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Oxytocin, vasopressin, and human social behavior

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Abstract

There is substantial evidence from animal research indicating a key role of the neuropeptides oxytocin (OT) and arginine vasopressin (AVP) in the regulation of complex social cognition and behavior. As social interaction permeates the whole of human society, and the fundamental ability to form attachment is indispensable for social relationships, studies are beginning to dissect the roles of OT and AVP in human social behavior. New experimental paradigms and technologies in human research allow a more nuanced investigation of the molecular basis of social behavior. In addition, a better understanding of the neurobiology and neurogenetics of human social cognition and behavior has important implications for the current development of novel clinical approaches for mental disorders that are associated with social deficits (e.g., autism spectrum disorder, social anxiety disorder, and borderline personality disorder). This review focuses on our recent knowledge of the behavioral, endocrine, genetic, and neural effects of OT and AVP in humans and provides a synthesis of recent advances made in the effort to implicate the oxytocinergic system in the treatment of psychopathological states.

1. Introduction

In non-human mammals, receptors for the neuropeptides oxytocin (OT) and arginine vasopressin (AVP) are distributed in various brain regions [94] associated with the central nervous control of stress and anxiety and with social behavior, including parental care, pair-bonding, social memory, and social aggression. Specifically, OT seems both to enable animals to overcome their natural avoidance of proximity and to inhibit defensive behavior, thereby facilitating approach behavior [24,26,28,45,84,124,147,164]. AVP has primarily been implicated in male-typical social behaviors, including aggression, pair-bond formation, scent marking, and courtship [24,28,45,104,165].

Aside from its effects on social behavior, OT shows significant binding in the limbic system, including the amygdala [80,81,94,132], and decreases anxiety and the neuroendocrine response to stress in social interactions [11,27,120,123,158,159]. In contrast, AVP seems to play an anxiogenic role, with elevated AVP expression in the hypothalamic paraventricular nucleus being associated with increased behavioral and neuroendocrine anxiety levels [117]. In addition, Ferris and colleagues [49] showed that the orally active AVP V1a receptor antagonist SRX251 selectively blocks aggressive behavior in hamsters. At a cellular level, Huber and colleagues [80] reported that distinct populations of neurons in the amygdala are activated by OT 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 OT 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 OT has behavioral and neural effects associated with reduced anxiety, relaxation, growth, and restoration. Thus, both peptide hormones are important in social stress and in social interaction, and in turn, a dysregulated activity may be associated with mental disorders of psychosocial relevance. While much of the knowledge regarding the ability of OT and AVP to regulate social interactions is based on data from animals using centrally administered agonists and antagonists or knockout mice, initial studies suggest similar social and stress-related effects of both neuropeptides in humans (for review, see [12,68]).

Here, we review recent advances in the endeavor to understand the role of OT and AVP in human social behavior. In the first part of this review, we summarize the methodological approaches in human neuropeptide research and examine the significance of OT in stress-responsiveness, anxiety, and prosocial behavior. In the second part, we address the role of AVP in social behavior. Finally, we conclude by outlining the clinical implications for mental disorders that are associated with social deficits, and provide a synthesis of the interactions of anxiety and stress, social approach behavior, and the oxytocinergic system.
2. Methodological approaches in human neuropeptide research

Our current knowledge of the behavioral effects of neuropeptides in humans is based on: (i) correlational studies measuring OT or AVP in urine, saliva, blood or CSF, (ii) correlational studies involving genotyping of receptor polymorphisms, and (iii) experimental studies manipulating the availability of OT or AVP using intravenous or intranasal administration. All of these approaches bear different levels of invasiveness and side effects and do not have an equivalent informative value in terms of the underlying central nervous mechanisms of the peptides.

Whereas the assessment and interpretation of urine or saliva measures provide inconsistent findings and need further investigation [9,29,51,79,157], CSF levels of OT or AVP are accompanied by high invasiveness. Besides the endogenous stimulation of OT during breastfeeding and positive physical contact, leading to attenuated endocrine responses to stress in women [3,38,66,72,103,146], studies in humans have also been carried out with exogenous administration of OT and AVP. Intravenous OT infusion has been shown to induce significant behavioral effects [76,77], but it appears that only a small fraction of the neuropeptide passes the blood-brain barrier [87], and possible side effects are more likely following intravenous infusion of neuropeptides.

Recent neuropharmacological research has shown that neuropeptides gain access to the human brain after intranasal administration [18,41,66,129], providing a useful method for studying the central nervous effects of OT and AVP in humans [68]. In particular, a potential clinical use is dependent on a more direct and secure pathway to the human brain. In addition, a neurogenetic approach provides new insight into the individual variation of social behavior and can easily be combined with behavioral measures and functional imaging [92,113].

The detailed mechanism of brain penetration of OT and AVP following different methods of administration and the relationship between plasma and central OT and AVP (including possible cross-talks of these neuropeptides at their respective central receptors) is an area that warrants further investigation [111]. In addition to in vitro studies on binding sites in the human brain [106] and recent advances made in identifying neural activity using fMRI [68], the development of specific radioactive labeling of neuropeptides in positron emission tomography will provide a better understanding about how OT and AVP receptors are mapped in the human brain.

3. Oxytocin and human social behavior

3.1. Social stress and anxiety

In animal studies, OT has been found to be released peripherally and within the brain in response to both physical and psychological stress and fearful situations [120,121]. Intracerebral OT has been shown to inhibit the stress-induced activity of the hypothalamic–pituitary–adrenal (HPA) axis responsiveness [119,123] and the activity of the amygdala in the modulation of the autonomic fear response [80]. Numerous studies on the inhibitory influence of OT on stress-responsive neurohormonal systems focused on the endogenous stimulation of OT during lactation in rodents. The suckling stimulus by the newborn was found to increase OT release and decrease basal plasma levels of ACTH and cortisol [26,27,121,148,149,160].

In lactating women, the increase of OT following breast-feeding is associated with dampened levels of ACTH and cortisol [7,31,72,122]. 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 [3,6,70]. As no effect of stress has been found on OT plasma levels, OT does not seem to mediate the attenuation of cortisol stress responses at the adrenal level [72]. Thus, the inhibitory effect of OT 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 [120,121]. Interestingly, breast-feeding mothers with increased plasma OT in response to a speech stressor that immediately followed baby-holding were found to have lower blood pressure than mothers with a decrease in OT after stress [103]. Furthermore, non-postpartum healthy women who showed increased plasma OT levels in response to positive emotion and massage and who maintained OT levels during negative emotion were less likely to report interpersonal problems associated with intrusiveness [146]. Maintaining OT levels during sadness has also been associated with lower anxiety in close relationships [146]. Recently, Ditzen and colleagues [38] 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. Another study by Holt-Lunstad and colleagues compared a warm touch intervention in couples with a monitoring-only control group [78]. Touch resulted in increased salivary OT and a subsequent reduction in sympathetic tone indicated by lower systolic blood pressure as well as reduced alpha amylase. Altogether, these results from human studies suggest a possible protective effect of endogenous OT 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 (see Neumann in this issue [140]). Moreover, plasma concentrations of OT have not proven to closely reflect the central nervous availability of the neuropeptide [94]. Thus, the specific effects of central OT as an underlying biological mechanism for the reduction of stress and anxiety in humans need to be investigated using challenge procedure methodologies involving OT 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 OT and social support in a standardized psychosocial stress protocol [67]. In a double-blind, placebo-controlled design, all participants were randomly assigned to receive intranasal OT (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 OT exhibited the lowest cortisol concentrations during stress exposure, whereas subjects who received no social support and placebo demonstrated the highest cortisol response [67]. Notably, there were corresponding results in terms of psychological measures: subjects without social support and with placebo showed the expected decrease in calmness and increase in anxiety during stress, while participants who received either social support or OT 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 OT administration. In another study, Ditzen and colleagues [39] show that 40 IU intranasal OT increases positive communication behavior during a couple conflict in both men and women, and significantly reduces cortisol reactivity, which is in line with animal studies indicating that central OT facilitates pair-bonding behavior. However, intranasal 24 IU OT treatment did not alter appetitive, consummatory, and refractory sexual behavior in men [22]. Altogether, OT seems to play an
important role as an underlying biological mechanism for the well-known stress-protective effects of positive social interaction.

As reported above, animal research indicates that central nervous OT modulates the autonomic fear response via OT receptors in the amygdala. In an initial functional magnetic resonance imaging (fMRI) study in humans, Kirsch and colleagues [91] assessed amygdala activation using aversive, fear-inducing visual stimuli in healthy men following double-blind, placebo-controlled cross-over substance administration. The authors found that 27 IU intranasal OT reduced amygdala activity and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear. Recently, a study reported that 32 IU intranasal OT attenuated the effect of aversive conditioning of neutral faces [127], which was associated with reduced activity in the caudal anterior cingulate cortex and the right medial temporal lobe. In addition, the authors reported a differential effect for faces with averted vs. direct gaze in terms of a specific attenuating effect of OT on the activity in the right amygdala and the right fusiform gyrus for direct gaze stimuli as compared to averted gaze stimuli [127].

In another fMRI study, we found that 24 IU intranasal OT reduced amygdala responses to fearful, angry, and happy faces 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 [43]. Interestingly, 32 IU intranasal OT also reduced amygdala activation when participants received painful stimulation themselves [139].

In conclusion, recent neuroimaging studies suggest a modulatory role of OT on amygdala responsiveness to unconditioned and conditioned socially relevant stimuli. The attenuating effect on amygdala activity in response to both positive and negative stimuli might reflect reduced certainty about the predictive value of a social stimulus and thereby facilitate social approach behavior.

3.2. Social cognition and social approach

Numerous animal studies have implicated OT and AVP in mating, pair-bonding, and adult–infant attachment [104]. It is well-known that pair-bonding in prairie voles, for example, is regulated by both OT and AVP [32], whereas maternal behavior in rats is modulated only by OT [83]. Besides its modulating role in psychosocial stress, OT is involved in the regulation of social approach behavior, social affiliation, and attachment.

An increasing number of experimental studies have begun to gain insights into how OT modulates social approach behavior, affiliation, and the associated cognitive processes in humans. To date, these studies have used paradigms examining trusting behavior, the processing of facial emotions and memory for socially relevant information.

Trust in other people is a prerequisite of social affiliation and social approach in humans. Using a trust game, a behavioral study showed that 24 IU intranasal OT substantially increased trust among humans. In particular, 45% of the participants in the OT group showed the maximal trust level compared to only 21% in the placebo group. Importantly, OT did not increase the readiness to bear risks in general but rather specifically increased the individual's willingness to accept social risks within social interactions [93]. In a subsequent study, we recently examined the effect of OT on the neural circuitry underlying trusting behavior using fMRI. In a modified trust game, the participants' initial trusting behavior was betrayed. The results indicate that 24 IU intranasal OT increases the tolerance to the betrayal of trust compared to placebo. This difference in trust adaptation was associated with the attenuation of activity in areas mediating emotional processing (amygdala, midbrain regions) and the behavioral adaptation to feedback (dorsal striatum) in subjects receiving OT [144].

Another behavioral study from our laboratory examined the effects of OT on the ability to infer the mental state of another individual from facial cues [44]. In this study, participants were given a set of pictures showing the eye region of facial expressions, and were asked to infer the mental state of the depicted person. A single dose of 24 IU OT administered intranasally enhanced performance in this test compared to placebo. Thus, OT improved the ability to infer the mental state of others. A recent study by Guastella and colleagues reported an increased number and duration of gazes toward the eye region of emotionally neutral human faces following intranasal OT administration (24 IU) as compared to placebo [61], indicating a key role of OT in facial processing and interpersonal communication in humans. However, enhanced attention for negative social cues (schematic angry faces) was not confirmed in a recent study [59].

Another study examining the possible differential effects of OT (24 IU) on the processing of positive compared to negative facial expressions reported slowed reaction times during facial fear recognition and reduced misclassifications of positive facial expressions as negative ones [37]. Regarding memory, intranasal OT (24 IU) selectively modulated implicit memory depending on the social relevance (reproduction-related vs. neutral) of semantic word stimuli [71]. A recent study showed that a post-learning dose of 20 IU intranasal OT enhanced immediate (30 min) and delayed (24 h) recognition for face identity. Although there was no effect of OT on the memory for face-facial expression associations, face identity memory was only affected for faces with angry or neutral expressions but not for faces with happy expressions [136]. In contrast, Guastella and colleagues showed that intranasal OT (24 IU) given before learning enhances the memory for happy faces compared to angry and neutral faces [62]. Importantly, another study from our laboratory demonstrated that intranasal OT (24 IU) specifically improves recognition memory for faces, but not for non-social stimuli, which suggests an immediate and selective effect of the peptide strengthening neuronal systems of social memory [134]. Notably, in an initial double-blind, placebo-controlled within-subject design on the effects of OT on attachment, we were recently able to show that a single intranasal administration of 24 IU OT increases the subjective experience of attachment security (assessed with an adult attachment projective picture test) in male students classified with an insecure attachment pattern [20]. As secure attachment is associated with lower stress reactivity and a better ability to socially interact [40], and mediates the implications of early trauma, namely on psychopathology [128], the neuroendocrine mechanisms of attachment may have direct clinical implications for several mental and developmental disorders (see clinical perspectives).

Finally, there are a few correlational studies which suggest an association between OT levels and different kinds of social interactions. The first study reported a positive correlation of OT with self-reported bonding to own parents and an inverse correlation with depressive symptoms in young adults [56]. Another study reported that women which showed an increase of OT from early to late pregnancy self-reported maternal–fetal bonding to their unborn child [100]. Two further studies showed that higher plasma levels of OT are associated with trustworthy behavior [166,167]. Although these studies are not conclusive, they do concur with animal studies and point to the role of OT in the modulation of prosocial behavior.

To summarize, there is accumulating evidence that in humans, OT modulates social perception, social cognition, and social behavior, thereby promoting social approach and affiliation. Besides the stress-reducing and anxiolytic effects, OT modulates social cognitive functions such as trust, emotion recognition and social
memory. Recent functional imaging studies support the idea that the central nervous effects of exogenously administered OT are at least in part mediated by a modulation of amygdala activity and associated cortical areas. Reduced emotional arousal during social encounters might also promote social approach and therefore contribute to the positive effects of OT on trust and social cognition. The detailed mechanisms will need to be investigated in future research, given the widespread distribution of OT receptors in the brain [94] and the distribution of the neural network underlying social cognition and emotion [1].

4. Arginine vasopressin and human social behavior

Whereas OT plays a key role both in prosocial behavior and in the central nervous control of stress and anxiety, AVP has primarily been implicated in male-typical social behaviors, including aggression and pair-bond formation, and in stress-responsiveness [55]. Although most of the studies conducted thus far on human social behavior have focused on OT, few studies on AVP suggest behavioral effects similar to those found in animal research.

Coccaro and colleagues [33] 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 behavior.

Two recent studies examined the effect of intranasal AVP administration on human facial responses related to social communication. In a first study, Thompson and colleagues [144] 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 toward, or autonomic arousal in response to, emotional facial expressions with different valence (neutral, happy, and angry), the authors did observe 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 the magnitudes of placebo subjects in response to angry facial expressions [144]. In view to the crucial role of this muscle group for species-specific agonistic social communication [86], 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 a further study focusing on possible sex-specific influences of AVP on human social communication, 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 [145]. 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.

Recently, genetic studies found a contribution of a vasopressin receptor subtype (Avpr-1a) in social behavior. The length of the Avpr-1a RS3 promoter region was associated with altruistic behavior. The amount of money allocated to an anonymous partner in an economic game (dictator game) was higher for participants with long Avpr-1a RS3 repeats compared to short repeats [92]. Several studies have previously shown an association between the Avpr-1a receptor gene and autism [90,143,156], as well as partner preference in the male prairie vole [165]. Interestingly, the association between the Avpr-1a and pair-bonding has also been observed in humans. The RS3 repeat polymorphism significantly predicted outcome measures in the Partner Bonding Scale (PBS) in men, while this association was not found for women. In addition one specific allele (334) was important for quality of the marital relationship. Carriers of the 334 allele reported lower marital quality and had more often experienced marital crisis or threat of divorce during the last year. Wives of 334 allele carriers reported lower marital satisfaction [154]. These results shift the attention towards the involvement of Avpr-1a polymorphisms in social disorders.

Altogether, central AVP seems to have similar influences on 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 toward same-sex faces in men and women, respectively. The Avpr-1a gene seems to be associated with differences in altruistic or prosocial behavior in men and women with and without bond-bonding and marital satisfaction in men.

5. Clinical perspectives

As social behavior in health is tightly regulated, and dysfunctional alterations can result in a psychopathological state, OT and AVP have been considered to play an important role in the development of a variety of mental disorders. Aside from social anxiety disorder, social deficits are associated with autism spectrum disorders, obsessive-compulsive disorder, borderline personality disorder, depression, and other mental disorders. In the following, we review studies that addressed the role of OT and AVP in these disorders.

5.1. Autism spectrum disorder

Autism and Asperger Syndrome belong to a group of pervasive developmental disorders termed autism spectrum disorders (ASD). ASD are characterized by a specific pattern of abnormalities in communication, impairments in social cognition, and repetitive behaviors. Some social deficits in ASD mimic the behavior of animals that lack OT. Thus some authors have suggested that there might be a link between ASD and OT/AVP [25,63,82,164].

Indeed, there is some evidence that patients with ASD show blunted plasma levels of OT. A first study found lower plasma levels in children with ASD and correlations between plasma OT levels and social functioning [115]. Another study extended these results by demonstrating enhanced OT precursor to OT ratios [57]. Numerous animal studies have shown that both Otr and Avpr genes play an important role in the regulation of social behavior [25,104]. The idea that Otr and Avpr genes also play a role in autism has been supported by some studies. Specifically, recent studies have emphasized the 3p25 region containing the Otr gene as the most promising linkage site for ASD [95,110,163]. An association between ASD and two single nucleotide polymorphisms (rs2254298 and rs53576) has been suggested by a study with Chinese Han families [161]. These results were confirmed in part in a Caucasian sample [85] and further extended in a family-based association study [99] showing interactions with social cognitive skills. Furthermore, there are studies suggesting that polymorphisms of Avpr-1a gene are also associated with ASD [90,156,162]. A recent study suggests that amygdala reactivity is associated with genetic variations of the Avpr-1a, and thereby might represent a neural mechanism mediating the genetic risk for ASD [113]. Finally, two studies suggest that systemic infusions of OT reduce repetitive
behavior [77] and improve emotion recognition in ASD [76]. Although these studies used systemic infusions of OT, 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 men [44].

To summarize, there is increasing evidence that both Otr and Avpr gene might be involved in the development of ASD. Furthermore, a number of studies show that the availability of OT 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 [19,116].

5.2. Social anxiety disorder

Social anxiety disorder (SAD), also known as social phobia, is the most common anxiety disorder, and the third most common psychiatric disorder after major depression and alcohol dependence [89]. Altogether, it is only possible to successfully treat less than 60% of all patients [65]. Important clues for understanding the neural substrates of SAD have come from affective neuroscience, which has utilized animal, lesion, and human brain imaging approaches. In particular, compared with healthy controls, patients with SAD exhibit exaggerated amygdala reactivity to neutral faces previously paired with an aversive stimulus [17].

As mentioned above, initial data from Kirsch and colleagues [91] and Domes and colleagues [43] indicate that intranasal oxytocin was found to suppress fear-related activation of the amygdala in healthy subjects. As oxytocin in humans was also associated with both an enhanced ability to interact socially [93] and a better central nervous control of stress and anxiety in social interactions [67], it is expected that the development of specific psychobiological approaches combining effective psychological methods, such as behavior therapy, with intranasal oxytocin administration constitutes a primary challenge in interdisciplinary research on the treatment of SAD [69]. Recent studies showed that higher social anxiety symptom severity was associated with altered OT levels in patients with SAD [75]. More importantly, a recent randomized, double-blind, placebo-controlled trial combined 24 IU intranasal oxytocin with a brief exposure therapy [60]. Patients administered with oxytocin showed improved self-evaluations of appearance and speech performance. However, these effects did not generalize to improve overall treatment outcome from exposure therapy.

In sum, future research is needed to determine whether oxytocin can enhance treatment outcomes for social anxiety disorder when used with greater frequency and a wider variety of social learning experiences.

5.3. Early trauma and associated disorders

Alterations in the OT/AVP system have been considered a possible factor in the pathogenesis in disturbed adult attachment [20,24]. It has been put forward that early stress interferes with the developing neuropeptide system and alters receptor binding of OT and AVP, thereby promoting the development of severe attachment disorders [23,28].

Borderline personality disorder (BPD) is associated with a remarkably high prevalence of severe childhood trauma and neglect and by a pervasive pattern of instability in affect and interpersonal relationships, (auto-) aggressive behaviors [102] as well as unresolved, preoccupied, and fearful types of attachment [2,101]. In particular, BPD has been associated with excessive socio-affective vigilance and enhanced reactivity to emotional and social stimuli [74]. Hypervigilance to emotionally laden social stimuli is further confirmed by studies showing enhanced amygdala reactivity to negative scenes [73] and to negative facial expressions [114], and even to neutral faces [46]. Furthermore, BPD patients have been described as hypersensitive to social signals, sometimes misinterpreting ambiguous subtle social cues in terms of a negativity bias [153], particularly towards the perception of anger [42]. Thus, neuropeptides might play a significant role in the development of the insecure attachment and the fundamental distrust in others that many BPD patients report. Although this hypothesis has not been tested explicitly, initial studies suggest that early childhood trauma and neglect are associated with dysregulations of AVP and OT.

A naturalistic study by Fries and coworkers found an association between reduced early physical and emotional contact and basal levels of plasma AVP. Moreover, early neglect had no effect on basal levels of OT, but rather impaired the increase of peripheral OT triggered by a mother–infant interaction [51]. A recent study showed attenuated CSF levels of OT in women which reported early childhood maltreatment. This effect seemed to be even more pronounced for women reporting emotional abuse during their early childhood [64]. In another study, Meinlschmidt and Heim [112] showed that the suppression of cortisol following the administration of a single dose of 24 IU intranasal OT was attenuated 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 and might contribute to the adverse consequences of early childhood maltreatment, including reduced stress resilience and higher prevalence for mental disorders.

5.4. Obsessive–compulsive disorder

Recurrent, intrusive thoughts and fears of danger or contamination, and compulsive behaviors (e.g., excessive hand-washing) or cognitions for relieving anxiety are the most prominent symptoms of obsessive-compulsive disorder (OCD). Given the mnemonic effects of OT and AVP reported by some studies mentioned above, and the possible role of both peptides in self-grooming behavior in animals [107,125], it has been suggested that OCD symptoms might be associated with alterations in central OT and AVP (cf. [96]). This idea stimulated several clinical studies on OT and AVP in OCD, which produced mixed results.

Adult OCD patients showed elevated basal CSF levels of AVP and increased secretion of AVP into the plasma in response to hypertonic saline administration [5], which could not be confirmed for basal CSF concentrations [97]. Developmental changes in AVP have been suggested by another study, in which CSF AVP concentration and the AVP/OT ratio were negatively correlated with obsessive–compulsive disorder symptom severity in children [142].

Further studies found enhanced CSF levels of OT in children and adolescents with OCD compared with other anxiety disorders and healthy controls [142], and in adults with non-tic-related OCD compared to tic-related OCD, Tourette syndrome and healthy controls [97]. In addition, an association was reported between the severity of compulsion and CSF OT in non-tic-related OCD [97]. Altemus and colleagues [4] were not able to confirm the finding of enhanced OT levels in OCD.

Although an initial case study reported symptomatic improvement in OCD patients treated with intranasal OT [10], subsequent controlled studies were not able to confirm therapeutic effects of systemic [30] or intranasal administration [36,47,48,135] of OT in OCD. These negative results are not conclusive, as they might be in part attributed to methodological shortcoming such as the commonly low statistical power due to insufficient sample sizes [36,47,48,135], the short-term treatment [47,48,135], or low doses of treatment [36,135].

Taken together, the findings on the role of OT and AVP in OCD are inconsistent. Since OT influences social behavior in particular by modulating emotional processing and social cognitive
functioning, further research should primarily focus on the potential role of OT and AVP on compulsive behavior and ruminative, obsessional thoughts and fears in OCD.

5.5. Depression

To date, only a small number of studies have investigated the role of OT and AVP in the development of affective disorders, in particular in unipolar depression. One study reported blunted plasma OT levels in depressed patients [50], whereas other studies did not confirm these results using plasma [34, 150] and CSF measures [130, 131]. Another study reported a negative correlation between symptom severity of depression and anxiety and OT plasma levels in fibromyalgia patients [8], which was confirmed in a recent study in patients with major depression [137]. A recent correlational study found a positive association between plasma OT levels and reward dependency, a stable trait that manifests itself in social attachment and the dependence on the approval of others [16]. In postmortem studies, the numbers of AVP- and OT-expressing neurons in the paraventricular nucleus of the hypothalamus have been reported to be increased in patients with unipolar depression [131]. Depression is accompanied by hyperactivity of corticotropin releasing factor (CRF) in the paraventricular nucleus. Together with other receptor genes, the Avpr-1a gene is involved in the activation of CRF neurons. An increased expression of the Avpr-1a gene was again found in postmortem tissue of depressed patients [155]. Another study partially supported the hypothesis of a reduced vasopressinergic activity in depression [138]. Finally, a negative association between plasma AVP and daytime motor activity [152] and a positive correlation with memory functioning [151] have been reported in depressed patients.

In sum, evidence for a role of OT and AVP in depression is too inconsistent to draw stringent conclusions. Initial data suggest that affective disorders may be related to excessive vasopressin function and consequently that a treatment with vasopressin receptor antagonists may be an effective treatment [141]. It might also be the case that some characteristics in depression (e.g., social withdrawal) are associated with blunted OT, but this hypothesis clearly needs further investigation.

5.6. Schizophrenia

Since Bujanow raised the question whether OT might have antipsychotic properties in 1974 [21], only a small number of studies have been conducted to explore the role of OT and AVP in schizophrenia. Initial studies suggested enhanced concentrations of OT [15] and neurophysin II, the hypothalamic–pituitary carrier of OT [98, 105], in patients with schizophrenia compared to healthy controls, whereas a follow-up study did not confirm these results [52]. In contrast, Goldman and colleagues showed that blunted OT levels in schizophrenia were associated with low performance in a facial affect rating task [53]. Another study investigating the effect of a trust-related interaction on peripheral OT levels revealed that schizophrenic patients lacked the interaction-induced increase in peripheral OT observed in healthy controls [88]. Not only OT but also AVP functioning was found to be abnormal based on the investigation of neurophysin immunoreactivity in different brain areas [108].

Several additional studies underline the role of AVP in the psychopathology of schizophrenia. Goldman and colleagues measured elevated plasma AVP levels in schizophrenic patients, who often exhibit osmotic dysregulation like polydipsia and hyponatremia and at the same time show the typical psychiatric symptoms and social impairment [54]. Neuroleptic drugs (haloperidol and clozapine) not only reduced psychiatric symptoms, but were also capable of normalizing AVP plasma levels [126, 133]. On the other hand, phencyclidine, a drug that evokes severe schizophrenia like symptoms that can last for days or weeks, alters vasopressin receptor expression, distribution and binding in animals [118].

The empirical evidence of neuropeptidergic functioning in schizophrenia is limited and controversial, although recent studies in humans and animals suggest impairments of OT and AVP metabolism in schizophrenia that might be related to impaired social cognitive functioning.

6. Conclusions

Based on the enormous advances in animal models of the role of neuropeptides in social cognition and behavior, recent human studies suggest that the basic social effects of OT and AVP from animal research may also be applicable to human social interaction. Although the translation of behavioral and neurobiological findings from animal studies to humans generally bears the risk of drawing oversimplified parallels between rodents and humans, the initial findings are encouraging in terms of providing a better understanding of the neurobiology and neurogenetics of human social behavior. Moreover, these translational findings suggest that OT and AVP may play an important role in the etiology and treatment of a number of clinical disorders involving social deficits and disrupted attachment.

Taken together, the main findings in human research regarding the role of OT can be summarized as follows:

(i) OT is associated with the regulation of the behavioral and endocrine stress response, i.e., OT is released in response to socially relevant challenges and attenuates endocrine and autonomic responses to stress.

(ii) OT 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 substrate for the anxiolytic effects of OT has been suspected in limbic areas, in particular in the amygdala. Specifically, OT has been found to attenuate amygdala reactivity to social stimuli and to reduce brainstem activity, which is associated with autonomic arousal.

(iv) OT has been found to promote social cognition and the interpretation of social signals, possibly representing an enhanced readiness to show social approach behavior and empathy.

(v) Finally, there is initial evidence that the central OT system is altered in several mental disorders that are characterized by severe social disturbances, such as ASD, OCD, personality disorders, and following early trauma. 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.

With regard to the role of AVP in human social behavior, initial studies also suggest behavioral 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 toward same-sex faces in men but affiliative responses in women.

As OT has been shown to reduce social anxiety and increase social abilities in animal and human studies, the neuropeptide might be a significant target for novel therapeutic approaches in several mental disorders that are characterized by social interaction pathology [68, 109]. As for the anxiogenic and aggression-related role of AVP, the development of selective V1a and V1b receptor antagonists, as known from animal studies [49, 58], is a promising...
Fig. 1. Integrative model of the interactions of oxytocin, social approach behavior, and social stress. Anxiety and stress encourage social approach behavior and stimulate oxytocin release in healthy individuals. Different kinds of positive social interaction (e.g., physical contact) are associated with oxytocin release, and in turn, oxytocin promotes social approach behavior. As oxytocin reduces hypothalamic–pituitary–adrenal 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 anxiety disorder, and borderline personality disorder), novel therapeutic approaches combining effective psychotherapy methods with oxytocin or oxytocin agonist administration offer the opportunity to develop a ‘psychobiological therapy’. (Figure modified from Heinrichs and Domes [68], with permission from Elsevier).

References


