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Oxytocin and Social Relationships: From Attachment to Bond Disruption

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Abstract

Social relationships throughout life are vital for well-being and physical and mental health. A significant amount of research in animal models as well as in humans suggests that oxytocin (OT) plays an important role in the development of the capacity to form social bonds, the mediation of the positive aspects of early-life nurturing on adult bonding capacity, and the maintenance of social bonding. Here, we focus on the extensive research on a socially monogamous rodent model organism, the prairie vole (*Microtus ochrogaster*). OT facilitates mating-induced pair bonds in adults through interaction with the mesolimbic dopamine system. Variation in striatal OT receptor density predicts resilience and susceptibility to neonatal social neglect in female prairie voles. Finally, in adults, loss of a partner results in multiple disruptions in OT signaling, including decreased OT release in the striatum, which is caused by an activation of the brain corticotropin releasing factor (CRF) system. The dramatic behavioral consequence of partner loss is increased depressive-like behavior reminiscent of bereavement. Importantly, infusions of OT into the striatum of adults prevents the onset of depressive-like behavior following partner loss, and evoking endogenous OT release using melanocortin agonists during neonatal social isolation rescues impairments in social bonding in adulthood. This work has important translational implications relevant to the disruptions of social bonds in childhood and in adults.

Keywords

Attachment; Bereavement; Grieving; Monogamy; Pair bond; Social loss

1 Social Relationships and Well-Being

Humans are highly social mammals that develop various forms of social attachments and relationships throughout life. The establishment of social attachments and bonds from infancy (Bowlby 1982; Harlow and Zimmermann 1959) through adulthood are essential for

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healthy psychological development and well-being. Indeed, the benefits arising from positive social relationships for adults are manifold and vital for physical and mental health (Berkman 1995; Biondi and Picardi 1996; House et al. 1988; Shear and Shair 2005; Uchino et al. 1996; Zisook et al. 1997). These health benefits can range from decreased risk for cardiovascular and infectious disease to increased stress resilience as well as a reduced likelihood to develop depression and anxiety disorders (Smith and Wang 2012; Lieberwirth and Wang 2014; Kikusui et al. 2006). The latter can be found as early as in childhood as it is associated with a positive relationship to the parents (for reviews, see Bogels and Phares 2008; Graziano et al. 2009). Early childhood abuse or neglect can lead to increased risk of depression (Heim et al. 2010). This is not surprising given the fact that the first and perhaps strongest relationship in life is between the child and its parents and, therefore, the most common and long-lasting bond among mammals (Numan and Young 2016; Rilling and Young 2014). Hence, disruptions in parent–offspring relationships can have long-lasting influences on later-life social relationships.

The mother–infant bond is thought to be the evolutionary and neurobiological origin for the capacity to form adult social bonds in species that form bonds between mates, like humans. This hypothesis is derived from the many common neurochemical mediators and neural pathways involved in maternal bond and pair bonds (for reviews, see Numan and Young 2016). Specifically, the neuropeptide oxytocin (OT) has been implicated in the onset of parental nurturing and maternal bonds (Bosch and Neumann 2012; Numan and Young 2016; Rilling and Young 2014), the consequences of parenting on the developing brain (Champagne et al. 2001; Barrett et al. 2015), pair bonding (Johnson et al. 2016; Johnson and Young 2015), empathy-based consoling behavior (Burkett et al. 2016), and in the consequences of social loss in animal models (Bosch et al. 2016).

2 Prairie Voles as a Model Organism for Understanding the Biology of Social Relationships

Among mammals, 95% of species display maternal care but do not develop socially monogamous pair bonds with their mate (Lukas and Clutton-Brock 2013). In contrast, approximately 5% of mammals, including humans, are capable of developing enduring pair bonds between partners, cooperate to raise their offspring, and display a socially monogamous mating system. Socially monogamous species do not typically mate exclusively with the bonded partner, but the bond with the partner withstands extra-pair copulations (Wolff and Dunlap 2002). Hence, we use the term “social monogamy” to describe a social organization where mating partners display selective – but not exclusive – affiliation, nest sharing, and also biparental care of offspring (Young and Wang 2004). One of these socially monogamous mammals that has provided remarkable insights into the neural and neurogenetic mechanisms of social attachments is the prairie vole (*Microtus ochrogaster*) (Carter and Getz 1993; Getz and Carter 1996; Young and Wang 2004; Ross and Young 2009; McGraw and Young 2010; Johnson and Young 2015). The prairie voles are amenable to laboratory experimentation, and the assessment of a pair bond is made possible by a highly reliable, automatable partner preference test which follows a period of cohabitation during which various experimental manipulations are possible (Williams et al.

1992; Ahern et al. 2009). In the partner preference test, the experimental animal (of either sex) can range free in a three-chamber apparatus where it can choose to spend its time next to the familiar/unfamiliar voles of the opposite sex (tethered to the wall; outer chambers) or in the neutral area (middle chamber). A pair bond is typically inferred when the experimental subject spends more than twice as much time in the chamber of, or huddling with the familiar "partner" than with the unfamiliar "stranger." In both sexually naïve male and female prairie voles, mating facilitates partner preferences; however, longer durations of cohabitation without mating can also result in a pair bond (Williams et al. 1992).

In this review, we briefly summarize the vast literature on the neural mechanisms underlying pair bond formation, as these have been reviewed extensively elsewhere (Johnson and Young 2015; Young and Wang 2004; Lieberwirth and Wang 2014). We will instead focus in more detail on new studies investigating the consequences of disruptions in attachments using repeated neonatal social isolations or parental manipulations, as a model of infant neglect, and disruptions of adult pair bonds as a model of social loss and bereavement. We will highlight recent evidence of an interaction of the OT and corticotropin releasing factor (CRF) systems in modulating social relationships, and the consequences of partner loss on the OT system.

3 Brain Mechanisms Underlying Pair Bond Formation

Numerous studies using prairie voles describe the brain mechanisms leading to the formation of a pair bond, which is facilitated by an increase in the activity of various neurotransmitters and their receptors in specific brain regions. While manipulating each neurotransmitter system is by itself sufficient to elicit or inhibit partner preference in prairie voles, it is likely that a concerted activation of these systems across multiple brain regions underlie the formation of a pair bond. Here, we will only briefly mention four of the most prominent neurotransmitter systems studied in pair bond formation; more in-depth reviews can be found elsewhere (e.g., Johnson and Young 2015; McGraw and Young 2010; Young et al. 2011; Young and Wang 2004).

Increased arginine-vasopressin (AVP) signaling, especially in the ventral pallidum (VP) and lateral septum (Liu et al. 2001), is a prerequisite for partner preference formation and expression in male prairie voles (Winslow et al. 1993; Lim and Young 2004; Donaldson et al. 2010; Barrett et al. 2013). In addition, prairie voles have a significantly higher density of AVP V1a receptors in the VP compared to, e.g., polygamous montane voles (Insel et al. 1994; Wang et al. 1997; Young and Wang 2004). Moreover, polygamous male meadow voles become monogamous when V1a receptor expression in the VP is increased and vice versa in monogamous prairie voles (Lim et al. 2004; Barrett et al. 2013). Furthermore, individual variation in the promoter of the V1a receptor gene (*Avpr1a*) influences septal V1a receptor density and the probability that males will display a partner preference (Hammock and Young 2005).

Dopamine (DA) acting on D2, but not on D1, receptors in the nucleus accumbens (NAc) promotes partner preference formation in both male and female prairie voles (e.g., Liu and Wang 2003; Aragona et al. 2006; for review, see Young et al. 2011; Young and Wang 2004).

In contrast, activation of D1 receptors is thought to play a key role in the maintenance of an established pair bond in male prairie voles (Aragona et al. 2006).

The brain CRF system, which consists of CRF and the urocortins 1–3 as well as of CRF receptor type 1 (CRF-R1), CRF-R2, and the CRF binding protein (Reul and Holsboer 2002), is the primary regulator of the HPA axis (Vale et al. 1981; Aguilera and Liu 2012). Importantly, the brain CRF system also modulates various social behaviors, like mother–infant interaction (Gammie et al. 2004; Klampfl et al. 2013, 2014, 2016) or pair bond formation in male prairie voles. In the latter, central activation of the CRF system facilitates pair bond formation, even in the absence of mating (DeVries et al. 2002). Within the NAc shell, CRF-R2 are more abundant in monogamous compared with non-monogamous vole species (Lim et al. 2005), thereby suggesting a significant role of the local CRF system in bonding behavior in prairie voles (Bosch et al. 2016). Indeed, local infusion of CRF into the NAc accelerates partner preference formation in male prairie voles (Lim et al. 2007). However, increased CRF signaling is not necessary to maintain a pair bond (Bosch et al. 2009).

The brain OT system is significantly contributing to pair bond formation as has been demonstrated initially in females by Sue Carter's group (Williams et al. 1994). Prairie voles have higher densities of OT receptor (OTR) OTR in the NAc than do non-monogamous vole species, and several studies have characterized the role of intra-NAc OR activation in facilitating partner preference formation in female, but not male, prairie voles (Liu and Wang 2003; Ross et al. 2009a, b; Keebaugh and Young 2011). More recently, viral vector mediated OTR silencing has confirmed a role for OTR expression in the NAc for female partner preference formation (Keebaugh et al. 2015). The exclusion of males in many of these earlier studies (with the exception of Cho et al. 1999) was based on the assumption that both neuropeptides modulate social behavior exclusively in one sex only (Insel and Hulihan 1995; Winslow et al. 1993); a hypothesis that has since been proven wrong (Johnson et al. 2016).

4 Oxytocin and Pair Bond Formation in Males

We now know that activation of the brain OT system is also important for the expression of affiliative behavior in male prairie voles. For example, central infusion of an OTR antagonist blocks the formation of partner preference in males (Johnson et al. 2016). This study also reveals that endogenous OTR signaling plays an important role in coordinating neural activity across brain regions involved in processing social information and those involved in reward. Furthermore, peripherally administered melanocortin agonist Melanotan II, which penetrates the blood–brain barrier and potentates OT release and OT-mediated social behaviors in an OTR-dependent manner, facilitates partner preference in male prairie voles (Modi et al. 2015). Partner preference formation in male prairie voles is predicted by a natural genetic polymorphism in the OTR gene (*Oxtr*) that robustly influences the density of OTR binding in the NAc (King et al. 2016). Furthermore, variation in NAc OTR binding mediated by viral vector gene transfer is associated with variation in pair bond formation in female prairie voles (Ross and Young 2009). In an independent epigenetic study, central infusion of trichostatin A, a histone deacetylase inhibitor, upregulated the expression of OTR

in the NAc of male (Duclot et al. 2016) and female (Wang et al. 2013) prairie voles, thereby promoting the formation of partner preference even in the absence of mating. Finally, high OTR density in the NAc is linked to social monogamy not only in laboratory but also in free-living male prairie voles (Ophir et al. 2012). Interestingly, as these results are in line with studies in female prairie voles (Liu and Wang 2003; Ross et al. 2009a, b; Wang et al. 2013; Keebaugh et al. 2015), it highlights the major contribution of the OT system in the NAc in the formation of pair bonds independent of the sex. In contrast, in humans there is less evidence that the OT system plays a role in pair bond formation (e.g., Schneiderman et al. 2012), but the brain OT system does seem to be important for its maintenance (Hurlemann and Scheele 2016). Indeed, intranasal OT administration in men caused them to increase the rating of their partners' attractiveness in pictures as well as heightened NAc activation (Scheele et al. 2013).

5 Oxytocin and Other Social and Stress-Related Behaviors

In addition to its role in pair bonding, OT is released centrally during pro-social interactions thereby regulating other social behaviors, e.g., social recognition, social memory, parental behavior, as mainly demonstrated in rodents (Bosch and Neumann 2012; Lukas and Neumann 2013; Dumais and Veenema 2016; Lukas and de Jong 2017). In male and female prairie voles, OT acting on the anterior cingulate cortex, a region implicated in empathy in humans (Lamm et al. 2011), regulates empathy-based consoling behaviors (Burkett et al. 2016). Furthermore, in both animal models and humans, OT has been identified as an important modulator of anxiety and depression (Neumann and Landgraf 2012; Neumann and Slattery 2016; Romano et al. 2015; Feldman et al. 2016) as well as of autonomic functions (Uvnas-Moberg 1998; Pyner 2009; Grippo et al. 2009, 2012; Quintana et al. 2013). Consequently, OT is thought to buffer against physical and emotional stressors (Uvnas-Moberg 1998; Neumann 2002; Smith and Wang 2014; Ditzen and Heinrichs 2014).

6 Early Social Experience and Neglect Influence Adult Pair Bonding Behavior

6.1 Family Structure During Development Influences Adult Bonding

Prairie voles have been used to explore how early infant–parent interactions influence the ability to form pair bonds later in life. In biparental prairie vole family units, both parents lick and groom their offspring (Ahern et al. 2011). Interestingly, compared to pups that experienced biparental care, those raised only by their mother display lower levels of alloparental behavior and impairments in partner preference formation as adults (Ahern and Young 2009). This difference is probably mediated by the fact that – compared to being raised in a biparental family unit – pups reared by the mother alone receive less parental care, which has long-lasting effects not only on behavior but also on the offspring's neuroendocrine systems (Bales and Saltzman 2016). Even when paired and becoming parents themselves, single mother-reared males and females provide less licking and grooming to their pups compared to parents who were raised themselves in a biparental unit (Ahern et al. 2011), providing a mechanism for transgenerational effects of social attachment behaviors. Furthermore, single mother-reared animals, particularly females, have

increased OT content in the hypothalamus and greater dorsal raphe CRF-R2 densities, and both measures correlated with licking and grooming experienced during the first 10 days of life (Ahern and Young 2009). These results suggest that naturalistic variation in social rearing conditions can introduce diversity into adult nurturing and attachment behaviors.

6.2 Neonatal Social Isolation Impairs Adult Pair Bonding: Influence of Oxytocin Signaling

In order to more precisely model disruptions in early attachment behavior and/or neglect, prairie vole pups were subjected to 3 h of daily social isolation from days 1–14 of life (Barrett et al. 2015). As adults (e.g., ~90 days of age), female, but not male, prairie voles displayed a significant impairment in pair bond formation even after 48 h of cohabitation with a male partner (Barrett et al. 2015). In-depth data analysis revealed that among female prairie voles experiencing the social isolation, some formed partner preferences normally, while others failed to show any partner preference, i.e., were susceptible to early disruptions in parental attachment. Prairie voles display remarkable individual variation in OTR density in the NAc (Young 1999), which have been linked to individual variation in alloparental behaviors in juveniles and adults (Olazabal and Young 2006a, b), and ~80% of the variation in OTR expression is explained by genetic polymorphism in the OTR gene. Neonatal social isolation did not influence OTR density in the NAc (Barrett et al. 2015). However, those females with naturally high densities of OTR binding in the NAc were resilient to disruptions in early-life attachment behaviors and formed partner preferences as adults normally. In contrast, those females with low densities of OTR in the NAc who also experienced neglect failed to form partner preferences (Fig. 1) (Barrett et al. 2015). These studies suggest that parental licking and grooming, which is heightened upon returning to the parental cage, stimulates OT release and those with high OTR densities experience more NAc OTR signaling compared to those with low expression. This helps strengthen the neural circuits important for social attachment later in life. Indeed, if pups experiencing the neonatal social isolations are injected with the OT system-stimulant Melanotan II (Barrett et al. 2015) they form normal social attachments as adults. This and other studies suggest that early-life OT signaling, which is likely influenced by parental nurturing and attachment behaviors, can help establish the neural networks needed later in life to form adult social bonds (Barrett et al. 2014, 2015; Rilling and Young 2014).

7 Sudden Disruption of Adult Pair Bond in Prairie Voles: Physiological and Psychological Consequences

Since positive attachment relationships promote our physical and emotional well-being, this implies that the abrupt isolation can have dramatic negative consequences. Indeed, in humans the absence or loss of social relationships is accompanied by an increased risk for health issues (Uchino 2006; Uchino et al. 1996; Biondi and Picardi 1996; DeVries et al. 2003; House et al. 1988; Kirschbaum et al. 1995; Cacioppo and Hawkley 2003), including cardiovascular diseases (Ramsay et al. 2008; Steptoe et al. 2013) and the development of depression (Biondi and Picardi 1996; Watanabe et al. 2004; Zisook et al. 1994, 1997; Assareh et al. 2015). To further advance our knowledge on the negative effects of a disrupted social relationship, various animal models have been studied including prairie voles. They are thought to be a powerful translational model to study the underlying physiological and

neurobiological mechanisms of being isolated from social contacts (Gobrogge and Wang 2015; McNeal et al. 2014; Grippo et al. 2007a). This has been quite well studied in same-sex prairie vole pairs by, e.g., Angela Grippo and colleagues (Grippo et al. 2007a, b, 2008, 2012, 2015; Peuler et al. 2012; Scotti et al. 2015). In contrast, studies engaging disrupted male–female pair bonds, as a model for the consequences of losing the significant other in humans, have only just begun (Bosch et al. 2009, 2016; McNeal et al. 2014; Sun et al. 2014).

In 2009, we started to study the physiological impact as well as the neurobiological mechanisms of acute pair bond separation in male prairie voles (Bosch et al. 2009). For five consecutive days, males were co-housed with a female partner or a male sibling in order to be able to dissect pair bond disruption from isolation. Afterwards, the pairs were either separated or continued to be co-housed until testing occurred 3–5 days later (Bosch et al. 2009, 2016). The same time-line for the housing/separation paradigm was used by McNeal et al. (2014), whereas Sun et al. (2014) co-housed male–female pairs for 24 h followed by 2 weeks or even 4 weeks of separation before testing. Intriguingly, the results from all three studies broadly overlap. Anxiety-related behavior is increased in separated males for up to 4 weeks (Bosch et al. 2009; McNeal et al. 2014; Sun et al. 2014) even in males separated from their siblings (Bosch et al. 2009) confirming results from same-sex separation studies (e.g., Stowe et al. 2005; Grippo et al. 2007b, 2008, 2014). Interestingly, only males separated from female, but not from male, siblings show heightened levels of passive stress-coping behavior after short- (3–5 days; Fig. 2a, b) and long-term (4 weeks) separation (Bosch et al. 2009; McNeal et al. 2014; Sun et al. 2014) in well-established tests for measuring depressive-like behavior in rodents (Slattery and Cryan 2012; Cryan 2005). The depressive-like state after breaking the pair bond is accompanied by decreased parasympathetic and increased sympathetic drive to the heart in conjunction with increased heart rate (McNeal et al. 2014), adrenal hypertrophy (Bosch et al. 2009), and higher basal plasma corticosterone concentration (Bosch et al. 2009; McNeal et al. 2014; Sun et al. 2014) indicating that losing the female partner is chronic stress (Bosch et al. 2009, 2016). The other way round, female prairie voles also experience loss of the bonded male partner as dramatic event; their passive stress-coping behavior as well as the basal levels of stress hormones in plasma samples are significantly increased compared with non-separated females (McNeal et al. 2014).

8 Brain OT System Becomes Dysregulated Following Partner Loss

Since the brain OT system facilitates formation of a partner preference/pair bond in both male and female prairie voles, we hypothesized that separation from the partner has significant effects on the OT system, which in turn may underlie the negative physiological and emotional effects of partner separation. Indeed, losing the female-bonded partner causes dysregulations of the fine-tuned brain OT system on multiple levels in male prairie voles (Bosch et al. 2016). On the fifth day of separation, OT mRNA expression is decreased within the hypothalamic paraventricular nucleus (PVN), but not the supraoptic nucleus, the two major sources for OT released within the brain, compared with non-separated males (Bosch et al. 2016). Furthermore, in both brain regions the density of OT-immunoreactive cells is increased after 4 weeks of separation versus co-housed male prairie voles, which has been attributed to decreased release and limited receptor activity (Sun et al. 2014). Arising from the PVN, OT neurons project to the NAc shell, thereby providing 90% of the OT fibers

innervating this brain region (Bosch et al. 2016). Here, OT facilitates the formation of a partner preference (see above) and, most likely, is also contributing to the maintenance of the pair bond. Importantly, within the NAc shell, OTR binding is reduced following separation from the female partner (Bosch et al. 2016). Thus, the data suggest that the OT signaling to the NAc shell is impaired following loss of the female partner. When combining these results with the fact that separation from the female partner causes increased passive stress-coping behavior in male prairie voles (see above), it is striking that chronic local infusion of OT within the NAc shell normalizes passive stress-coping behavior (Fig. 2c) (Bosch et al. 2016). Furthermore, as a proof of concept, within the same brain region chronic inactivation of the OTR by a selective OTR antagonist as well as local knock-down of OTR by shRNA increase passive stress-coping in males that are continuously housed with their female partner (Fig. 2c) (Bosch et al. 2016).

These partner loss-induced effects on the OT system in the NAc shell of male prairie voles are mediated via the brain CRF system (Fig. 3). Pair bonding and separation from the female partner causes increased CRF mRNA expression in the medial bed nucleus of the stria terminalis [5 days of separation (Bosch et al. 2009)] as well as increased CRF immunoreactivity in the PVN [4 weeks of separation (Sun et al. 2014)]. In separated males, chronic central infusion of the antagonist for CRF-R1 (CP-154526) or for CRF-R2 (astressin-2B) over 4 days normalizes passive stress-coping behavior (Bosch et al. 2009), an effect that is also seen after chronic local infusion of the CRF-R2 antagonist in the NAc shell (Bosch et al. 2016). On the contrary, chronic infusion of CRF-R2 agonist (stresscopin) increases passive stress-coping in non-separated males (Bosch et al. 2016). Importantly, CRF-R2 are abundantly expressed on OT neurons in the PVN as well as on its OT fibers projecting to the NAc shell (Bosch et al. 2016; Dabrowska et al. 2011). While these fibers release OT in the NAc shell, thereby facilitating the partner preference as well as probably maintaining it (see above), they also become less activated following separation from the female partner. In fact, central infusion of CRF-R2 agonist causes reduced local release of OT within the NAc shell in naïve male prairie voles (Bosch et al. 2016) in that way mimicking the neurobiological events occurring during/after partner loss. In contrast, central blockade of CRF-R2 increases OT release with the NAc shell (Bosch et al. 2016). In addition, even though not directly linked to this brain region, activation of CRF-R2 decreases the glutamate drive and excitability of OT neurons in the PVN of prairie voles (Bosch et al. 2016). Taken together, these data provide striking evidence for the significant negative impact of an activated brain CRF system following partner loss on striatal OT signaling, thereby causing the increased passive stress-coping behavior indicative of depressive-like behavior (Cryan and Mombereau 2004; Cryan et al. 2005). Hence, this negative emotional state during short separation, i.e., 5 days, encourages reunion with the partner and may have evolved to maintain long-term partnerships (Bosch et al. 2009).

Interestingly, both the OT and CRF systems in the NAc shell interact with the DA system, which regulates reward and is involved in depressive disorders (Kalia 2005; Russo and Nestler 2013) and addiction (Bardo 1998). In prairie voles, DA is important for pair bond formation (Young et al. 2011; Young and Wang 2004) with an overlap of brain regions also critical for the mesolimbic DA reward system, i.e., prefrontal cortex, ventral pallidum, and NAc (Young and Wang 2004). In humans, the NAc becomes activated in men viewing the

face of their female partner, but not other women, a physiological effect that can be enhanced by intranasal OT (Scheele et al. 2013). Interestingly, any form of attachment – including pair bond formation –is thought to induce feelings of pleasure and comfort (Resendez and Aragona 2013), to be rewarding (Young and Wang 2004) and has many parallels with addiction (Burkett and Young 2012; Insel 2003). Indeed, separation from a partner has been suggested to share neural mechanisms that occur during withdrawal from drugs of abuse, which may be another adaptive mechanism to maintain long-term bonds (Bosch et al. 2009; Burkett and Young 2012; Resendez and Aragona 2013).

9 Conclusions and Translational Implications

We reviewed the importance of social attachments during development and in adulthood on adult social behavior and mental health, with a primary focus on research conducted on a model organism ideally suited for this topic. The results in prairie voles parallel many studies in humans, suggesting that the findings from vole studies may have important translational implications for psychiatry. The studies examining the neural mechanisms of pair bond formation implicate roles for AVP, DA, CRF, and especially OT in mediating pair bond formation. The latter is a complex cognitive process that involves social information processing, social recognition, social reward, and socially reinforced learning (Modi and Young 2012). Oxytocin plays an important role in each of these processes. Thus, the mechanisms underlying pair bond formation may be useful for improving many aspects of social cognition in human subjects, including in psychiatric conditions characterized by social impairments, such as autism spectrum disorder (Modi and Young 2012; Young et al. 2002; Young and Barrett 2015).

Further studies involving manipulations of early-life attachment and social experience reveal that in prairie voles parental nurturing helps shape the neural systems that are critical for later life social bonding. These findings parallel studies in humans involving abuse and neglect, including those of Romanian orphans (Humphreys et al. 2015; Almas et al. 2012). In humans, early-life abuse and neglect in girls results in decreased OT concentrations in the cerebrospinal fluid (Heim et al. 2009). Our results in prairie voles reveal that OTR density in the striatum, which is robustly predicted by polymorphisms in the OTR gene (King et al. 2016), is indicative of resilience to early-life social isolation with respect to later life bonding. Several psychiatric genetic studies have suggested that polymorphisms in the human OTR predict not only social behavioral phenotypes, including those associated with autism (Skuse et al. 2014; Parker et al. 2014; LoParo and Waldman 2015), but also how early-life experiences shape later psychiatric outcomes (Schneider-Hassloff et al. 2016; Myers et al. 2014; Bradley et al. 2013). Consistent with these observations, a recent study identified epigenetic modifications of the OT gene that predicts many aspects of human sociability (Haas et al. 2016). These data suggest that future genetic or epigenetic screening of the OT system may be an important advancement to inform personalized medicine and therapeutic strategies related to disruptions in early-life attachment based on genetic and/or epigenetic information. The demonstration that pharmacological manipulations that evoke endogenous OT release, e.g., melanocortin agonist, may be worth exploring to reverse negative outcomes associated with disruption in attachment, whether they be due to genetic load, e.g., in autism, or to social experience (Young and Barrett 2015).

Finally, loss of a partner can be one of the most devastating experiences of a person's lifetime and is associated with increased depression (Biondi and Picardi 1996; Watanabe et al. 2004; Zisook et al. 1994, 1997; Assareh et al. 2015). Prairie voles have been the first model organisms to provide insights into the neural mechanism associated with psychiatric phenotypes based on the loss of a partner. Our research has shown that partner loss increases CRF signaling in the brain, which leads to an impoverished OT environment especially in the NAc; OTR in the NAc are reduced, as is the excitatory drive onto OT neurons. Each of these processes reduces OT tone, leading to an aversive state and eventually to passive coping behaviors reminiscent of bereavement. This system may play an adaptive role in the wild by serving to maintain pair bonds over a lifetime, but become maladaptive if reunion with the partner is not achievable. These observations suggest that drugs targeting the OT system and/or CRF-R2 antagonists may be useful for combating the dramatic psychological and physiological consequences of loss of a loved one. Clearly, when it comes to the many aspects of social attachment disruption, whether as a consequence of disorders such as autism, through early-life social neglect, or loss of a partner, the OT system should be considered a primary target for future investigations.

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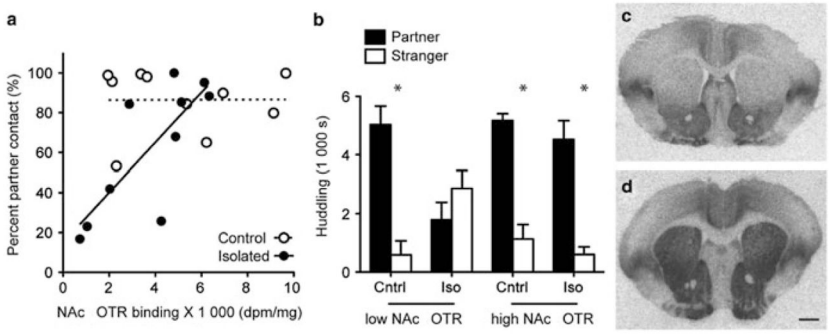

Fig. 1.

Female prairie voles with low NAc OTR are susceptible to early adversity. (**a**) The percentage of time females spent huddling with their partner vs total huddling significantly correlates with NAc OTR binding in the early-isolated, but not control females. (**b**) Only females with low OTR binding exposed to early isolation did not form a partner preference. Representative autoradiographs of (**c**) low and (**d**) high OTR NAc females. *$P < 0.05$ vs partner. Scale bar = 1 mm. Adapted from Barrett et al. (2015)

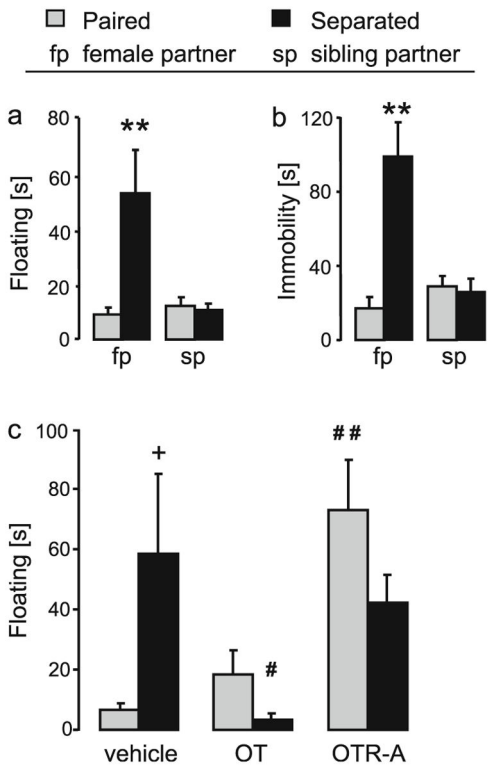

Fig. 2.

In male prairie voles, 4–5 days of separation from the female partner, but not from a male sibling, increases passive stress-coping behavior reflected as the time being inactive, i.e., floating in the forced swim test (**a**, **c** "vehicle") and immobile in the tail suspension test (**b**). Chronic infusion of synthetic OT bilaterally into the NAc shell abolishes the increased passive stress-coping after separation, whereas blocking OTR by an OTR antagonist (OTR-A) increases passive stress-coping in the non-separated males (**c**). $^{**}P < 0.01$ vs all other groups; $^{+}P = 0.05$ vs vehicle female-paired group; $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs corresponding vehicle group. (**a**, **b**) Adapted from Bosch et al. (2009), (**c**) Bosch et al. (2016)

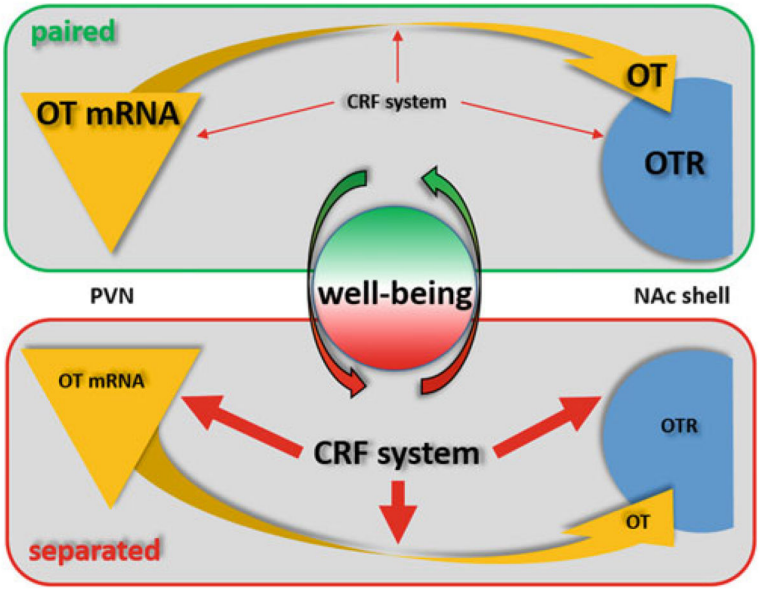

Fig. 3.

Schematic demonstrating our proposed model of the dynamic interaction of the brain CRF system on the OT system at multiple levels, from OT mRNA in the PVN and via OT release and OTR binding in the NAc shell to the resulting well-being when either with the partner (*top*) or after separation (*bottom*). *Red arrows* indicate inhibitory actions on multiple processes of the OT system by the CRF system