Available online at www.sciencedirect.com
ScienceDirect
Hormones and Behavior 50 (2006) 518–528
Hormones and Behavior
www.elsevier.com/locate/yhbeh

The neuroscience of affiliation: Forging links between basic and clinical research on neuropeptides and social behavior

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Received 16 May 2006; revised 15 June 2006; accepted 21 June 2006
Available online 1 August 2006

Abstract

Animal studies point to the role of two neuropeptides–oxytocin and vasopressin–in the regulation of affiliative behaviors including mating, pair-bond formation, maternal/parenting behavior, and attachment. These findings may have important implications for understanding and treating clinical disorders marked by social deficits and/or disrupted attachment. This review focuses on advances made to date in the effort to forge links between basic and clinical research in the area of neuropeptides and social behavior. The literature on oxytocin and its involvement in stress response, affiliation, and prosocial behavior is reviewed, and the implications of these findings for such disorders as autism as well as other social and stress-related disorders including social phobia, post-traumatic stress disorder, and some personality disorders are considered. Finally, unresolved issues and directions for future research are discussed.

Keywords: Neuropeptides; Oxytocin; Social behavior; Translational research; Autism

Introduction

Noting the ubiquity of abnormal social attachments in "virtually every form of psychopathology" (p. 726), Insel (1997) called attention to the importance of research investigating the neurobiology involved in social bond formation. Animal studies support the role of two neuropeptides, oxytocin and vasopressin, in the regulation of affiliative behaviors including mating, pair-bond formation, maternal/parenting behavior, and attachment. This article reviews advances made to date in the effort to forge links between basic and clinical research in the area of neuropeptides and social behavior. Because Lim and Young (see our companion article in this issue) review the animal literature in this area in detail, this article will focus on the implications of the findings from animal studies as well as those from studies of healthy humans regarding neuropeptides and social behavior for clinical disorders. Moreover, although findings from animal studies point to the involvement of oxytocin and vasopressin in social behavior, we will concentrate primarily on oxytocin because most of the studies conducted thus far in humans have focused on oxytocin. In the first part of this review, we examine the involvement of oxytocin in stress response, affiliation, and prosocial behavior; we touch briefly on the findings from animal studies, but our primary focus is studies of healthy humans. In the second part of this review, we address the clinical implications of these findings as well as of the findings from animal studies. In particular, we address the relevance of oxytocin for such disorders as autism as well as other social and stress-related disorders including social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and borderline personality disorder (BPD). Finally, we conclude with a discussion of unresolved issues and directions for future research.

Oxytocin, stress, and social affiliation

Before reviewing the evidence to date regarding the role of oxytocin in humans, it should be noted that research in this area has been hampered because of the methodological difficulties

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doi:10.1016/j.yhbeh.2006.06.018

involved. Whereas animal researchers have had a number of tools at their disposal (e.g., the ability to centrally administer oxytocin and oxytocin antagonists, manipulate the expression of oxytocin by knocking out specific genes, and directly assess oxytocin mRNA), researchers investigating the role of oxytocin in humans have had to rely on more indirect measures like assaying plasma oxytocin and, until recently, commercial assays were not even available (Taylor et al., 2000). Moreover, even as an indirect measure, plasma oxytocin has limited value because the relationship between central and peripheral oxytocin is not well understood and because the correlational nature of the findings cannot clarify issues about causality. Recently, however, progress has been made in this area; for example, researchers have begun to use challenge procedure methodologies involving the intravenous infusion of oxytocin as well as intranasal formulations, both of which allow for the use of use double-blind, placebo-controlled designs to more rigorously investigate the effect of oxytocin in humans. Researchers have also begun to combine these techniques with functional magnetic resonance imaging (fMRI) to investigate the neurobiological correlates of oxytocin activity in the human brain. With these caveats in mind, we now review the findings from the few human studies that have been conducted. Encouragingly, the results from these studies by and large parallel those from animal studies and suggest that oxytocin is involved in human stress response and affiliation.

Oxytocin and stress response

A number of animal studies suggest that oxytocin is involved in the stress response; in particular, oxytocin is thought to play a role in reducing stress by dampening hypothalamic–pituitary–adrenal (HPA) activity (Neumann, 2002). Much of the research supporting the association between oxytocin and stress response has focused on lactation because oxytocin is released during lactation in response to suckling to cause milk ejection (Uvnas-Moberg et al., 1990). Studies have shown that suckling in the post-partum period is linked to decreased HPA axis activity (Carter and Altemus, 1997; Lightman and Young, 1989) and that lactating rats evidence blunted adrenocorticotropic hormone (ACTH) and cortisol secretion to physical and psychosocial stressors (Neumann et al., 1998; Stern et al., 1973; Thoman et al., 1970; Walker et al., 1992; Windle et al., 1997). Moreover, oxytocin injections have been associated with decreased blood pressure and cortisol levels in female rats (Uvnas-Moberg, 1998), anxiolytic-like effects and sedation in male rats (Uvnas-Moberg et al., 1994), and reduced reactivity to painful stimuli (Lundeberg et al., 1994).

Lactation in humans also appears to dampen stress responsivity. Lactating women show attenuated ACTH, cortisol and glucose response to physical stressors (Altemus et al., 1995), post-partum lactating women show attenuated pituitary–adrenal reactivity to a psychosocial stressor after endogenous oxytocin stimulation (Heinrichs et al., 2001), and breast-feeding women with increased plasma oxytocin show decreased blood pressure in response to a psychosocial stressor after holding their baby, an event thought to enhance the effects of oxytocin (Light et al., 2000). Moreover, Uvnas-Moberg and colleagues (Uvnas-Moberg, 1996; Uvnas-Moberg et al., 1990) found that breast-feeding women score lower on scales measuring muscular tension and monotony avoidance and higher on a scale measuring social desirability than age-matched control women and also found strong correlations between oxytocin plasma levels assessed during breast-feeding and self-reported calmness and pleasantness. Finally, similar to studies with animals, studies have shown that exogenous oxytocin administration leads to decrease basal and pharmacologically stimulated ACTH and cortisol response in healthy humans (Chiodera and Coiro, 1987; Legros et al., 1982, 1984; Suh et al., 1986).

Although these findings are suggestive, as Heinrichs and colleagues (Heinrichs et al., 2003) noted, they are limited by a number of confounding factors, in particular, the release of other hormones (e.g., prolactin or opioid peptides), making it difficult to ascertain the specific role of oxytocin in stress reduction. To address this issue, Heinrichs et al. (2003) investigated the effects of exogenously administered oxytocin on cortisol and on subjective responses to a psychosocial stressor. Moreover, these researchers were interested in probing the interactive effects of oxytocin and social support on stress response. Given the well-known association between social support and mental and physical well-being (House et al., 1988), as well as animal studies documenting the role of oxytocin in affiliation, a number of researchers have speculated that oxytocin may mediate the association between social support and mental and physical well-being (Carter, 1998; DeVries et al., 2003; Henry and Wang, 1998; Insel and Young, 2001; Light et al., 2005; Taylor, 2002; Uvnas-Moberg, 1998; Uvnas-Moberg, 2004). That is, by dampening stress reactivity, oxytocin may be part of the physiological mechanism through which social support and contact promote mental and physical health.

Heinrichs et al. (2003) randomly assigned healthy men to receive intranasal oxytocin or placebo; social support was manipulated by having participants bring a friend to the testing session or not. Participants then underwent the Trier Social Stress Test, and cortisol and subjective responses (i.e., mood and anxiety) were assessed. Consistent with previous research, social support suppressed salivary free cortisol levels; although oxytocin did not independently affect salivary cortisol, those who received oxytocin and social support had the lowest cortisol levels and reported increased calmness and decreased anxiety during the psychosocial stressor. Moreover, those who received oxytocin either with or without social support reported decreased anxiety from pre- to post-test, supporting the hypothesized anxiolytic effects of oxytocin. Heinrichs et al. (2003) speculate that the effectiveness of social support may depend on the availability of oxytocin in the central nervous system. Indeed, central oxytocin may also boost the effectiveness of social support in other animals. Winslow et al. (2003) found that nursery-reared monkeys, who had significantly reduced cerebrospinal fluid (CSF) oxytocin levels compared to mother-reared monkeys, were less able to use a social companion as a buffer against a stressor.

Thus, research to date strongly suggests that oxytocin reduces the stress response and may also mediate the relationship between receiving social support, effective coping, and improved mental and physical well-being in humans and in other animals. That said, some studies suggest that elevated plasma oxytocin may be an indicator of some kinds of stress. Taylor et al. (2006) had women undergo a psychosocial stress test and assessed plasma oxytocin, cortisol, and blood pressure. Participants also completed self-report questionnaires assessing psychological distress and relationship functioning. Women with elevated plasma oxytocin reported less contact with significant others (e.g., mothers, best friends, pets, and social groups to which they belonged), felt less appreciated by their husbands, and felt they could not rely on their husbands for support. Moreover, plasma oxytocin was negatively associated with marital quality and frequency of affectionate contact, although these associations were marginal. Importantly, plasma oxytocin was not associated with general psychological distress, suggesting that elevated plasma oxytocin may be a specific indicator of social distress.

These findings are consistent with two other studies, one showing a positive association between plasma oxytocin and relationship distress in young women (Turner et al., 1999) and another showing a positive association between plasma oxytocin and chronic feelings of attachment anxiety (e.g., desire for closeness but concerns about abandonment) in a sample of healthy men and women (Marazziti, personal communication). Taylor et al. (2006) suggest that if plasma oxytocin acts as a signal for relationship distress, its function may be to motivate people to seek out positive social contacts. Further research, however, is needed to investigate this hypothesis and to clarify inconsistencies with other research showing an association between oxytocin and self-reported feelings of calmness and sociability (e.g., Uvnas-Moberg et al., 1990), as well as animal data showing that exogenous administration of oxytocin reduces stress.

Oxytocin and social affiliation

In addition to its role in stress response, research supports the involvement of oxytocin and vasopressin in social affiliation and attachment behavior. A host of animal studies have implicated oxytocin and vasopressin in adult–adult and mother–infant pair-bonding (see our companion paper, Lim and Young, 2006, in this issue). For example, intracerebroventricular (ICV) injections of oxytocin facilitate maternal behavior in female nulliparous rats (Pedersen et al., 1982), whereas injecting oxytocin antagonists inhibits the onset but not maintenance of maternal behavior (Insel, 1992). In addition, both peptides stimulate pair-bonding in prairie voles in the absence of mating and their antagonists block pair-bonding when administered before mating (Insel and Hulihan, 1995; Williams et al., 1994). Differences in oxytocin and vasopressin receptor expression may underlie individual differences in social behavior and differences between animal species (Insel and Shapiro, 1992; Insel et al., 1994). In fact, mice genetically engineered to express vasopressin receptors in a pattern similar to that of prairie voles show affiliative behavior resembling that of prairie voles (Lim and Young, 2006).

In contrast to the animal literature, very few studies have examined oxytocin and social affiliation per se in humans. Recently, however, Kosfeld et al. (2005) report intriguing findings suggesting that intranasal oxytocin promotes trust and prosocial behavior in humans. Male volunteers were randomly assigned to receive intranasal oxytocin or placebo and then played the "trust game," a variation on the classic prisoner's dilemma in which participants are given a sum of money and must decide whether to invest any of that money with an anonymous player. The money invested is tripled in value, but there is no guarantee that the other player will share the earnings. Thus, trusting the other player could lead to higher payoffs for both players, but the investor always runs the risk that the other may violate that trust. Intranasal oxytocin significantly increased trust among participants compared to placebo. Moreover, a control risk condition revealed that the effects of oxytocin were not simply due to an increased willingness to engage in risky behavior; rather, they were due to participants' willingness to accept social risks, providing evidence for the involvement of oxytocin in human prosocial behavior.

Another recent investigation also points to the role of oxytocin in mediating human social behavior (Kirsch et al., 2005). In this study, male participants were randomly assigned to receive intranasal oxytocin or placebo and then viewed fear-inducing stimuli of a social (angry and fearful faces) and non-social (threatening scenes) nature; fMRI was used to investigate changes in amygdala activity. Consistent with the hypothesized anxiolytic effects of oxytocin, participants receiving oxytocin showed reduced amygdala activation to both kinds of stimuli but, interestingly, oxytocin had a more pronounced effect on responses to the social stimuli. Moreover, the functional connection between the amygdala and structures in the upper brain stem (i.e., the periaqueductal gray and reticular formation), which have been implicated in autonomic and behavioral fear responses, was reduced for participants receiving exogenous oxytocin. This study is consistent with previous studies documenting the anxiolytic effects of oxytocin and, as the author's suggest, points to the possibility that oxytocin may increase trust and prosocial behavior by dampening amygdala responsivity to the potential dangers inherent in social situations (i.e., by dampening social fear). However, it is noteworthy that participants in Kosfeld et al.'s (2005) study did not report decreased anxiety or increased feelings of calmness following oxytocin administration, suggesting that the effect of oxytocin on trust involves more than anxiety reduction.

In summary, overall, the findings from studies of healthy humans parallel those from animal studies and point to the role of oxytocin in stress response and in enhancing social affiliation; however, the underlying mechanisms are not yet well understood. Oxytocin appears to dampen stress reactivity, but other hormones are likely involved in this process. There is also intriguing evidence that elevated plasma oxytocin levels may be a biomarker of relational distress. Moreover, research has found that oxytocin administered exogenously dampens

amygdala activity, suggesting a possible neurobiological pathway by which oxytocin reduces anxiety and, possibly, promotes prosocial behavior. Finally, exogenously administered oxytocin has been found to increase trust and prosocial behavior, and this process appears to be due to more than the anxiolytic effects of oxytocin.

Clinical implications

Oxytocin and autism

According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; DSM-IV-TR, American Psychiatric Association, 2000), autism is a developmental disorder characterized by abnormalities in speech and communication, impaired social functioning, and repetitive behaviors and restricted interests. A number of researchers have suggested that oxytocin and vasopressin may be implicated in the etiology of autism given that deficits in social interaction and affiliation are a core feature of autism and that these neuropeptides are involved in the regulation of affiliative behaviors (Hollander et al., 2003, in press; Insel et al., 1999; Lim et al., 2005; McCarthy and Altemus, 1997; Modahl et al., 1992; Panksepp, 1992; Waterhouse et al., 1996). Below, we outline evidence supporting the involvement of oxytocin and vasopressin in autism. We begin this section with studies investigating plasma oxytocin levels as the primary outcome variable. We then turn to genetic research focusing on the receptors for these neuropeptides; this research is particularly compelling because, in contrast to plasma levels, receptors have a greater potential for contributing to variability via different alleles as well as possible differences in signal transduction. We conclude this section with research that has exogenously manipulated the availability of oxytocin to investigate its functional role in autism and to probe the potential therapeutic benefits of oxytocin for this disorder.

Modahl et al. (1998) found significantly lower plasma oxytocin levels in children with autism compared to age-matched controls and found that autistic children failed to show the normal developmental increase in oxytocin blood levels that was characteristic of the healthy control children. These researchers also found a significant correlation between oxytocin blood levels and social impairment in a subgroup of their sample identified as severely affected (i.e., 'aloof'). Moreover, a subsequent study by this group showed that, not only were the plasma samples obtained from the autistic children associated with lower oxytocin levels, but they were also associated with higher oxytocin precursor levels, as well as an increased ratio of oxytocin precursor to oxytocin, suggesting that autism may be related to differences in the way oxytocin is processed in the brain (Green et al., 2001). With respect to the notion discussed earlier that elevated plasma oxytocin may be a biomarker of social distress (Taylor et al., 2006), if autistic individuals have decreased plasma oxytocin, then this biomarker may not be functioning properly to alert them to social distress and to promote prosocial behavior. Indeed, this is consistent with research showing that mouse pups with a null mutation in the gene coding for oxytocin production have significantly reduced separation distress calls compared to pups with oxytocin (Young et al., 1997).

It has been theorized that mutations occurring in the sequence of the oxytocin receptor gene could disrupt the behavioral effects of oxytocin, including those associated with affiliation and social bonding (Michelini et al., 1995). Studies showing that affiliative differences in prairie and montane voles correlate with oxytocin receptor expression levels (Insel and Shapiro, 1992) support this notion. Two recent studies support a genetic association between the oxytocin receptor gene and autism. Wu et al. (2005) sampled 195 homogenous Chinese Han family trios (singleton autistic disordered patients and their biological parents) and found evidence of transmissive disequilibrium for two single nucleotide polymorphisms (rs2254298 and rs53576), indicating that these two loci may be associated with autism. These findings suggest that genetic variability in the oxytocin receptor gene may be a risk factor for autism. In addition, Ylisaukko-oja et al. (2006) conducted a combined analysis of primary genome scanned data from the Autism Genetic Resource Exchange and samples from Finnish families to identify potential susceptibility loci for autism; findings from this study also highlight the potential importance of the oxytocin receptor gene in autism.

Polymorphisms in the vasopressin receptor have also been linked to autism. Kim et al. (2002) found evidence for disequilibrium between autism and one microsatellite polymorphism of the AVP receptor 1a gene (AVPR1a), Wassink et al. (2004) also found evidence for linkage disequilibrium in the AVPR1a, and Yirmiya et al. (2006) demonstrated a link between the AVPR1a gene and autism. Moreover, Yirmiya et al.'s (2006) study showed that the association between the AVPR1a gene and autism appears to be primarily due to the involvement of AVPR1a in shaping social skills, as evidenced by transmission disequilibrium between the AVPR1a gene and the Vineland and Autism Diagnostic Observation Scale-Generic assessments (Yirmiya et al., 2006).

These findings are consistent with animal studies, which have shown that both oxytocin and vasopressin genes are involved in many aspects of social behavior (again, the reader is referred to our companion article by Lim and Young, 2006, for a more detailed review of this literature). For example, Ferguson et al. (2000) found that male mice with a null mutation in the gene coding for oxytocin production ('oxytocin knockout mice') evidenced significant social memory deficits (i.e., they failed to recognize a previously encountered mouse, even over repeated exposures) compared to wild-type mice. Similarly, V1aR knockout mice have also been found to exhibit social memory deficits (Bielsky et al., 2004), whereas the over expression of the V1aR gene in the lateral septum of these mice has been found to enhance social recognition (Bielsky et al., 2005).

Recently, Hollander and colleagues (Hollander et al., 2003, in press) conducted research using a laboratory challenge methodology to examine the functional role of oxytocin in autism. Drawing upon the findings from animal studies showing that oxytocin is involved in grooming and stereotyped behaviors (Drago et al., 1986; Insel and Winslow, 1991; Meisenberg and Simmons, 1983; Nelson and Alberts, 1997),

Hollander and colleagues (2003) administered oxytocin or placebo via intravenous infusion to adults with autism spectrum disorders (i.e., those diagnosed with autism or Asperger's disorder). As predicted, oxytocin infusion resulted in a significant reduction in repetitive behaviors including need to know, repeating, ordering, need to tell/ask, self-injury, and touching compared to placebo. Moreover, a subsequent investigation revealed that oxytocin also facilitated social information processing in individuals with autism spectrum disorders (Hollander et al., in press). Specifically, oxytocin infusion facilitated patients' processing and retention of social information (i.e., their ability to assign affective significance to speech). This finding is consistent with animal studies showing that low doses of oxytocin facilitate social recognition in rodents (Popik et al., 1992), as well as the studies noted earlier showing that mice with a null mutation in the gene coding for oxytocin production show significant social memory deficits compared to wild-type mice (Ferguson et al., 2000), whereas a single ICV injection of oxytocin prior to the initial encounter with the conspecific enables social memory acquisition in these mice (Ferguson et al., 2001).

One noteworthy feature about the findings from Hollander's group is that the effect of oxytocin on social cognition was slightly more complex than the effect of oxytocin on repetitive behaviors. Whereas oxytocin infusion resulted in an overall decrease in repetitive behaviors over time, the increase in retention of social cognition following oxytocin was a function of time and order of administration. Specifically, those who received oxytocin first and those who received placebo first improved from pre- to post-test on the affective speech comprehension task; however, those who received placebo first tended to revert to baseline during their pre-test assessment after a delay (i.e., at the next testing session), whereas those who received oxytocin first did not revert to baseline—that is, they appeared to retain the ability to accurately assign emotional significance to speech intonation. This finding is consistent with animal studies and suggests that oxytocin may specifically be involved in the retention and preservation of social memory acquisition in autism.

In summary, these studies support the potential role of oxytocin in autism spectrum disorders and suggest that oxytocin may have therapeutic benefits for the treatment of these disorders, especially with respect to addressing repetitive behaviors and deficits in social functioning. Although initial findings by Hollander and colleagues are encouraging, future research is needed to determine the feasibility and long-term therapeutic effects of oxytocin for the treatment of autism spectrum disorders—a point to which we will return at the end of this article.

Oxytocin and other axis I disorders: social phobia and OCD

According to the *DSM-IV-TR* (American Psychiatric Association, 2000), social phobia is an anxiety disorder marked by persistent and excessive fear of social interaction and/or performance situations. Those afflicted with this disorder are worried they will be negatively evaluated by others and are plagued by fears that they will do or say something to humiliate or embarrass themselves. Thus, social situations, or situations in which evaluation by others is likely, are avoided, and if these situations must be endured, it is only with great discomfort and anxiety. Although social phobia is the most common anxiety disorder, little is known about its etiology or about effective treatments. Given that social phobia is marked by deficits in social functioning and anxiety/stress regulation problems and that oxytocin is implicated in both these areas, oxytocin is an ideal candidate for involvement in and for the potential treatment of social phobia (Kosfeld et al., 2005). In addition, oxytocin may also have potential therapeutic benefits for other disorders in which social withdrawal is a prominent symptom such as PTSD and mood disorders.

OCD is also a candidate for disrupted oxytocin because of the involvement of oxytocin in repetitive behaviors. Indeed, OCD was one of the first psychiatric disorders to be linked to oxytocin. As McDougle et al. (1999) summarize, a number of indirect findings point to the possible role of oxytocin in OCD: animal studies show a marked increase in stereotyped behaviors following the central administration of oxytocin (Drago et al., 1986; Insel and Winslow, 1991; Meisenberg and Simmons, 1983; Nelson and Alberts, 1997); women with OCD often report OCD onset or a worsening of symptoms during pregnancy or the puerperium (see McDougle et al., 1999 for a review); and research has found increased CSF oxytocin levels in an adult OCD subgroup (non-tic-related) (Leckman et al., 1994). Other evidence pointing to the role of oxytocin in OCD is that the oxytocin system has extensive interactions with the 5-HT and dopamine systems, which are known to be disrupted in OCD (McDougle et al., 1999).

The specific role that oxytocin plays in OCD, however, is unclear, and findings to date have been inconclusive or negative. One study investigating the long-term effects of clomipramine treatment in children and adolescents with OCD found increased oxytocin levels and decreased stereotypies following treatment (Altemus et al., 1994). However, a randomized, double-blind, six-week, placebo-controlled study investigating the therapeutic effects of intranasal oxytocin (18 IU/day) in 12 adults with OCD found no reduction of OCD symptoms following treatment (den Boer and Westenberg, 1992). Similarly, another trial in seven adults with OCD that used much higher doses of intranasal oxytocin (160 IU/day divided in 4 doses, with 2 of the subjects receiving a 320 IU/day daily dose) also found no OCD symptom reduction; however, the short duration of treatment (1 week) may have been a factor (Epperson et al., 1996a). Finally, a letter reporting on two adult subjects with trichotillomania (a putative obsessive-compulsive spectrum disorder) treated for 1 week with intranasal oxytocin (160 IU/day divided in 4 doses) also found no therapeutic benefit (Epperson et al., 1996b); again though, the duration of this study may not have been long enough to produce behavioral changes.

It is noteworthy that these findings are inconsistent with those obtained by Hollander et al. (2003) in which intravenous oxytocin administration produced a reduction in repetitive behaviors; however, two caveats are important to keep in mind

when comparing these studies. First, whereas oxytocin deficits are implicated in autism, too much oxytocin or an increased sensitivity to oxytocin may be implicated in OCD. Second, repetitive behaviors in autism may differ from those in OCD, not just phenomenologically but in terms of underlying neurobiology and, possibly, genetics. Indeed, this notion was supported in a recent factor analysis (Anagnostou et al., 2005), which found evidence for "higher-order" OCD-like repetitive behaviors as well as "lower order" repetitive behaviors characterized by self-stimulation in autism. Thus, oxytocin may be more effective in treating repetitive behaviors in autism than repetitive behaviors in OCD.

Oxytocin and axis II disorders: borderline personality disorder

Finally, oxytocin may be implicated in some personality disorders marked by disrupted social attachments. Borderline personality disorder (BPD) is characterized by affective instability, anger, impulsivity, and identity confusion. Disturbed interpersonal relationships–often marked by mental and/or physical abuse, as well as neglect–are believed to play a central role in the pathogenesis of BPD (Adler, 1986; Benjamin, 1993; Gunderson, 1984; Gunderson, 1996; Herman et al., 1989; Links et al., 1988; Masterson, 1972; Ogata et al., 1990; Paris et al., 1994a,b; Shearer et al., 1990; Simeon et al., 2003; Westen et al., 1990; Zanarini et al., 1989, 1997, 2000). In addition, BPD typically manifests itself in the interpersonal sphere. Individuals with BPD have a profound fear of abandonment, which leads to intense interpersonal relationships, marked by desperate attempts on the part of the BPD individual to avoid being left alone; in addition, their close relationships tend to be tumultuous, marked by frequent arguments, repeated breakups, and emotional volatility (Lieb et al., 2004). Given the link between oxytocin and trust/prosocial behavior, oxytocin may be a good candidate to target the disordered attachment and mistrust associated with BPD.

Indeed, a number of theorists speculate that early stress has important implications for adult affiliative behaviors and, furthermore, that oxytocin may be involved in this process (Carter, 2003; Henry and Wang, 1998; Teicher et al., 2002). Teicher et al. (2002) argue that severe early stress and maltreatment can alter brain development through its effects on the oxytocin–vasopressin stress–response system, leading to the subsequent development of a number of disorders including PTSD and BPD. Others have also suggested that early life stress affects adult affiliative behaviors and that this process may involve gonadal steroids and oxytocin (Henry and Wang, 1998). Again, though, the mechanisms by which this occurs in humans are not well understood. One hypothesis is that chronic early stress results in changes in corticotrophin-releasing hormone, which then alters oxytocin and vasopressin receptor binding (Bester-Meredith and Marler, 2003; Boccia and Pedersen, 2001; Champagne et al., 2001; Francis et al., 2002; Meaney, 2001). It has also been theorized that exposure to peptides during development may reprogram the neuronal system, altering thresholds for emotionality and sociability (Carter, 2003).

Although advances are being made in the study of early stress in animals, obvious ethical considerations have made it difficult to investigate such questions in humans. Recently, however, Fries et al. (2005) investigated the extent to which neurobiological systems involved in emotional and social behavior are affected by differences in early rearing experiences by comparing children raised in institutional settings–who received reduced emotional and physical contact–to those raised by their parents. Basal levels of oxytocin and vasopressin were assessed to determine whether stressful early experiences affect the regulatory capacity of these neuropeptides. Results revealed no group differences in basal oxytocin; however, lower levels of vasopressin were found in children reared in institutional settings compared to children reared by their parents. In addition, children reared by their parents evidenced an increase in peripheral oxytocin levels following a dynamic social interaction with their mother whereas children exposed to early neglect did not show this increase, suggesting that early neglect children may have central deficits in peptide synthesis and/or mutations in peptide genes (Fries et al., 2005).

Unresolved issues and future directions

In conclusion, most of the studies investigating the neurobiology of social behavior and affiliation have used animal models; however, recent methodological advances have allowed researchers to begin to ask more rigorous questions concerning the neurobiology of human social behavior. The findings to date have been encouraging and suggest that oxytocin and possibly vasopressin, which have been implicated in animal studies, are also involved in human affiliation. In addition to shedding light on the neurobiology of human social behavior, these findings may have implications for a number of clinical disorders involving social deficits and/or disrupted attachment including autism, social phobia, PTSD, and BPD, in terms of etiology and, possibly, with respect to treatment. Although research in this area is progressing, there are still a number of unresolved issues. Below, we highlight some areas for future research; we begin by discussing general issues regarding the translation of findings from animal studies to humans and then raise specific questions related to treatment.

Although animal research is vital to understanding many aspects of human behavior, it is important to be cautious when drawing parallels between animals and humans. As Young and Wang (2004) noted, there is no evidence to date showing that pair-bonding in voles and humans shares common physiological mechanisms. Moreover, as these researchers and others (Taylor et al., 2000) have emphasized, differences between the human brain and that of the vole (and other animal species) such as the development of the neocortex and higher order brain functions are factors that should be kept in mind when translating findings from animal studies to humans. Thus, future research is needed to explore how such human capabilities as modeling, learning, goals, and planning play into the relationship between oxytocin, vasopressin, and social affiliation.

Sex differences is another area that warrants further investigation. The animal literature points to a number of instances of sexual dimorphism in the effects of these neuropeptides on social behavior (e.g., oxytocin is critical in female prairie vole partner preference formation, whereas vasopressin is critical in male prairie vole partner preference formation). Indeed, sex differences in these neuropeptide systems have consistently been found in all vertebrate classes (De Vries and Panzica, 2006). An example of sex-specific influences of vasopressin in humans was demonstrated in a recent study showing that men perceive unfamiliar same-sex faces as less friendly and respond to those faces with more agonistic facial motor patterns, whereas women perceive unfamiliar same-sex faces as more friendly and respond to those faces with more affiliative facial motor patterns following intranasal vasopressin administration (Thompson et al., 2006). Given that most of the studies investigating oxytocin in healthy humans have restricted their samples to one sex (e.g., Heinrichs et al., 2003; Kosfeld et al., 2005; Kirsch et al., 2005; Taylor et al., 2006), research is needed to determine whether or not the obtained findings generalize to the opposite sex.

As described here, considerable research implicates oxytocin and vasopressin in the neurobiology of attachment; however, as Insel (1997) and others have noted, it is important to keep in mind that these neuropeptides are only two of many players and other agents including dopamine, endogenous opioids, ACTH, and gamma-aminobutyric acid are also likely involved in this process. For example, studies show that prairie voles have high levels of oxytocin and vasopressin receptors in the prelimbic cortex, nucleus accumbens and ventral pallidum–regions involved in the mesolimbic dopamine reward system–and some researchers theorize that pair-bonding may be a specialized form of conditioned reward learning whereby the unique interaction of dopamine, oxytocin, and vasopressin within the reward circuitry results in the development of social behaviors that promote monogamy (Insel, 2003; Insel and Young, 2001; Young and Wang, 2004). Indeed, this notion was supported in two recent studies showing the role of dopamine in prairie vole partner preference formation (Aragona et al., 2006; Liu and Wang, 2003). Similar research should be conducted to investigate the role of these other candidates in human social attachment.

Significant advances have been made in identifying the density and distributions of oxytocin and vasopressin receptors in animals, but little is known about how these neuropeptide receptors are mapped in the human brain. Post-mortem studies would be one way to investigate this question; however, given the limitations of post-mortem research, *in vivo* methodologies may be preferable. Specifically, the development of radio ligands to be used in conjunction with positron emission tomography and gadolinium ligands to be used in conjunction with MRI will be important in this endeavor. These technologies could also be coupled with genotyping to investigate whether certain haplotypes are associated with differences in receptor density and distributions.

Research is also needed to investigate the relationship between plasma and central oxytocin and vasopressin and to address questions related to brain penetration. Does oxytocin, administered peripherally, cross the blood–brain barrier (BBB)? If peripherally administered oxytocin enters the brain, how much enters the brain, in what form does it enter the brain, and by what mechanism? If it does not enter the brain, how does peripherally administered oxytocin (or vasopressin) exert its effects on behavior? Some of these questions were addressed in a recent review on the relevance of brain–fluid barriers for research on vasopressin and oxytocin (McEwen, 2004). The BBB protects the brain from toxins, provides the brain with essential nutrients, and maintains a stable environment for the brain. As McEwen (2004) noted, although the BBB was traditionally held to be a wall-like structure that prevented the entry of most substances into the brain, it is becoming increasingly clear that this conceptualization may be overly simplistic and that, in fact, "the BBB is a flexible and dynamic system regulating blood–brain interaction for many substances including AVP [vasopressin], OT [oxytocin], and a variety of other peptides" (p. 591).

Although there is no definitive answer to the question of how these neuropeptides cross the BBB, a number of theories have been put forward (for a thorough discussion of this topic the reader is referred to McEwen, 2004). One promising hypothesis concerns the possibility that active transport systems such as amino acid carriers or even specialized peptide-specific carrier mechanisms are involved in the transport of these peptides into the brain. Indeed, as McEwen (2004) noted, research using vascular brain perfusion methods has established the presence of such a carrier system for the entry of vasopressin into the brain (Zlokovic et al., 1990, 1992). Although a similar transport mechanism for oxytocin has not yet been identified, this is an important area for future research. In addition, peripherally administered oxytocin and vasopressin may affect behavior indirectly. For example, as McEwen (2004) explained, these neuropeptides may interact with BBB transport systems to facilitate the entry of other nutrients into the brain that are involved in the relevant behavior (e.g., certain amino acids that are precursors for the synthesis of neurotransmitters that then influence behavior) or they may interact with brain–blood vessels to influence blood-flow to regions of the brain involved in the relevant behavior.

A recent study by Ring et al. (2006) also speaks to the issue of brain penetration. This study investigated the anxiolytic effects of centrally and peripherally administered oxytocin in male mice. Although substantially larger doses of oxytocin were required for peripheral administration to achieve comparable behavioral effects to those achieved by central administration (suggesting that oxytocin exerts its anxiolytic effects through its action on the CNS), nonetheless, peripheral administration produced behavioral effects, suggesting, as these researchers argue, that "the anxiolytic-like effects of peripherally administered oxytocin can be accounted for by the passage of relatively small, but sufficient, amounts of the peptide across the BBB into the CNS" (p. 222). The claim that peripherally administered oxytocin penetrates the brain and exerts its behavioral effects by acting on the CNS was further supported by the finding that a centrally administered oxytocin antagonist that does not cross

the BBB was able to fully reverse the anxiolytic-like effects of peripherally administered oxytocin in this study.

The issue of brain penetration is especially important for the development of effective and feasible treatments using these neuropeptides. Currently, intravenous and intranasal are the only available routes of administration; although intranasal administration of peptides has been shown to penetrate into the cerebrospinal fluid (Born et al., 2002), research is needed to identify other mechanisms to deliver oxytocin into the brain. As noted, it is likely that specific transport mechanisms are involved in the influx and efflux of endogenous and exogenous compounds across the BBB, and it has been suggested that these mechanisms can be used to control the delivery of drugs–including peptides–into the brain (Tsuji, 2005; Tsuji and Tamai, 1999). An important line for future research will be to investigate the possibility of utilizing these transport mechanisms to enhance the delivery of oxytocin into the brain. In addition, peptidomimetic drugs (i.e., compounds that mimic the biological action of peptides) could be design to cross the BBB to act on specific peptide receptors (Smith et al., 2004). Finally, the development of small molecular agonists that easily pass the BBB could be of potential use in the development of pharmacological therapies. The success of this line of research was demonstrated in the aforementioned study by Ring et al. (2006) in which a peripherally administered brain-penetrant oxytocin receptor antagonist was found to fully reverse the effects of centrally administered oxytocin on anxiety behavior in male mice.

Finally, as described earlier, a number of studies implicate oxytocin in autism spectrum disorders and suggest that oxytocin may be beneficial in their treatment. Our group has found that intravenous oxytocin infusion reduces repetitive behaviors in adults with autism spectrum disorders (Hollander et al., 2003) and also facilitates social cognition in this population (Hollander et al., in press). These findings are promising, but the next step is to demonstrate the feasibility and long-term effects of oxytocin in the treatment of autism. Neuroimaging studies are also needed to identify possible surrogate markers for the effects of oxytocin in autism and to shed light on mechanisms that mediate treatment response. To this end, we have research underway combining fMRI with the intravenous administration of oxytocin and are also conducting controlled treatment trials to investigate the effects of intranasal oxytocin in the treatment of autism. In the long term, research is needed to determine the effects of oxytocin administration in children and the possibility of early intervention. Finally, as reviewed here, dysregulated oxytocin may be implicated in other clinical disorders marked by deficits in social functioning and/or disrupted attachment, and future research should investigate the potential therapeutic benefits of oxytocin for these disorders.

Acknowledgments

Preparation of this article was supported by grants from the National Institute of Health 5 U54 MH066673-03 STAART Autism Centers of Excellence, Beatrice and Samuel A. Seaver Foundation, National Institute on Neurological Disorders and Stroke, National Institute on Drug Abuse, and the Orphan Products Division of the Food and Drug Administration. We gratefully acknowledge Evdokia Anagnostou for comments on an earlier version of this article. Dr. Hollander is listed as an inventor on a patent for Treatment of Autism and Similar Disorders with Oxytocin.

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