Review

Biological Psychiatry

Dissecting the Role of Oxytocin in the Formation and Loss of Social Relationships

René Hurlemann and Dirk Scheele

ABSTRACT

Current concepts of human sociality highlight a fundamental role of the hypothalamic peptide oxytocin (OXT) in the formation and maintenance of social relationships. However, emerging evidence indicates that OXT does not invariably facilitate social bonding but also produces nonprosocial effects that may have evolved to promote offspring survival. From a mechanistic perspective, we hypothesize that OXT modulates interoceptive signals and self-referential processing, which may result in various social outcomes depending on context- and person-dependent variables such as early-life adversity. Based on this theoretical framework, we discuss translational implications for clinical trials and identify open questions for future research. Specifically, we propose that disrupted OXT signaling due to the loss of affectionate bonds may contribute to emotional disequilibrium and confer elevated risk for the onset of stress-related disorders.

Keywords: Attachment, Bond, Grief, Mental illness, Oxytocin, Social relationships

http://dx.doi.org/10.1016/j.biopsych.2015.05.013

A human ability to form and maintain interpersonal relationships, a product of evolutionary selective processes, is fundamental to mental health (1). For instance, social support by proximal others has been identified as a key resilience factor promoting successful coping with and adaptation to psychosocial stress (2). However, the underlying neurobiological mechanisms are not precisely understood. Current perspectives on the neurochemistry of human sociality suggest a central role of the peptide oxytocin (OXT) and its receptor (OXTR), which is expressed both in the brain and the periphery (3). As a peripherally acting hormone, OXT promotes parturition and lactation, whereas as a neuromodulator projected from the hypothalamus to brain areas implicated in social-emotional behavior, it helps create long-lasting social relationships ranging from infant-parent bonding in childhood to romantic relationships in adulthood. The loss of such affectionate bonds is associated with agonizing distress and elevated risk for the onset of multiple psychiatric disorders (4), suggesting that OXT signaling has a pivotal role in sustaining mental health.

OXYTOCIN AND SOCIAL ATTACHMENT IN NONHUMAN SPECIES

OXT has evolved over 700 million years and its homologs are present in various taxa from nonvertebrates to mammals (5), highlighting the ubiquitous role of the peptide in orchestrating social and reproductive behaviors. For example, genetically modified male nematodes (*Caenorhabditis elegans*) lacking an OXT-like molecule or the corresponding receptor perform poorly in mating (6). Further evidence supporting a key role of OXT-like peptides in pair-bond formation and offspring success comes from studies in monogamous zebra finches (*Taeniopygia guttata*) (7) and teleost fish (*Amatitlania nigrofasciata*) (8). The crucial influence of OXT on pair bonding has been best studied in two closely related species of vole, i.e., the monogamous prairie vole (*Microtus ochrogaster*) and the polygamous montane vole (*Microtus montanus*) (9,10). While the expression of OXT is similar among both species (11), brain distribution of the OXTR significantly differs between them, with high OXTR density in the prelimbic cortex and nucleus accumbens (NAcc) being crucial for the expression of monogamous behavior (12,13). However, accumulating evidence suggests that species differences in social relationships are not restricted to the OXT system per se but extend to other signaling pathways, including dopamine (DA) and arginine-vasopressin (AVP), and their reciprocal interactions (14,15). For example, heightened expression of AVP receptors (AVPRs) in the ventral forebrain of polygamous meadow voles (*Microtus pennsylvanicus*) elicits monogamous behavior (16). Current concepts hold that the AVP/OXT and DA systems closely interact in a site- and sex-specific manner to mediate partner preference formation, and similar cross-talk may also determine parenting styles (17). For instance, hypothalamic lesions block the initiation, but not the maintenance, of maternal behaviors in rats (18), suggesting that OXT may specifically facilitate the transition from avoidance of pups to caring for them (19,20). Recently, it was shown that OXT enables pup retrieval behavior in female mice by amplifying pup call responses in maternal auditory cortex (21). Furthermore, OXT has been implicated in maternal licking and grooming in rats (22), social affiliation of dogs toward their owners (23), and grooming of nonbond partners in chimpanzees, thus providing a cross-species mechanism that enables long-term

ISSN: 0006-3223

cooperative relationships between kin and nonkin mammals (24). Notably, the OXT system not only plays a pivotal role in the formation and maintenance of pair bonds but is also affected by their disruption. For example, social isolation through partner separation precipitates anxiety and depression-like behaviors in monogamous voles (25), which could be prevented by repeated subcutaneous injection of OXT (26). Furthermore, even short-term separation from their female partners induced profound grief reactions and heightened hypothalamic-pituitary-adrenal axis activity in male voles (27), suggesting that in highly social species, decreases in OXT signaling due to partner loss rapidly translate into stress-related disorders such as anxiety and depression.

OXYTOCIN AND INFANT-CAREGIVER ATTACHMENT

A plethora of studies in humans has focused on the potential validity of endogenous OXT concentrations as biomarkers for infant-caregiver attachment bonds and parenting styles. For instance, OXT plasma concentrations in the first trimester of pregnancy were shown to predict postpartum maternal attachment (28). Moreover, OXT plasma concentrations appear to correlate with the time devoted to affectionate parenting (such as soft hugs, caresses, or baby talk) in mothers and with stimulatory parenting (i.e., tossing the baby in the air or encouraging exploration and laughter) in fathers (29). Perhaps more informative than OXT concentrations at baseline is the rise in OXT levels during infant-caregiver interactions. The evidence suggests that the greater the amounts of OXT released in plasma during such interactions, the greater the mother's readiness for social reciprocity and flexible adaptation to the child's needs (30). Lower than normal cerebrospinal fluid (CSF) levels of OXT were measured in adult women with a history of childhood trauma and abuse (31), as well as in the urine of socially deprived children interacting with their mothers (32) [but see also (33)], indicating that early-life adversity has long-lasting impact on OXT signaling. However, the tempting idea that endogenous OXT concentrations specifically reflect and positively correlate with parenting contrasts with findings that OXT levels in urine tend to be higher in mothers interacting with unfamiliar children compared with their own children (34) and increase as a function of relationship anxiety and parenting stress (35).

A large body of evidence indicates a link between infant-caregiver attachment bonds and genetic variation in OXT pathways. For example, mothers with a silent G to A allele change in the OXTR gene (rs53576) show lower levels of sensitive parenting (36), and in a large twin sample, the same polymorphism was found to predict a mother's warmth toward her children (37). Additionally, there is evidence for an association between the A allele of OXTR (rs2254298) and attachment security in non-Caucasian infants (38). Indirect evidence for the relevance of rs2254298 also comes from a community study of women exhibiting higher or lower depression scores postpartum (39). Specifically, the rs2254298 GG homozygous genotype was overrepresented in depressed mothers and their families and was associated with lower OXT saliva concentrations. However, other studies have failed to establish a link between rs53576 or rs2254298 and attachment styles (40,41), and a recent study even identified a reverse association between genotype and positive parenting (i.e., that mothers with the GG genotype of rs53576 displayed lower levels of positive parenting) (42). It thus appears that genetic variation confers susceptibility for distinct attachment styles, but the extent to which a specific style is expressed in the behavioral phenotype is moderated by family environment (43,44).

Substantial evidence suggests that intranasal delivery of synthetic OXT (OXT^{IN}) is a useful means to dissect the peptide's contribution to infant-caregiver attachment. OXT^{IN} causes an increase in CSF levels of OXT (45), although we note that the exact transnasal route the peptide takes to reach the brain is still unclear and even a peripheral feedback mechanism enhancing endogenous release cannot be excluded. Recently, a single 24-IU dose of OXT^{IN} was found to be sufficient for inducing a significant increase in perceived attachment security in male adults previously classified as insecure (46). Furthermore, OXT^{IN} made fathers less hostile and motivated them to foster exploration behavior in their children (47). Interestingly, OXT^{IN} not only encouraged fathers to engage in stimulatory parenting but also increased the infant's salivary OXT concentrations in addition to changes in respiratory sinus arrhythmia response, an index of emotional reactivity, and social-emotional behavior (48). Together, these results suggest that heightened OXT levels may enhance social interactions between fathers and their children, perhaps by establishing closer proximity between them (49). Functional magnetic resonance imaging (fMRI) studies have sought to reveal the neural representations of parenting and its modulation by OXT^{IN}. For instance, OXT^{IN} in fathers was shown to alter globus pallidus responses to pictures of their own children (50). OXT^{IN} evoked greater responses in insula and inferior frontal gyrus, both of which are implicated in empathy (51) in women exposed to infant crying. OXT^{IN} also reduced amygdala responses to infant laughter (52). Notably, the effects of OXT^{IN} appear to be influenced by the attachment representations people possess. Less anxiously attached individuals remembered their mother as more caring and close after OXT^{IN}, but the opposite effect was observed for more anxiously attached individuals (53). In another study, OXT^{IN} decreased handgrip force in reaction to infant crying in female subjects without a childhood history of harsh parenting experiences (54). Together, these results challenge the popular notion that oxytocin has broad positive effects on social perception and instead suggest a strong dependency of OXT effects on person-dependent factors including early-life adversity.

OXYTOCIN AND ROMANTIC ATTACHMENT

During the early stages of romantic relationships, OXT plasma concentrations are elevated in new lovers compared with singles (55). OXT plasma levels are also increased in couples who exhibit higher interactive reciprocity and spend more time thinking of the partner and the relationship (55). In an instructed couple conflict scenario, participants showed more empathy if their partners had higher OXT plasma levels (56). In another study, OXT plasma levels were associated with more affectionate communication during a structured social support interaction task (57). In women, the expression of nonverbal affiliation cues was positively correlated with OXT plasma