Frontiers in Neuroendocrinology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

# Oxytocin, vasopressin, and human social behavior

Markus Heinrichs *, Bernadette von Dawans, Gregor Domes

*Department of Psychology, Clinical Psychology and Psychobiology, University of Zürich, Zürich, Switzerland*

ARTICLE INFO

*Article history:*
Available online xxxx

*Keywords:*
Neuropeptides
Oxytocin
Arginine vasopressin
Social behavior
Stress
Anxiety
Attachment
Affiliation
Approach behavior
Psychobiological therapy

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 [25]. 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.

* Corresponding author. Address: Department of Psychology, Clinical Psychology and Psychobiology, University of Zürich, Binzmühlestrasse 14/Box 8, CH-8050 Zürich, Switzerland. Fax: +41 44 635 7159.
*E-mail address:* m.heinrichs@psychologie.uzh.ch (M. Heinrichs).

0091-3022/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.yfrne.2009.05.005

## 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 breast-feeding and positive physical contact, leading to attenuated endocrine responses to stress in women [3,38,66,70,72,103,146], 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 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



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

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 uncertainty 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 [14].

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 mem-



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

ory. 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 promotor 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 and with pair-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 *Avpr* and *Otr* 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



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

behavior in ASD [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 [2101]. 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 function-



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

ing, 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 corticotrophin 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 clonidine) 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 target for human neuropsychopharmacological research, in partic-



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

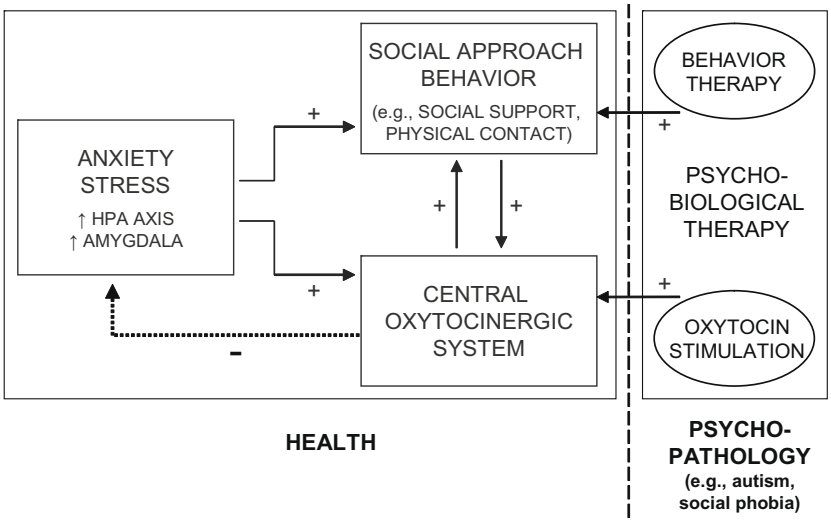


**Fig. 1.** Integrative model of the interactions of oxytocin, social approach behavior, and social stress. Anxiety and stress encourage social approach behavior and stimulate oxytocin release in healthy individuals. Different kinds of positive social interaction (e.g., physical contact) are associated 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).

ular in the treatment of stress-related disorders and disorders with interpersonal violence such as antisocial personality disorder [35].

There is initial evidence for the clinical benefit of an increase of the availability of OT in the central nervous system by exogenous administration of the neuropeptide or selective agonists (e.g., carbetocin). For example, peripheral infusion of OT increased retention of social cognition via enhanced emotional understanding of speech intonation and decreased repetitive behaviors in autism [13]. 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 OT administration. In particular, intranasal OT treatment is expected to improve the readiness to socially interact (e.g., in group therapy) and to facilitate more active and successful engagement in confronting feared social situations outside of the sessions. Fig. 1 shows an integrative model of the interactions of anxiety and stress, social approach behavior, and the oxytocinergic system, which also integrates the novel approach of a 'psychobiological therapy' in psychopathological states. The therapeutic potential of manipulating the oxytocinergic system in the treatment of mental and developmental disorders with social deficits (e.g., ASD, social anxiety disorder, and borderline personality disorder) has to be further investigated in clinical trials in which disorder-specific cognitive-behavioral therapy programs are combined with synergizing OT or OT agonist administration.

## Acknowledgments

This work was supported by grants from the Swiss National Science Foundation (SNSF PP001-114788) (to M.H.) and the Research Priority Program "Foundations of Human Social Behavior" at the University of Zurich (to M.H. and B.v.D.), and by a grant of the German Research Foundation (DFG Do1312/1-1) (to G.D.).

## References

[1] R. Adolphs, Cognitive neuroscience of human social behaviour, Nature Reviews Neuroscience 4 (2003) 165–178.
[2] H.R. Agrawal, J. Gunderson, B.M. Holmes, K. Lyons-Ruth, Attachment studies with borderline patients: a review, Harvard Review of Psychiatry 12 (2004) 94–104.
[3] M. Altemus, P.A. Deuster, E. Galliven, C.S. Carter, P.W. Gold, Suppression of hypothalamic–pituitary–adrenal axis responses to stress in lactating women, Journal of Clinical Endocrinology and Metabolism 80 (1995) 2954–2959.
[4] M. Altemus, K.R. Jacobson, M. Debellis, M. Kling, T. Pigott, D.L. Murphy, P.W. Gold, Normal CSF oxytocin and NPY levels in OCD, Biological Psychiatry 45 (1999) 931–933.
[5] M. Altemus, T. Pigott, K.T. Kalogeras, M. Demitrack, B. Dubbert, D.L. Murphy, P.W. Gold, Abnormalities in the regulation of vasopressin and corticotropin releasing factor secretion in obsessive–compulsive disorder, Archives of General Psychiatry 49 (1992) 9–20.
[6] M. Altemus, L.S. Redwine, Y.M. Leong, C.A. Frye, S.W. Porges, C.S. Carter, Responses to laboratory psychosocial stress in postpartum women, Psychosomatic Medicine 63 (2001) 814–821.
[7] J.A. Amico, J.M. Johnston, A.H. Vagnucci, Suckling-induced attenuation of plasma cortisol concentrations in postpartum lactating women, Endocrine Research 20 (1994) 79–87.
[8] U.M. Anderberg, K. Uvnas-Moberg, Plasma oxytocin levels in female fibromyalgia syndrome patients, Zeitschrift für Rheumatologie 59 (2000) 373–379.
[9] G.M. Anderson, Report of altered urinary oxytocin and AVP excretion in neglected orphans should be reconsidered, Journal of Autism and Developmental Disorders 36 (2006) 829–830.
[10] M. Ansseau, J.J. Legros, C. Mormont, J.L. Cerfontaine, P. Papart, V. Geenen, F. Adam, G. Franck, Intranasal oxytocin in obsessive–compulsive disorder, Psychoneuroendocrinology 12 (1987) 231–236.
[11] T.L. Bale, A.M. Davis, A.P. Auger, D.M. Dorsa, M.M. McCarthy, CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior, Journal of Neuroscience 21 (2001) 2546–2552.
[12] J.A. Bartz, E. Hollander, The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior, Hormones and Behavior 50 (2006) 518–528.
[13] J.A. Bartz, E. Hollander, Oxytocin and experimental therapeutics in autism spectrum disorders, Progress in Brain Research 170 (2008) 451–462.
[14] T. Baumgartner, M. Heinrichs, A. Vonlanthen, U. Fischbacher, E. Fehr, Oxytocin shapes the neural circuitry of trust and trust adaptation in humans, Neuron 58 (2008) 639–650.
[15] H. Beckmann, R.E. Lang, W.F. Gattaz, Vasopressin–oxytocin in cerebrospinal fluid of schizophrenic patients and normal controls, Psychoneuroendocrinology 10 (1985) 187–191.
[16] C.J. Bell, H. Nicholson, R.T. Mulder, S.E. Luty, P.R. Joyce, Plasma oxytocin levels in depression and their correlation with the temperament dimension of reward dependence, Journal of Psychopharmacology 20 (2006) 656–660.
[17] N. Birbaumer, W. Grodd, O. Diedrich, U. Klose, M. Erb, M. Lotze, F. Schneider, U. Weiss, H. Flor, fMRI reveals amygdala activation to human faces in social phobics, Neuroreport 9 (1998) 1223–1226.
[18] J. Born, T. Lange, W. Kern, G.P. McGregor, U. Bickel, H.L. Fehm, Sniffing neuropeptides: a transnasal approach to the human brain, Nature Neuroscience 5 (2002) 514–516.
[19] M. Boso, E. Emanuele, P. Politi, A. Pace, M. Arra, S. Ucelli di Nemi, F. Barale, Reduced plasma apelin levels in patients with autistic spectrum disorder, Archives of Medical Research 38 (2007) 70–74.

Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

[20] A. Buchheim, M. Heinrichs, C. George, D. Pokorny, E. Koops, P. Henningsen, M.-F. O'Connor, H. Gündel, Oxytocin enhances the experience of attachment security, Psychoneuroendocrinology, in press.
[21] W. Bujanow, Letter: is oxytocin an anti-schizophrenic hormone?, Canadian Psychiatric Association Journal 19 (1974) 323
[22] A. Burri, M. Heinrichs, M. Schedlowski, T.H. Kruger, The acute effects of intranasal oxytocin administration on endocrine and sexual function in males, Psychoneuroendocrinology 33 (2008) 591–600.
[23] C.S. Carter, Developmental consequences of oxytocin, Physiology and Behavior 79 (2003) 383–397.
[24] C.S. Carter, Neuroendocrine perspectives on social attachment and love, Psychoneuroendocrinology 23 (1998) 779–818.
[25] C.S. Carter, Sex differences in oxytocin and vasopressin implications for autism spectrum disorders?, Behavioural Brain Research 176 (2007) 170–186
[26] C.S. Carter, M. Altemus, Integrative functions of lactational hormones in social behavior and stress management, Annals of the New York Academy of Sciences 807 (1997) 164–174.
[27] C.S. Carter, M. Altemus, G.P. Chrousos, Neuroendocrine and emotional changes in the post-partum period, Progress in Brain Research 133 (2001) 241–249.
[28] C.S. Carter, A.J. Grippo, H. Pournajafi-Nazarloo, M.G. Ruscio, S.W. Porges, Oxytocin vasopressin and sociality, Progress in Brain Research 170 (2008) 331–336.
[29] C.S. Carter, H. Pournajafi-Nazarloo, K.M. Kramer, T.E. Ziegler, R. White-Traut, D. Bello, D. Schwertz, Oxytocin behavioral associations and potential as a salivary biomarker, Annals of the New York Academy of Sciences 1098 (2007) 312–322.
[30] G. Charles, R. Guillaume, M. Schittecatte, P. Pholien, J.P. Van Wettere, J. Wilmotte, Oxytocin in the treatment of obsessive–compulsive disorder: a report on two cases, Psychiatrie und Psychobiologie 4 (1989) 111–115.
[31] P. Chiodera, C. Salvarani, A. Bacchi-Modena, R. Spallanzani, C. Cigarini, A. Alboni, E. Gardini, V. Coiro, Relationship between plasma profiles of oxytocin and adrenocorticotropic hormone during suckling or breast stimulation in women, Hormone Research 35 (1991) 119–123.
[32] M.M. Cho, A.C. DeVries, J.R. Williams, C.S. Carter, The effects of oxytocin and vasopressin on partner preferences in male and female prairie voles (*Microtus ochrogaster*), Behavioral Neuroscience 113 (1999) 1071–1079.
[33] E.F. Coccaro, R.J. Kavoussi, R.L. Hauger, T.B. Cooper, C.F. Ferris, Cerebrospinal fluid vasopressin levels: correlates with aggression and serotonin function in personality-disordered subjects, Archives of General Psychiatry 55 (1998) 708–714.
[34] J.M. Cyranowski, T.L. Hofkens, E. Frank, H. Seltman, H.M. Cai, J.A. Amico, Evidence of dysregulated peripheral oxytocin release among depressed women, Psychosomatic Medicine 70 (2008) 967–975.
[35] G. Decaux, A. Soupart, G. Vassart, Non-peptide arginine–vasopressin antagonists: the vaptans, Lancet 371 (2008) 1624–1632.
[36] J.A. den Boer, H.G. Westenberg, Oxytocin in obsessive compulsive disorder, Peptides 13 (1992) 1083–1085.
[37] M. Di Simplicio, R. Massey-Chase, P. Cowen, C. Harmer, Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers, Journal of Psychopharmacology 23 (2009) 241–248.
[38] B. Ditzen, I.D. Neumann, G. Bodenmann, B. von Dawans, R.A. Turner, U. Ehlert, M. Heinrichs, Effects of different kinds of couple interaction on cortisol and heart rate responses to stress in women, Psychoneuroendocrinology 32 (2007) 565–574.
[39] B. Ditzen, M. Schaer, B. Gabriel, G. Bodenmann, U. Ehlert, M. Heinrichs, Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict, Biological Psychiatry 65 (2009) 728–731.
[40] B. Ditzen, S. Schmidt, B. Strauss, U.M. Nater, U. Ehlert, M. Heinrichs, Adult attachment and social support interact to reduce psychological but not cortisol responses to stress, Journal of Psychosomatic Research 64 (2008) 479–486.
[41] C. Dodt, R. Pietrowsky, A. Sewing, A. Zabel, H.L. Fehm, J. Born, Effects of vasopressin on event-related potential indicators of cognitive stimulus processing in young and old humans, Journal of Gerontology 49 (1994) M183–M188.
[42] G. Domes, D. Czieschnek, F. Weidler, C. Berger, K. Fast, S.C. Herpertz, Recognition of facial affect in borderline personality disorder, Journal of Personality Disorders 22 (2008) 135–147.
[43] G. Domes, M. Heinrichs, J. Glascher, C. Buchel, D.F. Braus, S.C. Herpertz, Oxytocin attenuates amygdala responses to emotional faces regardless of valence, Biological Psychiatry 62 (2007) 1187–1190.
[44] G. Domes, M. Heinrichs, A. Michel, C. Berger, S.C. Herpertz, Oxytocin improves "mind-reading" in humans, Biological Psychiatry 61 (2007) 731–733.
[45] Z.R. Donaldson, L.J. Young, Oxytocin vasopressin and the neurogenetics of sociality, Science 322 (2008) 900–904.
[46] N.H. Donegan, C.A. Sanislow, H.P. Blumberg, R.K. Fulbright, C. Lacadie, P. Skudlarski, J.C. Gore, I.R. Olson, T.H. McGlashan, B.E. Wexler, Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation, Biological psychiatry 54 (2003) 1284–1293.
[47] C.N. Epperson, C.J. McDougle, L.H. Price, Intranasal oxytocin in obsessive–compulsive disorder, Biological Psychiatry 40 (1996) 547–549.
[48] C.N. Epperson, C.J. McDougle, L.H. Price, Intranasal oxytocin in trichotillomania, Biological Psychiatry 40 (1996) 559–560.
[49] C.F. Ferris, S.F. Lu, T. Messenger, C.D. Guillon, N. Heindel, M. Miller, G. Koppel, F. Robert Bruns, N.G. Simon, Orally active vasopressin V1a receptor antagonist SRX251 selectively blocks aggressive behavior, Pharmacology Biochemistry and Behavior 83 (2006) 169–174.
[50] A. Frasch, T. Zetzsche, A. Steiger, G.F. Jirikowski, Reduction of plasma oxytocin levels in patients suffering from major depression, Advances in Experimental Medicine and Biology 395 (1995) 257–258.
[51] A.B. Fries, T.E. Ziegler, J.R. Kurian, S. Jacoris, S.D. Pollak, Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior, Proceedings of the National Academy of Sciences of the United States of America 102 (2005) 17237–17240.
[52] D. Glovinsky, K.T. Kalogeras, D.G. Kirch, R. Suddath, R.J. Wyatt, Cerebrospinal fluid oxytocin concentration in schizophrenic patients does not differ from control subjects and is not changed by neuroleptic medication, Schizophrenia Research 11 (1994) 273–276.
[53] M. Goldman, M. Marlow-O'Connor, I. Torres, C.S. Carter, Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits, Schizophrenia Research 98 (2008) 247–255.
[54] M.B. Goldman, G.L. Robertson, D. Hedeker, Oropharyngeal regulation of water balance in polydipsic schizophrenics, Clinical Endocrinology (Oxford) 44 (1996) 31–37.
[55] J.L. Goodson, A.H. Bass, Social behavior functions and related anatomical characteristics of vasotocin/vasopressin systems in vertebrates, Brain Research 35 (2001) 246–265.
[56] I. Gordon, O. Zagoory-Sharon, I. Schneiderman, J.F. Leckman, A. Weller, R. Feldman, Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress, Psychophysiology 45 (2008) 349–352.
[57] L. Green, D. Fein, C. Modahl, C. Feinstein, L. Waterhouse, M. Morris, Oxytocin and autistic disorder: alterations in peptide forms, Biological Psychiatry 50 (2001) 609–613.
[58] G. Griebel, J. Stemmelin, C.S. Gal, P. Soubrie, Non-peptide vasopressin V1b receptor antagonists as potential drugs for the treatment of stress-related disorders, Current Pharmaceutical Design 11 (2005) 1549–1559.
[59] A.J. Guastella, D.S. Carson, M.R. Dadds, P.B. Mitchell, R.E. Cox, Does oxytocin influence the early detection of angry and happy faces?, Psychoneuroendocrinology 34 (2009) 220–225
[60] A.J. Guastella, A.L. Howard, M.R. Dadds, P. Mitchell, D.S. Carson, A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder, Psychoneuroendocrinology 34 (2009) 917–923.
[61] A.J. Guastella, P.B. Mitchell, M.R. Dadds, Oxytocin increases gaze to the eye region of human faces, Biological Psychiatry 63 (2008) 3–5.
[62] A.J. Guastella, P.B. Mitchell, F. Mathews, Oxytocin enhances the encoding of positive social memories in humans, Biological Psychiatry 64 (2008) 256–258.
[63] E.A. Hammock, L.J. Young, Oxytocin, vasopressin and pair bonding: implications for autism, Philosophical Transactions of the Royal Society of London 361 (2006) 2187–2198.
[64] C. Heim, L.J. Young, D.J. Newport, T. Mletzko, A.H. Miller, C.B. Nemeroff, Lower CSF oxytocin concentrations in women with a history of childhood abuse, Molecular Psychiatry 112 (2008), doi:10.1038/mp.2008 (Epub ahead of print).
[65] R.G. Heimberg, Cognitive-behavioral therapy for social anxiety disorder: current status and future directions, Biological Psychiatry 51 (2002) 101–108.
[66] M. Heinrichs, Oxytocin and behavior: psychobiological effects of oxytocin on human cognitive performance and stress reactivity, Cuvillier, Göttingen, Germany, 2000.
[67] M. Heinrichs, T. Baumgartner, C. Kirschbaum, U. Ehlert, Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress, Biological Psychiatry 54 (2003) 1389–1398.
[68] M. Heinrichs, G. Domes, Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans, Progress in Brain Research 170 (2008) 337–350.
[69] M. Heinrichs, J. Gaab, Neuroendocrine mechanisms of stress and social interaction: implications for mental disorders, Current Opinion in Psychiatry 20 (2007) 158–162.
[70] M. Heinrichs, G. Meinlschmidt, I. Neumann, S. Wagner, C. Kirschbaum, U. Ehlert, D.H. Hellhammer, Effects of suckling on hypothalamic–pituitary–adrenal axis responses to psychosocial stress in postpartum lactating women, Journal of Clinical Endocrinology and Metabolism 86 (2001) 4798–4804.
[71] M. Heinrichs, G. Meinlschmidt, W. Wippich, U. Ehlert, D.H. Hellhammer, Selective amnesic effects of oxytocin on human memory, Physiology and Behavior 83 (2004) 31–38.
[72] M. Heinrichs, I. Neumann, U. Ehlert, Lactation and stress: protective effects of breast-feeding in humans, Stress 5 (2002) 195–203.
[73] S.C. Herpertz, T.M. Dietrich, B. Wenning, T. Krings, S.G. Erberich, K. Willmes, A. Thron, H. Sass, Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study, Biological psychiatry 50 (2001) 292–298.
[74] S.C. Herpertz, A. Gretzer, E.M. Steinmeyer, V. Muehlbauer, A. Schuerkens, H. Sass, Affective instability and impulsivity in personality disorder. Results of an experimental study, Journal of Affective Disorders 44 (1997) 31–37.
[75] E.A. Hoge, M.H. Pollack, R.E. Kaufman, P.J. Zak, N.M. Simon, Oxytocin levels in social anxiety disorder, CNS Neuroscience Therapy 14 (2008) 165–170.
[76] E. Hollander, J. Bartz, W. Chaplin, A. Phillips, J. Sumner, L. Soorya, E. Anagnostou, S. Wasserman, Oxytocin increases retention of social cognition in autism, Biological Psychiatry 61 (2007) 498–503.



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005

[77] E. Hollander, S. Novotny, M. Hanratty, R. Yaffe, C.M. DeCaria, B.R. Aronowitz, S. Mosovich, Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders, Neuropsychopharmacology 28 (2003) 193–198.
[78] J. Holt-Lunstad, W.A. Birmingham, K.C. Light, Influence of a "warm touch" support enhancement intervention among married couples on ambulatory blood pressure oxytocin alpha amylase and cortisol, Psychosomatic Medicine 70 (2008) 976–985.
[79] M. Horvat-Gordon, D.A. Granger, E.B. Schwartz, V.J. Nelson, K.T. Kivlighan, Oxytocin is not a valid biomarker when measured in saliva by immunoassay, Physiology and Behavior 84 (2005) 445–448.
[80] D. Huber, P. Veinante, R. Stoop, Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala, Science 308 (2005) 245–248.
[81] C.D. Ingram, T.S. Adams, Q.B. Jiang, M.G. Terenzi, R.C. Lambert, J.B. Wakerley, F. Moos, Mortyn Jones Memorial Lecture Limbic regions mediating central actions of oxytocin on the milk-ejection reflex in the rat, Journal of Neuroendocrinology 7 (1995) 1–13.
[82] T.R. Insel, A neurobiological basis of social attachment, American Journal of Psychiatry 154 (1997) 726–735.
[83] T.R. Insel, Oxytocin – a neuropeptide for affiliation: evidence from behavioral, receptor autoradiographic, and comparative studies, Psychoneuroendocrinology 17 (1992) 3–35.
[84] T.R. Insel, L.J. Young, The neurobiology of attachment, Nature Reviews Neuroscience 2 (2001) 129–136.
[85] S. Jacob, C.W. Brune, C.S. Carter, B.L. Leventhal, C. Lord, E.H. Cook Jr., Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism, Neuroscience Letters 417 (2007) 6–9.
[86] L. Jancke, Facial EMG in an anger-provoking situation: individual differences in directing anger outwards or inwards, International Journal of Psychophysiology 23 (1996) 207–214.
[87] Y.S. Kang, J.H. Park, Brain uptake and the analgesic effect of oxytocin – its usefulness as an analgesic agent, Archives of Pharmacal Research 23 (2000) 391–395.
[88] S. Keri, I. Kiss, O. Kelemen, Sharing secrets: oxytocin and trust in schizophrenia, Social Neuroscience (2008) 1–7.
[89] R.C. Kessler, K.A. McGonagle, S. Zhao, C.B. Nelson, M. Hughes, S. Eshleman, H.U. Wittchen, K.S. Kendler, Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey, Archives of General Psychiatry 51 (1994) 8–19.
[90] S.J. Kim, L.J. Young, D. Gonen, J. Veenstra-VanderWeele, R. Courchesne, E. Courchesne, C. Lord, B.L. Leventhal, E.H. Cook Jr., T.R. Insel, Transmission disequilibrium testing of arginine vasopressin receptor 1A (AVPR1A) polymorphisms in autism, Molecular Psychiatry 7 (2002) 503–507.
[91] P. Kirsch, C. Esslinger, Q. Chen, D. Mier, S. Lis, S. Siddhanti, H. Gruppe, V.S. Mattay, B. Gallhofer, A. Meyer-Lindenberg, Oxytocin modulates neural circuitry for social cognition and fear in humans, Journal of Neuroscience 25 (2005) 11489–11493.
[92] A. Knafo, S. Israel, A. Darvasi, R. Bachner-Melman, F. Uzefovsky, L. Cohen, E. Feldman, E. Lerer, E. Laiba, Y. Raz, L. Nemanov, I. Gritsenko, C. Dina, G. Agam, B. Dean, G. Bornstein, R.P. Ebstein, Individual differences in allocation of funds in the dictator game associated with length of the arginine vasopressin 1a receptor RS3 promoter region and correlation between RS3 length and hippocampal mRNA, Genes, Brain and Behavior 7 (2008) 266–275.
[93] M. Kosfeld, M. Heinrichs, P.J. Zak, U. Fischbacher, E. Fehr, Oxytocin increases trust in humans, Nature 435 (2005) 673–676.
[94] R. Landgraf, I.D. Neumann, Vasopressin and oxytocin release within the brain a dynamic concept of multiple and variable modes of neuropeptide communication, Frontiers in Neuroendocrinology 25 (2004) 150–176.
[95] M.B. Lauritsen, T.D. Als, H.A. Dahl, T.J. Flint, A.G. Wang, M. Vang, T.A. Kruse, H. Ewald, O. Mors, A genome-wide search for alleles and haplotypes associated with autism and related pervasive developmental disorders on the Faroe Islands, Molecular Psychiatry 11 (2006) 37–46.
[96] J.F. Leckman, W.K. Goodman, W.G. North, P.B. Chappell, L.H. Price, D.L. Pauls, G.M. Anderson, M.A. Riddle, C.J. McDougle, L.C. Barr, et al., The role of central oxytocin in obsessive compulsive disorder and related normal behavior, Psychoneuroendocrinology 19 (1994) 723–749.
[97] J.F. Leckman, W.K. Goodman, W.G. North, P.B. Chappell, L.H. Price, D.L. Pauls, G.M. Anderson, M.A. Riddle, M. McSwiggan-Hardin, C.J. McDougle, et al., Elevated cerebrospinal fluid levels of oxytocin in obsessive–compulsive disorder. Comparison with Tourette's syndrome and healthy controls, Archives of General Psychiatry 51 (1994) 782–792.
[98] J.J. Legros, C. Gazzotti, T. Carvelli, P. Franchimont, M. Timsit-Berthier, R. von Frenckell, M. Ansseau, Apomorphine stimulation of vasopressin- and oxytocin-neurophysins. Evidence for increased oxytocinergic and decreased vasopressinergic function in schizophrenics, Psychoneuroendocrinology 17 (1992) 611–617.
[99] E. Lerer, S. Levi, S. Salomon, A. Darvasi, N. Yirmiya, R.P. Ebstein, Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland adaptive behavior scales and cognition, Molecular Psychiatry 13 (2008) 980–988.
[100] A. Levine, O. Zagoory-Sharon, R. Feldman, A. Weller, Oxytocin during pregnancy and early postpartum: individual patterns and maternal–fetal attachment, Peptides 28 (2007) 1162–1169.
[101] K.N. Levy, The implications of attachment theory and research for understanding borderline personality disorder, Development and Psychopathology 17 (2005) 959–986.
[102] K. Lieb, M.C. Zanarini, C. Schmahl, M.M. Linehan, M. Bohus, Borderline personality disorder, Lancet 364 (2004) 453–461.
[103] K.C. Light, T.E. Smith, J.M. Johns, K.A. Brownley, J.A. Hofheimer, J.A. Amico, Oxytocin responsivity in mothers of infants: a preliminary study of relationships with blood pressure during laboratory stress and normal ambulatory activity, Health Psychology 19 (2000) 560–567.
[104] M.M. Lim, L.J. Young, Neuropeptidergic regulation of affiliative behavior and social bonding in animals, Hormones and Behavior 50 (2006) 506–517.
[105] P. Linkowski, V. Geenen, M. Kerkhofs, J. Mendlewicz, J.J. Legros, Cerebrospinal fluid neurophysins in affective illness and in schizophrenia, European Archives of Psychiatry and Neurological Sciences 234 (1984) 162–165.
[106] F. Loup, E. Tribollet, M. Dubois-Dauphin, J.J. Dreifuss, Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study, Brain Research 555 (1991) 220–232.
[107] L.A. Lumley, C.L. Robison, W.K. Chen, B. Mark, J.L. Meyerhoff, Vasopressin into the preoptic area increases grooming behavior in mice, Physiology and Behavior 73 (2001) 451–455.
[108] J.K. Mai, K. Berger, M.V. Sofroniew, Morphometric evaluation of neurophysin-immunoreactivity in the human brain: pronounced inter-individual variability and evidence for altered staining patterns in schizophrenia, Journal für Hirnforschung 34 (1993) 133–154.
[109] D. Marazziti, M. Catena Dell'osso, The role of oxytocin in neuropsychiatric disorders, Current Medicinal Chemistry 15 (2008) 698–704.
[110] J.L. McCauley, C. Li, L. Jiang, L.M. Olson, G. Crockett, K. Gainer, S.E. Folstein, J.L. Haines, J.S. Sutcliffe, Genome-wide and ordered-subset linkage analyses provide support for autism loci on 17q and 19p with evidence of phenotypic and interlocus genetic correlates, BMC Medical Genetics 6 (2005) 1.
[111] B.B. McEwen, Brain-fluid barriers: relevance for theoretical controversies regarding vasopressin and oxytocin memory research, Advances in Pharmacology 50 (2004) 531–592.
[112] G. Meinlschmidt, C. Heim, Sensitivity to intranasal oxytocin in adult men with early parental separation, Biological Psychiatry 61 (2007) 1109–1111.
[113] A. Meyer-Lindenberg, B. Kolachana, B. Gold, A. Olsh, K.K. Nicodemus, V. Mattay, M. Dean, D.R. Weinberger, Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans, Molecular Psychiatry 54 (2008), doi:10.1038/mp.2008 (Epub ahead of print).
[114] M.J. Minzenberg, J. Fan, A.S. New, C.Y. Tang, L.J. Siever, Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study, Psychiatry Research 155 (2007) 231–243.
[115] C. Modahl, L. Green, D. Fein, M. Morris, L. Waterhouse, C. Feinstein, H. Levin, Plasma oxytocin levels in autistic children, Biological Psychiatry 43 (1998) 270–277.
[116] N. Momeni, B.M. Nordstrom, V. Horstmann, H. Avarseji, B.V. Sivberg, Alterations of prolyl endopeptidase activity in the plasma of children with autistic spectrum disorders, BMC Psychiatry 5 (2005) 27.
[117] C. Murgatroyd, A. Wigger, E. Frank, N. Singewald, M. Bunck, F. Holsboer, R. Landgraf, D. Spengler, Impaired repression at a vasopressin promoter polymorphism underlies overexpression of vasopressin in a rat model of trait anxiety, Journal of Neuroscience 24 (2004) 7762–7770.
[118] J.B. Murray, Phencyclidine (PCP) a dangerous drug, but useful in schizophrenia research, Journal of Psychology 136 (2002) 319–327.
[119] I.D. Neumann, Involvement of the brain oxytocin system in stress coping: interactions with the hypothalamic–pituitary–adrenal axis, Progress in Brain Research 139 (2002) 147–162.
[120] I.D. Neumann, S.A. Kromer, N. Toschi, K. Ebner, Brain oxytocin inhibits the (re)activity of the hypothalamic–pituitary–adrenal axis in male rats: involvement of hypothalamic and limbic brain regions, Regulatory peptides 96 (2000) 31–38.
[121] I.D. Neumann, A. Wigger, L. Torner, F. Holsboer, R. Landgraf, Brain oxytocin inhibits basal and stress-induced activity of the hypothalamic–pituitary–adrenal axis in male and female rats: partial action within the paraventricular nucleus, Journal of Neuroendocrinology 12 (2000) 235–243.
[122] E. Nissen, K. Uvnas-Moberg, K. Svensson, S. Stock, A.M. Widstrom, J. Winberg, Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route, Early Human Development 45 (1996) 103–118.
[123] K.J. Parker, C.L. Buckmaster, A.F. Schatzberg, D.M. Lyons, Intranasal oxytocin administration attenuates the ACTH stress response in monkeys, Psychoneuroendocrinology 30 (2005) 924–929.
[124] C.A. Pedersen, Oxytocin control of maternal behavior Regulation by sex steroids and offspring stimuli, Annals of the New York Academy of Sciences 807 (1997) 126–145.
[125] C.A. Pedersen, J.D. Caldwell, F. Drago, L.R. Noonan, G. Peterson, L.E. Hood, A.J. Prange Jr., Grooming behavioral effects of oxytocin. Pharmacology, ontogeny, and comparisons with other nonapeptides, Annals of the New York Academy of Sciences 525 (1988) 245–256.
[126] E.R. Peskind, M.A. Raskind, R.D. Leake, M.G. Ervin, M.G. Ross, D.M. Dorsa, Clonidine decreases plasma and cerebrospinal fluid arginine vasopressin but not oxytocin in humans, Neuroendocrinology 46 (1987) 395–400.
[127] P. Petrovic, R. Kalisch, T. Singer, R.J. Dolan, Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity, Journal of Neuroscience 28 (2008) 6607–6615.
[128] B. Pierrehumbert, R. Torrisi, N. Glatz, N. Dimitrova, M. Heinrichs, O. Halfon, The influence of attachment on perceived stress and cortisol response to

acute stress in women sexually abused in childhood or adolescence, Psychoneuroendocrinology 34 (2009) 924–938.
[129] R. Pietrowsky, A. Thiemann, W. Kern, H.L. Fehm, J. Born, A nose–brain pathway for psychotropic peptides: evidence from a brain evoked potential study with cholecystokinin, Psychoneuroendocrinology 21 (1996) 559–572.
[130] A.F. Pitts, S.D. Samuelson, W.H. Meller, G. Bissette, C.B. Nemeroff, R.G. Kathol, Cerebrospinal fluid corticotropin-releasing hormone, vasopressin, and oxytocin concentrations in treated patients with major depression and controls, Biological Psychiatry 38 (1995) 330–335.
[131] J.S. Purba, W.J. Hoogendijk, M.A. Hofman, D.F. Swaab, Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression, Archives of General Psychiatry 53 (1996) 137–143.
[132] M. Raggenbass, Vasopressin- and oxytocin-induced activity in the central nervous system: electrophysiological studies using in-vitro systems, Progress in Neurobiology 64 (2001) 307–326.
[133] M.A. Raskind, N. Courtney, M.M. Murburg, F.I. Backus, J.A. Bokan, R.K. Ries, D.M. Dorsa, R.E. Weitzman, Antipsychotic drugs and plasma vasopressin in normals and acute schizophrenic patients, Biological Psychiatry 22 (1987) 453–462.
[134] U. Rimmele, K. Hediger, M. Heinrichs, P. Klaver, Oxytocin makes a face in memory familiar, Journal of Neuroscience 29 (2009) 38–42.
[135] A.D. Salzberg, S.E. Swedo, Oxytocin and vasopressin in obsessive–compulsive disorder, American Journal of Psychiatry 149 (1992) 713–714.
[136] E. Savaskan, R. Ehrhardt, A. Schulz, M. Walter, H. Schachinger, Post-learning intranasal oxytocin modulates human memory for facial identity, Psychoneuroendocrinology 33 (2008) 368–374.
[137] G. Scantamburlo, M. Hansenne, S. Fuchs, W. Pitchot, P. Marechal, C. Pequeux, M. Ansseau, J.J. Legros, Plasma oxytocin levels and anxiety in patients with major depression, Psychoneuroendocrinology 32 (2007) 407–410.
[138] G. Scantamburlo, M. Hansenne, S. Fuchs, W. Pitchot, E. Pinto, J. Reggers, M. Ansseau, J.J. Legros, AVP- and OT-neurophysins response to apomorphine and clonidine in major depression, Psychoneuroendocrinology 30 (2005) 839–845.
[139] T. Singer, R. Snozzi, G. Bird, P. Petrovic, G. Silani, M. Heinrichs, R.J. Dolan, Effects of oxytocin and prosocial behavior on brain responses to direct and vicariously experienced pain, Emotion 8 (2008) 781–791.
[140] D.A. Slattery, I.D. Neumann, No stress please! Mechanisms of stress hyporesponsiveness of the maternal brain, Journal of Physiology 586 (2008) 377–385.
[141] A. Surget, C. Belzung, Involvement of vasopressin in affective disorders, European Journal of Pharmacology 583 (2008) 340–349.
[142] S.E. Swedo, H.L. Leonard, M.J. Kruesi, D.C. Rettew, S.J. Listwak, W. Berrettini, M. Stipetic, S. Hamburger, P.W. Gold, W.Z. Potter, et al., Cerebrospinal fluid neurochemistry in children and adolescents with obsessive–compulsive disorder, Archives of General Psychiatry 49 (1992) 29–36.
[143] M. Thibonnier, M.K. Graves, M.S. Wagner, C. Auzan, E. Clauser, H.F. Willard, Structure, sequence, expression, and chromosomal localization of the human V1a vasopressin receptor gene, Genomics 31 (1996) 327–334.
[144] R. Thompson, S. Gupta, K. Miller, S. Mills, S. Orr, The effects of vasopressin on human facial responses related to social communication, Psychoneuroendocrinology 29 (2004) 35–48.
[145] R.R. Thompson, K. George, J.C. Walton, S.P. Orr, J. Benson, Sex-specific influences of vasopressin on human social communication, Proceedings of the National Academy of Sciences of the United States of America 103 (2006) 7889–7894.
[146] R.A. Turner, M. Altemus, T. Enos, B. Cooper, T. McGuinness, Preliminary research on plasma oxytocin in normal cycling women: investigating emotion and interpersonal distress, Psychiatry 62 (1999) 97–113.
[147] K. Uvnas-Moberg, Oxytocin may mediate the benefits of positive social interaction and emotions, Psychoneuroendocrinology 23 (1998) 819–835.
[148] K. Uvnas-Moberg, Role of efferent and afferent vagal nerve activity during reproduction: integrating function of oxytocin on metabolism and behaviour, Psychoneuroendocrinology 19 (1994) 687–695.
[149] K. Uvnas-Moberg, E. Bjokstrand, V. Hillegaart, S. Ahlenius, Oxytocin as a possible mediator of SSRI-induced antidepressant effects, Psychopharmacology 142 (1999) 95–101.
[150] L. van Londen, J.G. Goekoop, G.M. van Kempen, A.C. Frankhuijzen-Sierevogel, V.M. Wiegant, E.A. van der Velde, D. De Wied, Plasma levels of arginine vasopressin elevated in patients with major depression, Neuropsychopharmacology 17 (1997) 284–292.
[151] L. van Londen, J.G. Goekoop, A.H. Zwinderman, J.B. Lanser, V.M. Wiegant, D. De Wied, Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression, Psychological Medicine 28 (1998) 275–284.
[152] L. van Londen, G.A. Kerkhof, F. van den Berg, J.G. Goekoop, K.H. Zwinderman, A.C. Frankhuijzen-Sierevogel, V.M. Wiegant, D. de Wied, Plasma arginine vasopressin and motor activity in major depression, Biological Psychiatry 43 (1998) 196–204.
[153] A.W. Wagner, M.M. Linehan, Facial expression recognition ability among women with borderline personality disorder: implications for emotion regulation?, Journal of Personality Disorders 13 (1999) 329–344
[154] H. Walum, L. Westberg, S. Henningsson, J.M. Neiderhiser, D. Reiss, W. Igl, J.M. Ganiban, E.L. Spotts, N.L. Pedersen, E. Eriksson, P. Lichtenstein, Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans, Proceedings of the National Academy of Sciences of the United States of America 105 (2008) 14153–14156.
[155] S.S. Wang, W. Kamphuis, I. Huitinga, J.N. Zhou, D.F. Swaab, Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: the presence of multiple receptor imbalances, Molecular Psychiatry 13 (2008) 786–799.
[156] T.H. Wassink, J. Piven, V.J. Vieland, J. Pietila, R.J. Goedken, S.E. Folstein, V.C. Sheffield, Examination of AVPR1a as an autism susceptibility gene, Molecular Psychiatry 9 (2004) 968–972.
[157] R. White-Traut, K. Watanabe, H. Pournajafi-Nazarloo, D. Schwertz, A. Bell, C.S. Carter, Detection of salivary oxytocin levels in lactating women, Development and Psychopathology 51 (2009) 367–373.
[158] R.J. Windle, Y.M. Kershaw, N. Shanks, S.A. Wood, S.L. Lightman, C.D. Ingram, Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamic–pituitary–adrenal activity, Journal of Neuroscience 24 (2004) 2974–2982.
[159] R.J. Windle, N. Shanks, S.L. Lightman, C.D. Ingram, Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats, Endocrinology 138 (1997) 2829–2834.
[160] R.J. Windle, S. Wood, N. Shanks, P. Perks, G.L. Conde, A.P. da Costa, C.D. Ingram, S.L. Lightman, Endocrine and behavioural responses to noise stress: comparison of virgin and lactating female rats during non-disrupted maternal activity, Journal of Neuroendocrinology 9 (1997) 407–414.
[161] S. Wu, M. Jia, Y. Ruan, J. Liu, Y. Guo, M. Shuang, X. Gong, Y. Zhang, X. Yang, D. Zhang, Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population, Biological Psychiatry 58 (2005) 74–77.
[162] N. Yirmiya, C. Rosenberg, S. Levi, S. Salomon, C. Shulman, L. Nemanov, C. Dina, R.P. Ebstein, Association between the arginine vasopressin 1a receptor (AVPR1a) gene and autism in a family-based study: mediation by socialization skills, Molecular Psychiatry 11 (2006) 488–494.
[163] T. Ylisaukko-oja, M. Alarcon, R.M. Cantor, M. Auranen, R. Vanhala, E. Kempas, L. von Wendt, I. Jarvela, D.H. Geschwind, L. Peltonen, Search for autism loci by combined analysis of autism genetic resource exchange and Finnish families, Annals of Neurology 59 (2006) 145–155.
[164] L.J. Young, L.J. Pitkow, J.N. Ferguson, Neuropeptides and social behavior: animal models relevant to autism, Molecular Psychiatry 7 (Suppl 2) (2002) S38–S39.
[165] L.J. Young, Z. Wang, The neurobiology of pair bonding, Nature Neuroscience 7 (2004) 1048–1054.
[166] P.J. Zak, R. Kurzban, W.T. Matzner, The neurobiology of trust, Annals of the New York Academy of Sciences 1032 (2004) 224–227.
[167] P.J. Zak, R. Kurzban, W.T. Matzner, Oxytocin is associated with human trustworthiness, Hormones and Behavior 48 (2005) 522–527.



Please cite this article in press as: M. Heinrichs et al., Oxytocin, vasopressin, and human social behavior, Front. Neuroendocrinol. (2009), doi:10.1016/j.yfrne.2009.05.005