of OXT on amygdala responsiveness irrespective of the emotional valence of stimuli. The attenuating effect on amygdala activity in response to both positive and negative social stimuli might reflect reduced uncertainty about the predictive value of a social stimulus and thereby facilitate social approach behaviour.

Oxytocin, social cognition and social approach

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 (Lim and Young, 2006). It is well known that pair-bonding in prairie voles, for example, is regulated by both OXT and AVP (Cho et al., 1999), whereas maternal behaviour in rats is modulated only by OXT (Insel, 1992). In addition, aggressive behaviour seems to be modulated selectively by AVP (Ferris et al., 1992).

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 (Heinrichs et al., 2003). 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 (Heinrichs et al., 2004).

In humans, trust in other people is a prerequisite of social affiliation and social approach. Therefore, the experiment by Kosfeld et al. (2005) 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.

Focusing on the modulation of social cognitive processes, a recent study from our laboratory examined the effects of intranasally administered OXT on the ability to infer the affective state of another individual from facial cues (Domes et al.,

2007b). In this study, participants were given a set of pictures showing the eye region of emotional faces, and were asked to infer the internal state of the depicted person — a test originally developed for the assessment of social attributional deficits of "mind-reading" in autism spectrum disorder (ASD) (Baron-Cohen et al., 2001; Dziobek et al., 2006). A single dose of 24 IU OXT administered intranasally enhanced performance in this test compared to placebo. Thus, OXT improves the ability to infer the mental state of others. Although the causal mechanisms are not clear, OXT-induced facilitation of certain social cognitive functions might be associated with social approach behaviour. A recent study by Guastella et al. (2008) reported an increased number and duration of gazes towards the eye region of emotionally neutral human faces following intranasal OXT administration (24 IU) as compared to placebo (Guastella et al., 2008), indicating a key role of OXT in facial processing and interpersonal communication in humans.

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 (Landgraf and Neumann, 2004) and the distribution of the neural network underlying social cognition and emotion (Adolphs, 2003).

Effects of arginine vasopressin on human social behaviour

Whereas OXT plays a key role both in prosocial behaviour and in the central nervous control of stress and anxiety, AVP has primarily been implicated in male-typical social behaviours, including aggression and pair-bond formation and in stress responsiveness (Goodson and Bass, 2001). Although most of the studies conducted thus far on human social behaviour have focused on OXT, few studies on AVP suggest behavioural effects similar to those found in animal research.

To examine the facilitatory role of central AVP in human aggressive behaviour, Coccaro et al. (1998) examined the relationship between cerebrospinal fluid (CSF) AVP and indices of aggression in personality-disordered subjects. The authors found a positive correlation between levels of CSF AVP and life histories of general aggression and aggression against other persons, suggesting an enhancing effect of central AVP in individuals with impulsive aggressive behaviour.

Using a laboratory challenge methodology, two recent studies examined the effect of intranasal AVP administration on human facial responses related to social communication. In a first study, Thompson et al. (2004) examined the effects of 20 IU intranasal AVP on cognitive, autonomic, and somatic responses to emotionally expressive facial stimuli in healthy male students using a placebo-controlled, double-blind design. Whereas AVP did not affect attention towards, nor autonomic arousal in response to, emotional facial expressions with different valence (neutral, happy, angry), the authors observed selective enhancements of the corrugator supercilii electromyogram (EMG) responses evoked by emotionally neutral facial expressions. Interestingly, subjects of the AVP group yielded magnitudes in response to neutral facial expressions that were similar to placebo subjects' magnitudes in response to angry facial expressions (Thompson et al., 2004). Due to the crucial role of this muscle group for species-specific agonistic social communication (Jancke, 1996), these results suggest that AVP may influence aggression by biasing individuals to respond to emotionally ambiguous social stimuli as if they were threatening or aggressive.

In order to investigate possible sex-specific influences of AVP on human social communication, Thompson et al. (2006) conducted a further experiment. Men and women received 20 IU

intranasal AVP or placebo, and their facial EMG, heart rate, and skin conductance responses to pictures of same-sex models posing various facial expressions of emotion were tested. In addition, subjects rated the friendliness of the faces. In men, AVP stimulated agonistic facial motor patterns in response to the faces of unfamiliar men. Interestingly, AVP also decreased perceptions of the friendliness of these faces. In women, by contrast, AVP stimulated affiliative facial motor patterns in response to unfamiliar female faces and increased perceptions of friendliness of these faces. Notably, AVP also affected autonomic responses to threatening faces and increased anxiety.

Altogether, central AVP has the ability to influence social communication processes in humans, as is the case in numerous other vertebrates. Moreover, the effects of AVP appear to be sex-specific, promoting agonistic and affiliative types of responses towards same-sex faces in men and women, respectively.

Clinical implications

Social behaviour in health is tightly regulated and dysfunctional alterations can result in a psychopathological state. Aside from social anxiety, social deficits may also occur as ASDs, obsessive-compulsive disorder (OCD) or as borderline personality disorder (BPD). In the following, we discuss the role of OXT and AVP in mental disorders that are associated with social deficits.

Autism spectrum disorder

ASD is a group of developmental disorders comprising autism, Asperger syndrome, and high functioning autism (DSM-IV). ASD is characterized by a specific pattern of abnormalities in communication, impairments in social cognition and repetitive behaviours. It has been argued that deficits in theory of mind or ''mind-reading'', that is the ability to attribute mental states to behavioural cues, represent the core deficit underlying the social impairments of ASD (Frith and Happe, 1994; Frith, 2001; Schultz, 2005).

Because some social deficits in ASD mimic the deficits of animals that lack OXT, some authors have argued that there might be a link between ASDs and OXT/AVP (Insel, 1997; Young et al., 2002; Hammock and Young, 2006; Carter, 2007). We will review three lines of evidence that support this notion: (1) plasma-level studies, (2) genetic studies, and (3) administration studies in ASD.

First, there is some evidence that patients with ASD show blunted plasma levels of OXT. Modahl et al. (1998) found lower plasma levels in children with ASD and correlations between plasma OXT levels and social functioning. Green et al. (2001) extended these results by demonstrating alterations in OXT metabolism in ASD. In particular, children with ASD showed enhanced OXT precursor to OXT ratios.

The second line of evidence highlights the possible role of the OXT receptor (*Oxtr*) gene in ASD. A number of studies have emphasized the 3p25 region containing the *Oxtr* gene as the most promising linkage site for ASD (McCauley et al., 2005; Lauritsen et al., 2006; Ylisaukko-oja et al., 2006). A study with a sample of Chinese Han families suggests an association between ASD and two single nucleotide polymorphisms (rs2254298 and rs53576) (Wu et al., 2005). These results were confirmed in part in a Caucasian sample (Jacob et al., 2007) and further extended in a family-based association study (Lerer et al., 2007) showing interactions with social cognitive skills. Despite these studies, which revealed associations of certain *Oxtr* polymorphisms with ASD, there are other studies suggesting that polymorphisms of *Avpr-1a* gene are also associated in ASD (Kim et al., 2002; Wassink et al., 2004; Yirmiya et al., 2006). Taken together, these studies highlight the possible role of genetic variations of neuropeptide receptors in the development of ASD. This is in line with a large body of animal studies that have revealed the importance of both *Avpr* and *Oxtr* genes in the regulation of social behaviour (Lim and Young, 2006; Carter, 2007).

Finally, two studies suggest that systemic infusions of OXT reduce repetitive behaviour in ASD (Hollander et al., 2003) and improve emotion recognition in ASD (Hollander et al., 2007). Although these studies used systemic infusions of

OXT, giving rise to the above-mentioned concerns about the transmission of the peptide to the brain, the results are consistent with the effects reported after intranasal administration in healthy males (Domes et al., 2007b).

To summarize, there is increasing evidence that the *Oxtr* gene might be involved in the development of ASD. Furthermore, a number of studies show that the availability of OXT is associated with socio-cognitive functioning in ASD. It should be noted that there are also studies that link ASD to alterations of AVP and related neuropeptides, such as apelin (Momeni et al., 2005; Boso et al., 2007).

Obsessive-compulsive disorder

According to DSM-IV, recurrent, intrusive thoughts and fears of danger or contamination, and compulsive behaviours (e.g. excessive hand-washing) or cognitions for relieving anxiety are the most prominent symptoms of OCD. Based on the mnemonic effects of OXT and AVP (see above) and the possible role of both peptides in self-grooming behaviour in animals (Pedersen et al., 1988; Lumley et al., 2001), it has been put forward that OCD symptoms might be associated with alterations in central neuropeptide functioning (cf. Leckman et al., 1994a). This idea stimulated several clinical studies on OXT and AVP in OCD, which we will review in the following section.

Regarding CSF and plasma levels of AVP, adult OCD patients showed elevated basal CSF levels of AVP and increased secretion of AVP into the plasma in response to hypertonic saline administration (Altemus et al., 1992). In contrast, Leckman et al. (1994b) reported normal CSF concentrations of AVP for OCD patients. In a study with children, CSF AVP concentration and the AVP/OXT ratio were negatively correlated with OCD symptom severity (Swedo et al., 1992), which might suggest developmental changes in AVP in patients with OCD.

Studies investigating CSF levels of OXT found enhanced CSF levels of OXT in children and adolescents with OCD compared with other anxiety disorders and healthy controls (Swedo et al., 1992), and in adults with non-tic-related OCD compared to tic-related OCD, Tourette Syndrome, and healthy controls (Leckman et al., 1994b). In addition, Leckman et al. (1994b) found a strong correlation between the severity of compulsion (measured with the Yale–Brown Obsessive Compulsive Scale) and CSF OXT in non-tic-related OCD. Altemus et al. (1999) were not able to confirm the finding of enhanced OXT levels in OCD.

Although an early case study reported symptomatic improvement in OCD patients treated with intranasal OXT (Ansseau et al., 1987), subsequent controlled studies did not confirm therapeutic effects of systemic (Charles et al., 1989) or intranasal administration (den Boer and Westenberg, 1992; Salzberg and Swedo, 1992; Epperson et al., 1996a, b) of OXT in OCD. These negative results might be attributed to the commonly low statistical power due to insufficient sample sizes (den Boer and Westenberg, 1992; Salzberg and Swedo, 1992; Epperson et al., 1996a, b), the short-term treatment (Salzberg and Swedo, 1992; Epperson et al., 1996a, b) or to low doses of treatment (den Boer and Westenberg, 1992; Salzberg and Swedo, 1992). Another study revealed significant changes in CSF neuropeptide concentrations following long-term clomipramine treatment of child and adolescent OCD patients: AVP decreased (among corticotropin-releasing hormone and somatostatin), whereas OXT increased in response to clomipramine treatment (Altemus et al., 1994).

Taken together, the findings on the role of OXT and AVP in OCD are inconsistent. Thus, further research is needed to elucidate the potential role of OXT and AVP on compulsive behaviour and ruminative, obsessional thoughts and fears in OCD.

Borderline personality disorder and early trauma

BPD is characterized by a pervasive pattern of instability in affect and interpersonal relationships as well as by (auto-)aggressive behaviours (Lieb et al., 2004). In particular, BPD has been associated with excessive socio-affective vigilance and enhanced reactivity to emotional and social stimuli (Herpertz et al., 1997). Hypervigilance to emotionally laden social stimuli is further confirmed by studies showing enhanced amygdala reactivity to negative scenes (Herpertz et al., 2001), negative facial expressions (Minzenberg et al., 2007), and

even to faces of neutral valence (Donegan et al., 2003). Furthermore, BPD patients have been described as hypersensitive to social signals, sometimes misinterpreting ambiguous subtle social cues in terms of a negativity bias (Wagner and Linehan, 1999), particularly towards the perception of anger (Domes et al., 2008).

Some researchers have reviewed the role of attachment theory for understanding BPD. According to these reviews, BPD is best characterized by unresolved, preoccupied and fearful types of attachment (Agrawal et al., 2004; Levy, 2005). The insecure attachment style exhibited by many BPD patients may be the basis for the fundamental distrust that BPD patients report with regard to their social relationships. Thus, alterations in the OXT/AVP system have been considered as a possible factor in the pathogenesis in disturbed adult attachment (Carter, 1998). Given the high prevalence of severe childhood trauma and neglect in BPD (Lieb et al., 2004), it has been speculated that early stress interferes with the developing neuropeptide system and alters receptor binding of OXT and AVP, thereby promoting the development of severe attachment disorders (Carter, 2003).

In line with this notion, Fries et al. (2005) found an association between reduced early physical and emotional contact and basal levels of plasma AVP. In this naturalistic study, early neglect had no effect on basal levels of OXT, but rather impaired the increase of peripheral OXT triggered by a mother–infant interaction (Fries et al., 2005). In addition, Meinlschmidt and Heim (2007) showed that a single dose of 24 IU intranasal OXT reduces salivary cortisol concentrations in healthy men with early parental separation in comparison with healthy control subjects. Thus, early neglect seems to impair the central regulation of peptide release and/or synthesis in social interaction.

Conclusion

Over the last decades, animal models have achieved enormous insights into how neuropeptides contribute 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 and AVP 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 and AVP 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: (1) 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. (2) 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. (3) The neural correlate for the anxiolytic effects of OXT has been suspected in limbic areas, in particular in the amygdala. OXT has been found to attenuate amygdala reactivity to emotional and social stimuli and to reduce brainstem activity, which is associated with autonomic arousal. (4) OXT has been found to promote social cognition and the interpretation of social signals, possibly representing an enhanced readiness to show social approach behaviour and empathy. (5) Finally, there is initial evidence that the central OXT system is altered in several mental disorders that are characterized by severe social disturbances, such as ASDs, OCD, personality disorders, and following early trauma. Although the role of OXT and other neuropeptides is not yet clear in terms of the etiology of these clinical disorders, there is preliminary evidence suggesting that genetic alterations of neuropeptide receptors and developmental challenges (e.g. early adverse experience) interact in the etiology and development of these disorders.

Although most of the studies conducted thus far on human social behaviour have focused on OXT, initial studies on AVP also suggest behavioural effects similar to those found in animal research. Specifically, central AVP has been shown to influence social communication in a sex-specific manner, promoting agonistic facial responses towards same-sex faces in men but affiliative responses in women.

Despite the progress of animal and human research on behaviourally relevant effects of the neuropeptides OXT and AVP, there are still a number of unresolved issues. Most of the studies investigating the effects of OXT in humans have restricted their samples to male volunteers. Future studies should include both sexes to determine whether the sexual dimorphism in the behavioural effects of OXT and AVP known from several vertebrate classes (De Vries and Panzica, 2006) also holds for human behaviour. The detailed mechanism of brain penetration of OXT and AVP following different methods of administration and the relationship between plasma and central OXT and AVP (including possible crosstalks of these neuropeptides at their respective central receptors) is another area that warrants further investigation (McEwen, 2004). Besides recent advances made in identifying neural activity using fMRI, the development of specific radioactive labelling of neuropeptides in positron emission tomography will be needed to understand how OXT and AVP receptors are mapped in the human brain.

Finally, basic research in animals and humans has stimulated studies regarding the idea that neuropeptides might be a significant target for novel therapeutic approaches aimed at reducing social anxiety and increasing social abilities in several mental disorders that are characterized by social interaction pathology. In a recent review, Carter (2007) noted that "Knowledge of natural ways to stimulate the release of endogenous OXT or to inhibit 'excess' AVP might be protective against the development of the features of ASD [autism spectrum disorder], perhaps even remediating the expression of ASD-like behaviours in later life" (p. 180). As for the anxiogenic and aggression-related role of AVP, the development of selective V1a and V1b receptor antagonists, as known from animal studies (Griebel et al., 2005; Ferris et al., 2006), is a promising target for human neuropsychopharmacological research, in particular in the treatment of stress-related disorders and disorders with interpersonal violence such as anti-social personality disorder. Unfortunately, to date, there are no V1a or V1b receptor antagonists available for use in humans.

The currently most promising approach seems to be to increase the availability of OXT in the central nervous system by exogenous administration of the neuropeptide or selective agonists. Notably, there is initial evidence for the applicability of this approach using systemic infusions of OXT in autism (Hollander et al., 2003, 2007). Although these studies show good potential, further studies are needed to test the hypothesis that patients with mental disorders associated with severe social deficits benefit from a combination of psychotherapy and OXT administration. In general, OXT treatment is expected to improve the readiness to socially interact (e.g. in role-played simulations) and to facilitate more active and successful engagement in confronting feared social situations outside of the sessions. To this end, a clinical research program being carried out in our laboratory aimed at developing and evaluating new clinically relevant approaches for disorders with social deficits (especially in social phobia, ASD, BPD). More specifically, we are currently conducting controlled treatment trials to investigate the effects of intranasal OXT administration in combination with standardized cognitive-behavioural therapy programs in different mental disorders with social deficits. Figure 1 shows an integrative model of the interactions of anxiety and stress, social approach behaviour, and the oxytocinergic system, which also integrates the novel approach of a psychobiological therapy in psychopathological states. Considering the large number of patients suffering from disorders that are associated with social deficits, the development of specific psychobiological approaches combining effective psychological methods with synergizing OXT or OXT agonist administration constitutes a primary challenge in interdisciplinary research on the treatment of mental and developmental disorders.

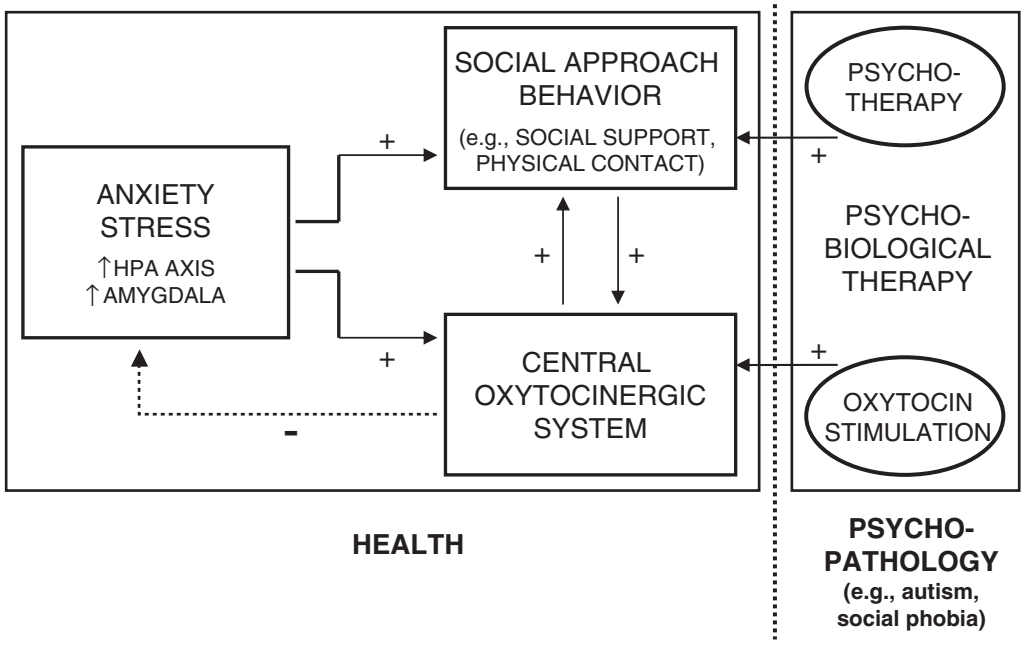

Fig. 1. Interactions between anxiety and stress, social approach behaviour, and the oxytocinergic system. Anxiety and stress encourage social approach behaviour and stimulate OXT release in healthy individuals. Different kinds of positive social interaction (e.g. physical contact) are associated with OXT release, and in turn, OXT promotes social approach behaviour. As OXT reduces HPA axis responses and limbic reactivity (especially amygdala) to social stressors, the neuropeptide plays an important role as an underlying neurobiological mechanism for the anxiolytic/stress-protective effects of positive social interaction. In mental and developmental disorders that are associated with severe deficits in social interactions (e.g. autism, social phobia, BPD), novel therapeutic approaches combining effective psychotherapy methods with OXT or OXT agonist administration offer the opportunity to develop a ''psychobiological therapy''.

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