

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

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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

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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

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

release (58). In both sexes, greater self-reported levels of partner support and partner intimacy were related to higher OXT plasma concentrations (59,60). Early studies could not establish a relationship between interpersonal touch and OXT release (61–63), but more recent studies have detected a rise in OXT plasma levels after light touch or a massage (64–66). The impact of sexual activity on endogenous OXT release is informed by numerous studies showing increased OXT plasma concentrations after orgasm in humans (67–70) [but see also (71)].

Moreover, there are also reports documenting a positive correlation between OXT plasma concentrations and attachment anxiety (72) and interpersonal distress (61,73). As such, the tend and befriend model has been proposed (74,75), which states that gaps in positive social relationships are accompanied by elevations in OXT and that these increased OXT levels prompt affiliative efforts aimed at restoring positive social contact. Of note, the interpretation of peripheral OXT measurements is hampered by methodological issues (76) and the absence of a strong linear relationship between peripheral and central OXT concentrations (77). It is also still elusive whether peripheral or CSF measurements can reflect the subtle release of OXT from axons in a manner specific to a certain brain region (78). Associations between peripheral OXT levels and a specific type of social behavior may result from a positive feedback system such that one particular behavior elicits the release of endogenous OXT and vice versa. In addition, peripheral OXT may affect a diverse repertoire of social behaviors by modulating visceral target organs of the autonomic nervous system, many of which (e.g., the heart or digestive system) both locally synthesize OXT and express OXTRs (79).

OXTR gene variations (rs7632287) have also been associated with traits reflecting pair bonding, such as the quality of interactions with their romantic partners in women (80). Furthermore, a cumulative genetic risk for social dysfunctions was computed by summing up risk alleles on different polymorphisms, with high-risk individuals exhibiting difficulties in empathic communication in couple interactions (81).

Evidence for effects of OXT^{IN} on behaviors related to pair bonding is scarce. It has been shown, for example, that the peptide enhances positive communication in relation to negative behavior during couple conflicts and reduces cortisol saliva levels after the conflict (82). In women, OXT^{IN} also reduced salivary alpha-amylase, an index of sympathetic activity, whereas in men the peptide increased salivary

alpha-amylase levels and emotional arousal during couple conflict (83). Interestingly, men under OXT were faster to detect the valence of positive stimuli conceptually associated with sexuality, bonding, and social relationships (84). Notably, OXT^{IN} further augmented epinephrine plasma responses to sexual activity in men (85) and increased the intensity of orgasm and contentment following sexual intercourse in heterosexual couples (86). By contrast, an early study using a 32-IU dose of OXT^{IN} failed to detect any behavioral or neural effects in 21 men who observed their female partner receiving painful stimulation (87).

Few studies have sought to explore a role of OXT^{IN} in partner preference. In one study, OXT^{IN} stimulated subjects to seek out information about an old partner but had no effect on the participant's choice for company (to work with or date) (88). In another study, OXT^{IN} motivated pair-bonded, but not single, men to keep a larger social distance from an unknown female experimenter (Figure 1) and inhibited approach toward attractive women depicted in photos (89). Previous fMRI studies have revealed that viewing the face of a romantic partner while recalling experiences with them activates reward-associated regions such as the ventral tegmental area (VTA) and NAcc (90,91). In healthy pair-bonded men, OXT^{IN} facilitated neural responses to the partner compared with unfamiliar women in the VTA and NAcc (Figure 2). On the behavioral level, these neural effects were paralleled by a more favorable attractiveness perception of the female partner (92). Interestingly, viewing pictures of a romantic partner also reduced self-reported thermal pain and greater analgesia was associated with increased activity in several reward-processing regions including the NAcc (93). To our knowledge, no study so far has tested whether partner-induced analgesia is related to OXT-mediated pain inhibition (94). Furthermore, by employing a mental imagery task, it has been shown that OXT^{IN} diminishes subjects' arousal judgments of and anterior cingulate cortex (ACC) responses to scenes describing sexual infidelity of the partner (95). Collectively, these data provide little support that OXT is involved in the formation of new pair bonds in humans but rather suggest that OXT may be more important for the maintenance of an already established pair bond. As such, this discrepancy compared with the role of OXT in prairie voles, where the peptide is necessary for the formation of new pair bonds (96), may be related to methodological differences in the assessment of pair bonding in rodents and humans or indicate a species-specific function of OXT.

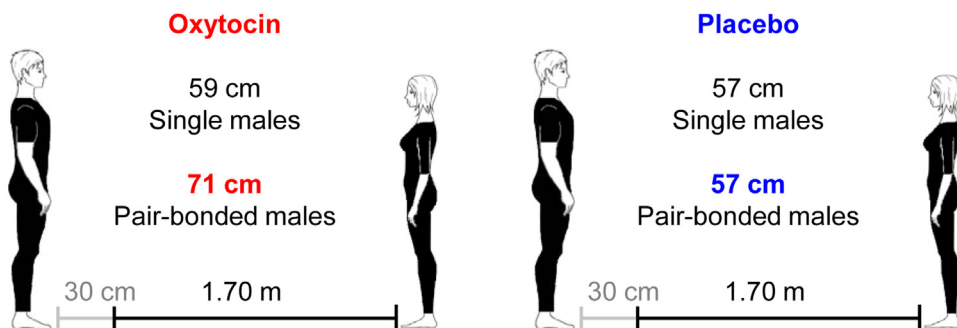


Figure 1. Oxytocin effects on the social distance between women and men. Male participants were asked to choose the ideal (most comfortable) distance to an attractive female experimenter. In the first half of the trials, the experimenter moved either toward (far, i.e., start distance of 2 m) or away from the subject (close, start distance of 30 cm), whereas in the second half, the male volunteer was the one approaching or withdrawing. Oxytocin increased the ideal distance that pair-bonded men maintained in relation to the unknown attractive woman across all conditions.

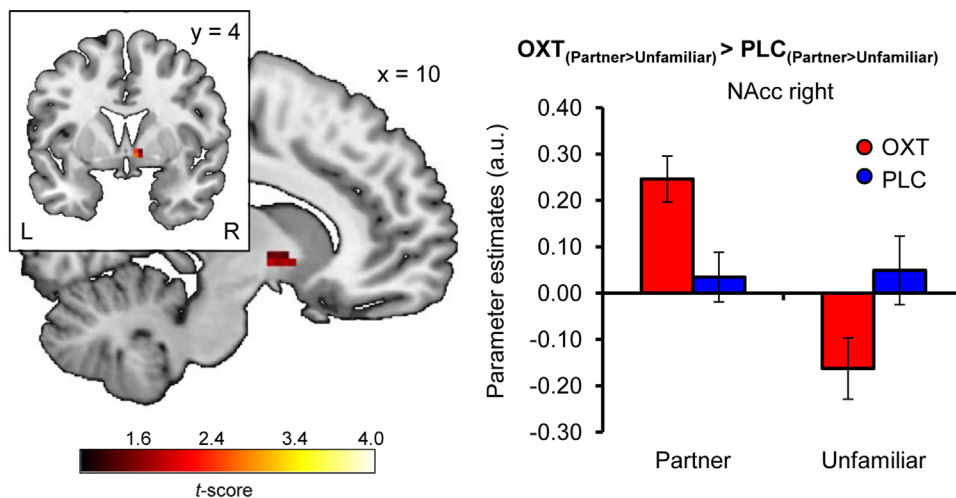


Figure 2. Oxytocin (OXT) effects on nucleus accumbens (NAcc) responses. The intranasal administration of OXT increased NAcc response to the female partner's face compared with a matched, unfamiliar woman. Error bars indicate the standard error of the mean. L, left hemisphere; PLC, placebo; R, right hemisphere.

It would stand to reason that OXT effects on pair bonding are mediated by DA, as the NAcc and VTA form two central hubs of the mesolimbic DA pathway. In a recent [^{11}C]raclopride positron emission tomography study, DA release was measured during a face-attraction rating task after OXT^{IN} administration (97). The authors could replicate the previous finding that OXT, in the absence of any partner stimuli, can enhance the perceived attractiveness of unfamiliar women (98), but this effect was not accompanied by an altered raclopride binding in the striatum. Instead, they observed increased binding in subregions of the right dorsomedial prefrontal gyrus and superior parietal gyrus under OXT. These data could mean that an OXT-DA interplay in the striatum is restricted to the domain of pair bonding or that OXT interacts with a different family of DA receptors or a completely different class of neurotransmitters. For instance, the rewarding properties of social interactions in mice require the coordinated activity of OXT and serotonin in the NAcc (99) and a recent [^{18}F]MPPF positron emission tomography study demonstrated that OXT^{IN} modulates serotonergic signaling in humans (100).

As of yet, no study has examined the behavioral and neural effects of OXT^{IN} on the processing of partner stimuli in women. In an fMRI study (101), OXT^{IN} did not alter amygdala responses, but it did selectively increase arousal ratings of infant stimuli in nulliparous, but not postpartum, women. In all women, OXT^{IN} administration resulted in greater VTA, but not NAcc, activation to infant and sexual images (102). A recent study also points to the importance of moderator variables for OXT effects on pair-bonding behavior (103). For instance, OXT^{IN} specifically increased the inclination for intimate partner violence in participants prone to physical aggression but not in participants with low aggressiveness traits. These data resonate well with the idea that OXT enhances an a priori existing predisposition, possibly by modulating self-referential processing and interoception.

A SELF-REFERENCE MODEL OF OXYTOCIN

Several theoretical frameworks have been proposed to explain the wide repertoire of social OXT effects (Table S1 in Supplement 1). On the one hand, OXT enhances the

stress-and anxiety-buffering effect of social support from proximal others (104) and facilitates fear extinction by strengthening the control of regulatory prefrontal areas over amygdalar fear responses (105). On the other hand, in the absence of social support, OXT may increase the sensation of social stress, augment the impact of aversive information on defensive responses (i.e., the startle reflex), and induce a privileged recall of negative information by increasing neural responses in insular cortex (106,107). In an attempt to reconcile this conflicting evidence, it has been proposed that OXT exerts a lower-level general effect on general states and dispositions (108) and that the outcome of OXT administration is constrained by features of situations and/or individuals (109). In fact, OXT^{IN} effects are often moderated by the subject's gender (110,111) and context-dependent factors. One example for the latter is an fMRI study in which the subjective valence of interpersonal touch was experimentally manipulated (112). Specifically, OXT^{IN} was found to augment behavioral pleasantness ratings only in a positively framed social context. On the neural level, OXT^{IN} enhanced responses in a neural circuitry spanning the insula, precuneus, orbito-frontal cortex, and pregenual ACC. Interestingly, both the behavioral and neural effects were blunted in subjects with higher autistic-like traits. Modulatory influences of OXT^{IN} on neural reactivity of the insula, precuneus, and ACC have been observed across various cognitive and emotional domains in fMRI studies (95,107,111). Current concepts of human emotional awareness (113) highlight that the anterior insula cortex, which is often jointly activated with the ACC, contains representations that provide an emergent basis for subjective feelings from the body. The precuneus belongs to a widespread neurocircuitry of higher association cortical and sub-cortical areas and has been implicated in interoceptive awareness and consciousness (114). Thus, the observed pattern of results has been interpreted as indicating an OXT-induced self-referential processing bias that could explain the increased pleasantness in an already pleasant context and a diminished effect for participants with high autistic-like traits who experience social touch as less pleasant (115). This view was recently extended by the hypothesis that OXT's influence

on self-referential processing and interoception is also context-dependent (116). The authors predict that OXT augments interoceptive prediction errors through top-down modulation in the context of passive perception and that the peptide participates in interoceptive sensory attenuation in the context of self-generated action.

The idea that OXT influences self-referential processing and interoception is further supported by a recent study that indicates that OXT sharpens self-other perceptual boundaries (117). In a video-morphing task, OXT-treated participants exhibited a significantly shorter latency when discriminating between self and other. In two other studies (118,119), OXT^{IN} influenced participants' self-perception assessed by personality questionnaires and an adjective-sorting task. Specifically, subjects under OXT reported higher ratings of extraversion and openness to experiences and stronger positive attitudes toward themselves. At first glance, an OXT-induced self-referential processing bias seems hard to reconcile with the above mentioned bonding-related OXT effects and the fact that OXT has also been found to enhance other-regarding tendencies such as mind reading and emotional empathy (120,121). However, empathy and interoception are closely linked (122) and improved empathy may even be the by-product of sharpened interoceptive awareness. Furthermore, it is increasingly recognized that self-processing extends to incorporate significant others (123,124). By increasing self-referential processing in this way, OXT may be acting to promote in-group survival. Such a mechanism could help to explain why OXT promotes parochial altruism and ethnocentrism (125,126) and it may also account for the surprising observation that a pharmacologic augmentation of a first individual psychotherapy session via OXT caused more rather than less anxiety over the course of the session in patients with depression (127). Given this background, we conclude that one common denominator across diverse social OXT effects may be that the peptide induces a self-referential processing bias that can produce various social outcomes by enabling subjects to represent emotional experiences more consciously. Along these lines, the use of OXT as a pharmacologic augmentation of established treatments for psychiatric disorders not only contains the promise of an improved social functioning but may also aggravate an already distorted social perception. Clearly, future studies are warranted to selectively test the predictions of our preliminary model.

TRANSLATIONAL IMPLICATIONS AND NEW AVENUES FOR FUTURE RESEARCH

Intact social relationships can bring the elation of profound joy and they are an important resilience factor that can help to buffer the deteriorating consequences of stress preponderance. However, throughout life, humans are confronted with the breakup of relationships, which can be the source of sorrow and despair. In fact, acute grief after a relationship breakup (128,129) or the loss of an unborn child (130) is related to intense responses of the physical pain network encompassing the ACC and insula. Grief is a major risk factor for clinical depression (131), and in a substantial minority, the grief reaction does not abate but instead develops into complicated grief, which is associated with enduring functional impairments (132). Based on the strong overlap between human love and drug addiction, from initial encounter to

withdrawal, it has been proposed that social attachment can be understood as a behavioral addiction, with OXT hijacking the brain reward system to promote bonding and affiliative behavior, and that treatments used to reduce drug cravings may also be effective in treating grief resulting from the loss of a loved one or a bad breakup (133). In two recent studies, OXT^{IN} was found to suppress stress-induced craving in cannabis-dependent individuals (134) and to block alcohol withdrawal (135). Against this background and given the strong body of evidence implicating OXT as a key modulator of human pair bonding reviewed above, future studies should probe OXT's potential to ameliorate withdrawal symptoms after a relationship breakup.

Another open question is related to the optimal treatment protocol. Considering the previous finding that OXT augments the antistress effects of social support (104), we expect that OXT should produce the most powerful effects as an adjunct to social interventions relying on the human attachment system. Previous clinical trials exploring the clinical potential of OXT have consistently shown that the OXT system is an enticing pharmacologic target for enhancing social cognition (136), but relatively few studies have focused on the bonding-related effects of OXT. A reduced capacity to form and maintain long-lasting social relationships is a hallmark of several conditions, including borderline personality disorder and autism and schizophrenia spectrum disorders; OXT could be a promising treatment option selectively targeting attachment dysfunctions. Based on our self-referential processing model, it also seems promising to combine OXT^{IN} with non-pharmacologic treatments of autism spectrum disorder such as real-time fMRI neurofeedback aimed at restoring control over anterior insula activity (137).

Furthermore, the effects of a single dose may deviate from that of a long-term OXT treatment, seeing as other antianxiety agents also produce anxiogenic effects after first-time dosage (138). In male voles, a long-term developmental treatment with low doses of OXT^{IN} resulted in a deficit in partner preference behavior (139), and in mice, chronic OXT treatment even induced an anxiogenic phenotype (140). In humans, OXT^{IN} treatment over 10 days in elderly subjects produced no significant effects on mood or the cardiovascular indices but yielded positive changes in psychological well-being and physical functioning (141). Similarly, the optimal dose for an OXT^{IN}-based intervention is still elusive. In voles, the propensity to display behaviors such as pair bonding is modulated in a dose-dependent manner (142), and in humans, 24-IU, but not 48-IU, of OXT^{IN} attenuates cortisol levels in response to physical stress (143). The selectivity of OXT for the OXTR relative to AVPRs is at least twentyfold (cf. Psychoactive Drug Screening Program K_i database), but AVPR cross-binding may occur and dominate resultant effects at higher doses. The majority of OXT studies in humans include a dose of 24-IU, but dose-response investigations are clearly necessary to establish individually tailored treatment regimens that consider additional factors such as gender, age, and weight.

In conclusion, the OXT system plays an integral role for human parenting and pair bonding, but future clinical trials are warranted to elucidate specific conditions and treatment parameters under which an OXT-induced self-referential processing bias may lead to the most beneficial clinical outcome.

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