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Review

Lost connections: Oxytocin and the neural, physiological, and behavioral consequences of disrupted relationships

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ABSTRACT

In humans and rodent animal models, the brain oxytocin system is paramount for facilitating social bonds, from the formation and consequences of early-life parent-infant bonds to adult pair bond relationships. In social species, oxytocin also mediates the positive effects of healthy social bonds on the partners' well-being. However, new evidence suggests that the negative consequences of early neglect or partner loss may be mediated by disruptions in the oxytocin system as well. With a focus on oxytocin and its receptor, we review studies from humans and animal models, i.e. mainly from the biparental, socially monogamous prairie vole (*Microtus ochrogaster*), on the beneficial effects of positive social relationships both between offspring and parents and in adult partners. The abundance of social bonds and benevolent social relationships, in general, are associated with protective effects against psycho- and physiopathology not only in the developing infant, but also during adulthood. Furthermore, we discuss the negative effects on well-being, emotionality and behavior, when these bonds are diminished in quality or are disrupted, for example through parental neglect of the young or the loss of the partner in adulthood. Strikingly, in prairie voles, oxytocinergic signaling plays an important developmental role in the ability to form bonds later in life in the face of early-life neglect, while disruption of oxytocin signaling following partner loss results in the emergence of depressive-like behavior and physiology. This review demonstrates the translational value of animal models for investigating the oxytocinergic mechanisms that underlie the detrimental effects of developmental parental neglect and pair bond disruption, encouraging future translationally relevant studies on this topic that is so central to our daily lives.

1. Introduction

Social relationships are vital for the well-being of humans. The first and most crucial social relationship in life is developed at birth between the offspring and the parents. The formation of relationships persists throughout life, where new ties are established between individuals and family, friends, co-workers, and partners. Here, the neuropeptide oxytocin (OT) plays an important role in the formation of bonds of many kinds, including those between parents and offspring and between partners. OT is a ring-structured neuropeptide consisting of nine amino acids that is mainly synthesized in the hypothalamic paraventricular (PVN) and supraoptic nucleus (SON) (Burbach et al., 2006; Neumann and Landgraf, 2012). When released within the brain, OT facilitates the formation of pair bonds and friendships as well as the positive effects that result thereof. By contrast, the consequences of disruption or the loss of a bond severely impair the OT system. The subsequent dysfunction of the OT system then results in detrimental physiological as well as psychological effects. This review will briefly summarize the significance of positive social relationships and the negative effects of disrupting the parent-infant relationship or breaking the bond in humans with a focus on the OT system. Moreover, we review the existing literature on studies concerning impaired maternal care and models of neglect. In the case of the neural mechanisms of impairments of paternal care and partner loss, the focus is on studies using the biparental and socially monogamous prairie vole (*Microtus ochrogaster*). We present links between the maladaptive behavior as well as physical and psychological effects following impaired parental care and partner loss and the dysregulation of the OT system.

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2. Positive impact of social relationships in humans

Humans, being naturally social, show a fundamental need to connect with others and gain acceptance within a social group (Ryan and Deci, 2000). The presence of rewarding social relationships is regarded as an important factor in the regulation of health and well-being, exerting a beneficial influence on both physical and emotional health not only in early life but also during adulthood (Holt-Lunstad et al., 2017; House et al., 1988; Uchino, 2006; Yang et al., 2016). For example, studies show a positive correlation between the abundance of social relationships and longevity. A multidimensional assessment of the integration in social structures revealed a 91% increase in the likelihood of survival in more socially integrated individuals (Holt-Lunstad et al., 2010). Interestingly, not only the quantity but also the perception of possessing ample social connectedness is linked to a lower risk for the development of neurotic symptoms and mental health problems (Cruwys et al., 2014; Henderson, 1981; Saeri et al., 2017). Studies investigating the effect of relationships between friends, co-workers, and roommates show a negative correlation between the quality of relationships with susceptibility towards depression and distress (Beach et al., 1993; Kenny et al., 2013; Lepore, 1992). Furthermore, the prognosis of personality disorders is positively correlated with the quantity of rewarding interpersonal relationships (Skodol et al., 2007). Qualitatively, family relationships and marriage exert the biggest influence on the human well-being (Glenn and Weaver, 1981; Uchino et al., 1996), partly by buffering against negative events or experiences in life, as do other positive social relationships. Such buffering effects are associated with a higher resilience against stress and the curtailment of the risk for the development of psychiatric or physiological illnesses following adverse events (Cassel, 1976; Cobb, 1976; Cohen and Wills, 1985; Hostinar et al., 2014). Social buffering attenuates the cortisol response by dampening the reactivity of the HPA axis and has been shown to elevate the levels of peripheral OT (Grewen et al., 2005). Additionally, intranasal administration of OT potentiates the calming effects of social support; these effects are most likely based on a reduction of the stress-induced cortisol levels (Ditzen and Heinrichs, 2014; Heinrichs et al., 2003; Heinrichs et al., 2009; Olff et al., 2013; Quirin et al., 2011). In addition to the calming effects of intranasal OT, several other studies investigate its pro-social properties, e.g. in social interactions, enhancement of trust, emotion recognition, and social cognition, by potentially increasing the sensitivity to social cues (Baumgartner et al., 2008; Ebstein et al., 2009; Guastella et al., 2010; Kirsch et al., 2005; Kosfeld et al., 2005; Meyer-Lindenberg, 2008; Opar, 2008). Interestingly, the latter not only increases the perception of positive, but also of negative, cues hinting at context-dependent regulation of the perception of social cues by OT (Olff et al., 2013). However, while human studies on intranasal OT reveal interesting and important effects on social behavior, the results should be viewed in the light of their statistical power to ensure the exclusion of false-positives (Walum et al., 2016).

2.1. The bond between parents and their infants

The first bond in life develops immediately after parturition. This bond between the parents and their child is of utmost importance. Not only is it ensuring the survival of the progeny, but it is also decisive for the child's cognitive, social and emotional development, thereby influencing physiological and psychological health even later in life (Ammerman, 1991; Fernald and Gunnar, 2009; Insel and Young, 2001; Rilling and Young, 2014). The developing infant is highly responsive to changes in the environment and received maternal care due to the high plasticity of the brain that is still present (Ammerman, 1991; Fernald and Gunnar, 2009; Kolb and Gibb, 2011). For example, sufficient care and sensitivity for the offspring's needs can prime them for coping with stressful events in adulthood by shaping their reactivity towards stress (Kundakovic and Champagne, 2015; Rutter, 1979; Smith and Prior, 1995). Therefore, the quality of child care, expressed through affection, emotional warmth, empathy, and closeness, lowers the susceptibility for the development of psychiatric disorders such as depression and positively influences the child's functionality and health later in life (Campbell et al., 2014; Liu, 2003; Rilling and Young, 2014). Furthermore, children that receive undisrupted parental care (i.e. parents not separated) show a more secure attachment style in adulthood and report fewer marital problems (Amato and Rogers, 1997; Braithwaite et al., 2016).

2.2. Bonding to a partner in humans

Only up to 5% of mammalian species live in a monogamous relationship (Cockburn, 2006; Kleiman, 1977). Among primate species, this form of sociality is more abundant with approximately 29% being socially monogamous (Lukas and Clutton-Brock, 2013). Interestingly, it is speculated that the bond between partners in adulthood originates evolutionarily from the mother-infant bond since both types of bonds rely on overlapping brain areas and neurotransmitter systems (Numan and Young, 2016; Young, 2009; Young and Alexander, 2012).

Marriage has beneficial effects for general well-being in humans as it promotes better physical health and a lower susceptibility to develop long-term illnesses or work disability (Murphy et al., 1997; Waite and Lehrer, 2003). Like the general abundance of social relationships, successful marriages also increase longevity which can be attributed to its beneficial effects on general health (Waite and Gallagher, 2002; Waite and Lehrer, 2003). The formation of a partnership and cohabitation increase the general satisfaction with life. Interestingly, there are no differences in satisfaction between unmarried cohabitating couples and married couples (Zimmermann and Easterlin, 2006).

The formation of relationships and partnerships is governed by social interactions. One important mediator of social behaviors is OT. It has been proposed that OT enhances the perception and salience of social cues, e.g. social recognition, social memory, and trust (Bartz et al., 2011; Meyer-Lindenberg et al., 2011; Young, 2015). Intranasal administration of OT increases the perception of the partners' attractiveness compared to the perceived attractiveness of familiar and unfamiliar women and, at the same time, increases the activity of the nucleus accumbens (NAcc) when viewing images of the partner (Scheele et al., 2013), an effect that has been explored in detail in prairie voles (Johnson and Young, 2015).

3. Negative effects of adverse relationships in humans

However, as always in life - the pendulum swings both ways. Antagonistic to the beneficial effects of social relationships lies their maleficial nature when they are troubled or terminated, e.g. through breakup or death. This accounts for detrimental consequences of negative social relationships in work life or between close friends as well as in partnerships and marriages (Curtis, 1995; Steptoe, 1991). In general, stressful relationships or even the loss of a partner are associated with psychiatric conditions and health irregularities. Conflict within the family or between two partners is regarded as being the most influential on health and everyday functioning and has been linked to elevated plasma OT concentrations in women (Taylor et al., 2010). Interestingly, another study (Holt-Lunstad et al., 2015) did not report such correlation; here, higher plasma and salivary OT levels are associated with higher relationship quality, not distress. This contradictory finding might be due to differences in the context in which the samples were collected, or also due to differences in controlling for potential covariates, e.g. stress and depression levels (Holt-Lunstad et al., 2015).

3.1. Impaired parent-infant bond impacts on the offspring's well-being

Impaired parental investment in the offspring is often the result of the separation of the caregivers, either through termination of their

relationship or even death of one parent. When single mothers raise their children without the regular presence of the fathers both quality and quantity of the contact between the fathers and their children are reduced (Amato, 1987). The resulting negative effects of impaired parental care on the offspring's psychological and physiological health can even last into adulthood. For example, early life adversity is linked to physiological dysregulation, socio-behavioral maladaptation during adulthood, increased susceptibility for the development of psychopathologies like depression and post-traumatic stress disorder (PTSD) as well as substance abuse later in life (Agorastos et al., 2014; Felitti et al., 1998; Friedman et al., 2015; Heim and Binder, 2012; Heim et al., 2002; Nusslock and Miller, 2016).

In general, single parent-raised children show a deterioration of their physical and mental health in comparison to children raised by both parents (Scharte et al., 2013). Also, single parent-raised adults or those raised by families with inter-parental or parent-child conflicts, report lower life satisfaction with a worse marital quality, a higher risk for the development of depression, internalizing or externalizing problems, and lower socio-economic status indicated by lower education and income (Buss et al., 2017; Cherlin et al., 1998; Cummings et al., 2012; Fergusson et al., 2014). Furthermore, lower levels of education, a higher marital divorce rate, and lower quality of relationships with their parents are even observed in grandchildren of divorced parents, thereby hinting at long-lasting concomitants of marital dissolution (Amato and Cheadle, 2005; Buss et al., 2017).

Interestingly, the factors that precede a divorce, like inter-parental conflict, can already influence the child's well-being (Amato and Anthony, 2014). In addition, among the effects of divorce on the child's well-being are factors such as positive parenting by the single mother, child IQ, pre-divorce family income, as well as mental health status of the mother following divorce, and risk factors such as genetic predispositions or (prenatal) epigenetic changes (Mitchell et al., 2016; Monk et al., 2012; Nestler et al., 2016; Provencal and Binder, 2015; Wang et al., 2017; Weaver and Schofield, 2015; Weder et al., 2014; Yang et al., 2016).

Regarding the underlying neuroendocrinology, negative early life experiences have the power to modulate the OT system, even lasting into adulthood. A history of maltreatment during childhood negatively influences the cerebrospinal fluid OT concentrations in adult women and substantially decreases OT levels in the plasma of adult men (Heim et al., 2009; Opacka-Juffry and Mohiyeddini, 2012). Moreover, parental separation influences the sensitivity to intranasally administered OT; the decrease of plasma cortisol following OT administration is attenuated in men that experienced parental separation compared to control individuals (Meinlschmidt and Heim, 2007).

3.2. Physiological and psychological consequences of separation from the partner

In contrast to the beneficial effects on physical and psychological health arising from social kinships, social isolation or even the loss of the bonded partner are associated with a deterioration of both physical (e.g. immune system disruption and cardiovascular diseases) and mental health (Barger, 2013; Cacioppo and Hawkley, 2003; Carey et al., 2014; Gerra et al., 2003; Goforth et al., 2009; Holt-Lunstad and Smith, 2016; Shear and Shair, 2005; Uchino, 2006). Interestingly, even though divorce or separation from a partner exerts a negative influence on the health and survival of individuals, never having been married is even more closely linked to the development of poor health conditions (Kaplan and Kronick, 2006). With respect to mental health, never having been married has similar effects as being married, with divorce/separation inducing the most negative influence (Afifi et al., 2006). The unexpected parting of the spouse is oftentimes referred to as the most traumatic experience in one's life (Keyes et al., 2014). The loss of the partner or bereavement causes acute grief lasting up to 6 months and is not regarded as being harmful to the individual's health in the long-term (Shear et al., 2011). However, in roughly 10–20% of bereaved people, the manifestation of complicated grief is observed (Prigerson et al., 2009; Shear, 2015). In contrast to acute grief, complicated grief persists for a prolonged period, marked by the disability to show normal functioning in everyday life, social relationships, and work (Boelen and Prigerson, 2007; Monk et al., 2006; Simon et al., 2007). Complicated grief can also be accompanied by increased consumption of alcohol and nicotine, an elevated risk for the development of cardiovascular diseases, sleep disturbances, psychosomatic and psychiatric disorders, and an elevated suicidal risk (Buckley et al., 2012; Latham and Prigerson, 2004; Shear, 2015). The observed psychiatric outcomes following the breakup of a romantic relationship or even the death of a loved one range from a heightened risk for the first onset of a major depressive disorder to PTSD and anxiety disorders (Keyes et al., 2014; Monroe et al., 1999; Zisook et al., 1998). Interestingly, these disorders have been described as being modulated by the OT system (Dodhia et al., 2014; Heim et al., 2009; Labuschagne et al., 2010; Ozsoy et al., 2009; Parker et al., 2010) (for a review on the relationship between OT and stress-related disorders, see (Sippel et al., 2017)). One brain area that has been associated with changes during complicated grief in humans is the NAcc. When questioned for the self-reported yearning for the deceased, higher NAcc activity correlates with the amount of longing, independent of the time that has passed since the loss (O'Connor et al., 2008). This might indirectly link the psychological and physiological maladaptation observed in complicated grief to animal models, as the NAcc has also been linked to dysregulations of the OT-ergic signaling following the disruption of a pair bond in animal models (see following section).

4. Prairie voles as a model organism to understand the neuroendocrine basis of social relationships

The ability to study the underlying mechanisms of social relationships or of the consequences of their disruptions are limited in humans. However, supportive social relationships are advantageous for the development and well-being in social animals, too. Therefore, research has focused on animal models that exhibit the formation of a pair bond and/or biparental care to explore the underlying neurobiological mechanisms contributing to the adverse effects of bond disruption or neglect. In that context, the behavioral and neuroendocrine factors associated with social bonding in male and female prairie voles have been investigated extensively in the past decades. The first study to describe the prairie vole as a monogamous species characterized the mating system in laboratory settings (Thomas and Birney, 1979). Follow-up studies examined the social structures of wild prairie voles using multiple-capture live-trap data (Getz et al., 1981). Strikingly, previously caught male-female pairs were repeatedly re-caught together, independent of the breeding season, thereby indicating the existence of pair bonds and social monogamy in prairie voles. Because prairie voles are highly affiliative, form enduring social bonds between both sexes, and provide biparental care towards the offspring, they are a valuable model organism for examining social monogamy and to investigate the neuronal pathways involved in the formation of a partner preference (Johnson and Young, 2015; Lieberwirth and Wang, 2016; McGraw and Young, 2010; Young and Wang, 2004).

4.1. Molecular underpinnings of the formation of a pair bond in prairie voles

Monogamous behavior in prairie voles, including the formation of a pair bond, is associated with the brain neuropeptides OT and arginine vasopressin (AVP), both being also involved in the development of mother-infant bonds and the onset of maternal behavior (Bosch and Neumann, 2012; Numan and Young, 2016; Young, 2003), as well as in reproductive behavior (Donaldson and Young, 2008). For a detailed review of the OT/AVP neural network and its implications in social

behavior, see (Johnson and Young, 2017).

In male prairie voles, AVP-ergic signaling in the ventral pallidum (VP) facilitates the formation of a partner preference (Barrett et al., 2013; Donaldson et al., 2010; Lim and Young, 2004; Young and Wang, 2004). In addition to AVP, the brain OT system is significantly involved in the formation of pair bonds. Centrally administered OT or endogenous OT signaling facilitates the formation of pair bonds in female (Williams et al., 1994) and male prairie voles (Cho et al., 1999; Johnson et al., 2016). Furthermore, the expression of OT receptors (OTR) within the caudate putamen (CP) and the NAcc is higher in the monogamous prairie vole compared to the non-monogamous montane vole (*Microtus montanus*) (Young and Wang, 2004). In prairie voles, blockade of OTR by infusion of a receptor-specific antagonist locally into the prefrontal cortex (PFC) or the NAcc impairs partner preference formation (Johnson et al., 2016; Young et al., 2001). In confirmation, silencing the expression of OTR within the NAcc by RNAi knockdown inhibits social attachment (Keebaugh et al., 2015), whereas selective overexpression of OTR accelerates partner preference formation in female prairie voles (Keebaugh and Young, 2011; Ross et al., 2009). Furthermore, male prairie voles with a genetic polymorphism in the OTR gene that results in lower OTR density in the NAcc show an impairment in social bond formation (King et al., 2016). Also, OT is thought to interact with dopamine to link the neural encoding of the partner with the reward system (Young and Wang, 2004). More recent electrophysiological and optogenetic studies have demonstrated that dynamic communication between the PFC and the NAcc is critical for partner preference formation, and OT signaling may influence the strength of the communication and the latency to display huddling behavior (Amadei et al., 2017).

4.2. Importance of positive early life social experience

The first and undoubtedly one of the most important social relationships in life is established between the newborn and the mother. The quality and quantity of care provided by the mother is important for the current physical well-being of the offspring (Bosch and Neumann, 2012). Furthermore, parental nurturing is of significance for the offspring's gene expression on an epigenetic basis and, consequently, for their social- and non-social behavior in adulthood as well as their response to fearful stimuli, as has been extensively studied in rats (Caldji et al., 2004; Parent et al., 2013; Perkeybile et al., 2013). For example, increased levels of maternal care can be induced by early handling of the offspring and the subsequent reunion with their mother (Liu et al., 1997; Pryce et al., 2001). Such treatment results in increased nursing behavior in motherhood compared to mothers that were raised without early handling (Fleming et al., 1999; Francis and Meaney, 1999; Liu et al., 1997; Pryce et al., 2001). Maternal care decisively impacts the development of the offspring's OT system, thereby modulating the behavioral phenotype in adulthood including maternal behavior (Champagne, 2011; Champagne and Meaney, 2007). For example, high levels of pup-directed licking and grooming are associated with higher OTR levels in the hypothalamus and the medial preoptic area (MPOA) of the offspring at maturity, which in turn leads to high licking and grooming behavior as they become mothers (Champagne et al., 2001; Francis et al., 2000; Francis et al., 1999b).

Recent studies aimed at investigating specifically the role of biparental care, thereby mirroring the human parenting strategy. Biparental care is thought to be present in species where there is a high probability that the father is caring for his own offspring or the offspring of a close relative (Lukas and Clutton-Brock, 2013; Thomas and Birney, 1979). Interestingly, monogamy does not exclusively coincide with biparental care as in only 59% of the investigated monogamous mammals both parents contribute care towards the offspring (Lukas and Clutton-Brock, 2013). In many cases though, the offspring profit from being raised by both parents as the quantity of parental care is higher and, hence, this has beneficial effects on the offspring's well-being (Ahern and Young, 2009). Therefore, this aides the development of the offspring, either directly by increased licking and grooming or indirectly by defending the territory and the nest (Oliveras and Novak, 1986).

4.3. Impaired parent-offspring interactions have long-lasting effects on the young

The early life period is very sensitive and susceptible not only to positive but also to negative influences from outside as the brain still has a high degree of plasticity (Kolb and Gibb, 2011). Therefore, various kinds of disturbances within this sensitive time effectively influence the development of the brain and consequently behavior.

The experience of impaired parental care can induce a multitude of behavioral changes in the offspring. Among those are an increase in the response to fearful stimuli, a dysregulation of the stress reactivity, as well as impairments in social interactions (Chen and Baram, 2016; Sanchez, 2006; Sanchez et al., 2001). However, differences between the sexes as well as the period during which adverse life conditions are encountered can be decisive for its impact on health later in life (Curley and Champagne, 2016; Lehmann et al., 1999).

For example, in rats, impairments of maternal care are associated with lower maternal nurturing behavior towards pups in the F1 generation (Champagne and Meaney, 2001; Francis et al., 1999a; Lomanowska et al., 2017). This effect persists even into the F2 generation (Francis et al., 1999b). Such differences in the natural variation of maternal care are mimicked under laboratory conditions by maternal separation and/or artificial rearing (Bosch and Neumann, 2012; Champagne and Meaney, 2007; Lovic et al., 2001). Aversive rearing conditions induce alterations of the stress response (Murgatroyd et al., 2009; Wigger and Neumann, 1999), modulate anxiety-like behavior (Ishikawa et al., 2015), cause cognitive and social impairments in adulthood (Aisa et al., 2007; Haller et al., 2014), and even induce lower pup-directed maternal care in adulthood of artificially reared pups (Gonzalez and Fleming, 2002; Gonzalez et al., 2001; Lovic et al., 2001) (but also see (Zhang et al., 2014)). Strikingly, deficits in maternal nurturing behavior are linked to a dysregulation of the brain OT signaling (Jin et al., 2007; Takayanagi et al., 2005); the offspring's OTR density in the MPOA is decreased when receiving less maternal care (Champagne et al., 2001).

Similar to those findings, in prairie voles, the disruption of the postnatal rearing period or post-weaning isolation are linked to changes in gene expression, neural pathways, and social behavior (Ahern et al., 2011; Ahern and Young, 2009; Barrett et al., 2015; Pan et al., 2009; Tabbaa et al., 2017). Moreover, prairie voles are biparental (Thomas and Birney, 1979; Young and Wang, 2004), which paved the way for studies investigating the effects of single mother- versus biparental-rearing on the offspring. The absence of the father results in being less licked and groomed and increases the time in which the pups are left unattended, especially since deserted mothers do not compensate for the loss of the father (Ahern et al., 2011; Ahern and Young, 2009; McGuire et al., 2007; Tabbaa et al., 2017; Bosch et al., 2018). Furthermore, paternally deprived pups mature slower in comparison to biparentally reared ones (Ahern et al., 2011; Ahern and Young, 2009). Consequently, paternal deprivation causes long-lasting behavioral changes; the single mother-reared prairie voles show impaired alloparental and socio-sexual behavior, marked by the manifestation of delayed partner preference formation (Ahern et al., 2011; Ahern and Young, 2009). Interestingly, investigation of the brain OT system reveals sex-specific differences following single mother-rearing. Female, but not male, offspring reared by the mother alone have higher OT mRNA expression in the PVN compared to biparentally-reared conspecifics (Ahern and Young, 2009) (but also see (Tabbaa et al., 2017)). However, in the socially monogamous and biparental mandarin voles (*Lasiopodomys mandarinus*) single mother-rearing and parental separation cause lower social interaction and higher anxiety-related behaviors in adulthood (Jia et al., 2009).

In addition, female prairie voles that were socially isolated for 3 h per day during the neonatal period exhibit impairments in the formation of a partner preference in adulthood (Barrett et al., 2015). This study further hints at the interplay between the susceptibility to malignant early life experiences and the natural variation of OTR density in the NAcc (Barrett et al., 2015). Juvenile females that naturally express a high NAcc OTR density seem to be resilient against early life adversity as they spend more time in contact with their partner in adulthood compared to females that have a low OTR density. These findings suggest that in those pups the OT release stimulated by licking and grooming following the reunion with the parents has important developmental consequences such as the ability to form relationships in adulthood (Barrett et al., 2015; Rilling and Young, 2014). Interestingly, the natural variation in OTR density in the NAcc that determines susceptibility or resilience to early life neglect is not determined by epigenetic factors induced by experience as it is the case in rats, but is genetically determined by polymorphisms in the OTR gene (King et al., 2016). Importantly, the induction of endogenous OT release by pharmacological intervention during the neonatal period buffers against the negative effects of early isolation on partner preference formation (Barrett et al., 2015).

4.4. Positive impact of persisting social relationships in adult prairie voles

Comparable to the beneficial properties of social support in humans (see Section 2), prairie voles also show lower anxiety-related and depressive-like behavior following a stressor in the presence of the partner, termed social buffering (Smith and Wang, 2014). Briefly, female prairie voles (*demonstrator*) that are subjected to immobilization stress show increased stress-related behaviors such as route tracing and repetitive auto grooming but only when recovering alone (Smith and Wang, 2014). In contrast, when the stressed females are returned to their male partners (*observer*), these stress-related behaviors are absent. In addition, the males display increased female-directed social behavior interpreted as consoling behavior. Interestingly, the soothing effect of the male partner's presence on the stressed female is mediated by the brain OT system. Females that recover with their partner have a substantial increase of OT release within the PVN compared to females that recover alone. Importantly, in the latter, OT microinjection into the PVN normalizes their stress-related behaviors to a similar level as females experiencing social buffering (Smith and Wang, 2014).

When switching perspectives, the consoling behavior together with the parallel processes in the brain of the unstressed observer is also fascinating (Burkett et al., 2016). After the stressed (mild foot shock) demonstrator is placed back in the home cage, the observing prairie vole displays increased grooming towards the stressed pair bonded partner, but not towards a stranger. Furthermore, the stress-induced heightened levels of anxiety-related behavior are diminished when receiving consolation from the bonded partner. This consoling behavior is mediated by OT-ergic signaling in the anterior cingulate cortex (ACC), a brain region linked to empathy in humans (Lamm et al., 2011). Validating the previous findings, subsequent infusion of an OTR antagonist locally into the ACC blocks stress-induced consolation behavior in the observing partner (Burkett et al., 2016).

4.5. Physiological and psychological consequences of pair bond disruption in adult prairie voles

In the past years, studies characterized the consequences of social isolation in general and the loss of a bonded partner more specifically on behavioral, physiological, and molecular levels. Social isolation from same-sex individuals evokes gender-specific responses. In female voles, separation from other females causes depressive-like symptoms (Grippo et al., 2011; Grippo et al., 2007a; Grippo et al., 2007b; Grippo et al., 2007c; Grippo et al., 2008), whereas such an emotional consequence is absent in males separated from other males (Bosch et al., 2009). In contrast to same-sex isolation, the sudden disruption of opposite-sex pair bonds provokes an increase in behaviors associated with psychological maladies (Bosch et al., 2016; Bosch et al., 2009; Bosch and Young, 2017; McNeal et al., 2014; Sun et al., 2014; Tabbaa et al., 2016; Bosch et al., 2018). Both separated male and female prairie voles display increased passive stress-coping behavior, reminiscent of depressive-like behavior (Cryan and Slattery, 2007), as well as increased anxiety-related behavior (Bosch et al., 2009; McNeal et al., 2014; Sun et al., 2014). These maladaptations are even further pronounced when the separated prairie vole is exposed to chronic mild stress (McNeal et al., 2017), probably due to the absence of the consoling behavior of the partner (Burkett et al., 2016). On a physiological level, the cardiovascular system becomes dysregulated (McNeal et al., 2014); losing the partner induces an upregulation of the heart rate and downregulation of its variability. In addition, the sympathetic drive increases, whereas the parasympathetic innervation of the heart is downregulated (McNeal et al., 2014). Furthermore, basal plasma adrenocorticotropic hormone and corticosterone levels are upregulated and the adrenal weight is increased hinting at a chronically activated stress axis (Bosch et al., 2009; McNeal et al., 2014; Sun et al., 2014). In line with that, blocking the corticotropin-releasing factor (CRF) receptors centrally normalizes the emotionality of separated males (Bosch et al., 2009) and separated lactating mothers (Bosch et al., 2018). Interestingly, CRF mRNA expression in the bed nucleus of the stria terminalis is increased in male prairie voles separated from the female partner but not when isolated from a male cage mate (Bosch et al., 2009). Surprisingly, CRF mRNA is also upregulated in the PVN of males that are still with the female partner; this might indicate that the CRF system is not active but primed for the event of separation (Bosch and Young, 2017). It is hypothesized that this constellation guarantees that the CRF system is able to swiftly respond to the separation, thereby causing all of the above-mentioned negative changes and, hence, ensuring the maintenance of the pair bond possibly by motivating the partners to actively seek the presence of each other in order to reduce the separation-induced stress reaction.

4.6. The impact of partner loss on the dysregulation of the brain OT system

The formation of a pair bond relies on the activity of the brain OT system in the NAcc (see Section 4.1). However, separation of both partners induces impairments of the OT signaling on multiple levels, partly through an activation of CRF receptor type 2 (CRFR2) (Bosch et al., 2016). Upon short-term separation from the female bonded partner for five days, the expression of OT mRNA in the PVN, but not SON, is significantly reduced (Bosch et al., 2016). Consistent with this finding, the immunoreactivity for OT positive cells in the PVN is increased following a long-term separation of four weeks, which is interpreted to reflect a decrease of release and receptor activity in respective areas (Sun et al., 2014). Moreover, the OT neurons from the PVN represent the main source for OT released within the NAcc with approximately 90% of the innervations of OT fibers arising from the PVN (Bosch et al., 2016). This highlights the PVN's significance for OT signaling within the NAcc. Importantly, these OT fibers express CRFR2 (Bosch et al., 2016). When activating CRFR2 via acute central infusion of stresscopin (i.e. urocortin 3), the local release of OT within the NAcc decreases (Fig. 1). On the other hand, reduced CRFR2 signaling via acute central blockade with astressin-2b increases OT release locally in the NAcc (Bosch et al., 2016). Importantly, chronic infusion of OT into the NAcc reverses passive stress-coping in males separated from their partner (Fig. 1). Furthermore, and as proof of concept, chronic inhibition of OTR via local infusion of an antagonist (Bosch et al., 2016) or downregulation of OTR expression by 60% via shRNA (Keebaugh et al., 2015) induces passive stress-coping in non-separated males (Bosch et al., 2016). Moreover, electrophysiological measurements of the excitability of OT neurons in the PVN following the central infusion of stresscopin reveals that activation of CRFR2 is decreasing the

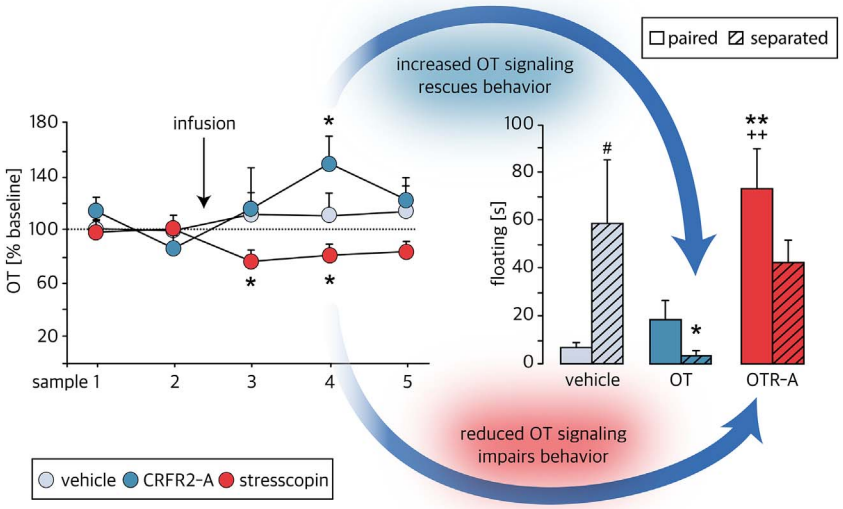

Fig. 1. Local OT release within the NAcc shell of male prairie voles is affected by central CRFR2 manipulations.
Blockade of CRFR2 by astressin-2B (CRFR2 antagonist) increases the release of OT, whereas activation of CRFR2 by stresscopin (CRFR2 agonist) decreases OT release. In continuation, such CRFR2-evoked (de-) activation of OT signaling in the NAcc shell has similar effects on passive-stress coping as local OTR manipulation in the NAcc shell. In detail, synthetic OT rescues the increased passive stress-coping after separation whereas the OTR antagonist increases passive stress-coping in non-separated males.

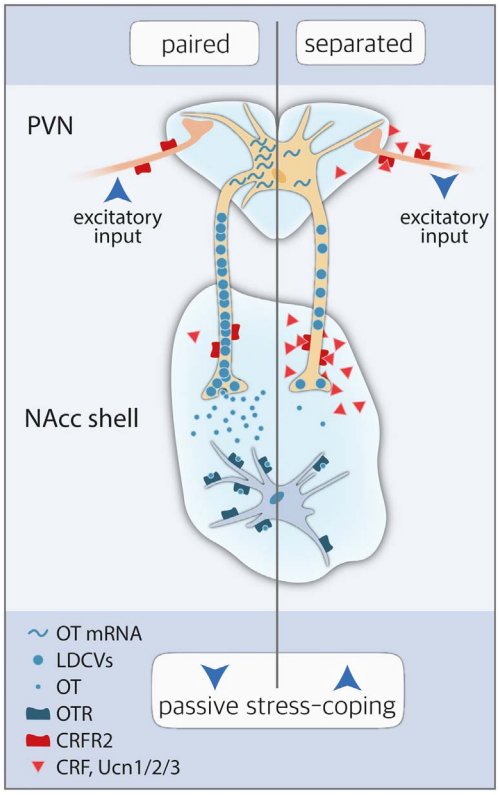

Fig. 2. Scheme of the influence of CRFR2 on OT signaling from the PVN to the NAcc shell under paired conditions as well as following the loss of the partner.
Separation from the pair bonded partner induces the release of CRFR ligands, which bind to CRFR2 on glutamatergic neurons, thereby inhibiting their activity. The resulting decreased excitability of OT neurons in the PVN causes decreased OT mRNA expression in neurons projecting to the NAcc shell. Subsequently, reduced OT mRNA expression may cause reduced OT-carrying large dense-core vesicles (LDCVs), thereby leading to impaired OT release within the NAcc shell. Furthermore, activation of CRFR2 on the terminals of OT neurons in the NAcc causes a decrease of OT release within the NAcc. In addition, OTR density within the NAcc shell is decreased following separation from the partner. Hence, loss of the partner results in impaired OT signaling from the PVN to the NAcc shell on multiple levels due to heightened brain CRFR2 activation.

frequencies of sEPSCs and, thereby, presynaptically regulating the excitability of PVN OT neurons by downregulating glutamatergic transmission (Bosch et al., 2016). Hence, short-term separation leads to increased CRFR2 activation thereby significantly impairing OT signaling within the NAcc (Fig. 2). In addition, the OTR density within the NAcc is decreased after short-term separation (Bosch et al., 2016). Thus, these findings not only show that breaking the pair bond has strong emotional and physical effects on the prairie voles but, furthermore, also indicate that healthy OT signaling is important for the maintenance of the pair bond.

5. Conclusions

In this review, we discussed the importance of social relationships for the individuals' well-being partly by examining the negative outcomes when subjects are separated from a loved one. Intact social relationships are accompanied by increased brain OT signaling, which helps to buffer against adverse life experiences and to promote lower susceptibility to the development of psychiatric conditions and health deterioration. However, broken social relationships, e.g. neglect early in life or through the loss of a partner, can induce negative long-lasting effects on both physiological and psychological health. This is mediated at least partly by an impaired OT signaling. Treatments targeting the brain OT system might be a powerful tool to counteract the maladaptation following such adverse events. Nevertheless, trials that shed light on the long-term effects of chronic treatment with OT have not yet been conducted in humans as seen in animal models (Bales et al., 2013; Bales et al., 2014). However, animal models have demonstrated that stimulating the OT system has the potential to reverse the deleterious effects of maternal separation and/or paternal deprivation as well as of the outcomes following pair bond disruption. Furthermore, prairie voles are a well-suited model organism for the investigation of the adverse effects of social neglect (Bosch and Young, 2017; Tabbaa et al., 2016). Therefore, forthcoming studies investigating the role of OT in social relationships as well as the effects on OT when being disrupted are valuable for translational implications to understand and - at most - to reverse the resulting adverse effects. Future studies involving manipulation of the OT system either directly via intranasal OT or indirectly by pharmacologically evoked OT release via targeting systems such as the melanocortin system (Modi et al., 2015; Young and Barrett, 2015) may have important translational value for psychiatric and physiological consequences of neglect and social loss.

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