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The neurobiology of pair bond formation, bond disruption, and social buffering

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Abstract

Enduring social bonds play an essential role in human society. These bonds positively affect psychological, physiological, and behavioral functions. Here, we review the recent literature on the neurobiology, particularly the role of oxytocin and dopamine, of pair bond formation, bond disruption, and social buffering effects on stress responses, from studies utilizing the socially monogamous prairie vole (*Microtus ochrogaster*).

Keywords

Dopamine; oxytocin; pair bonding formation; social buffering

Introduction

Long-lasting, positive social bonds between spouses (pair bonds), parents and their children, and peers play an essential role in human health. These bonds can buffer against stress, depression, anxiety, and drug misuse [1,2]. Furthermore, health problems such as cardiovascular pathologies, asthma, and infectious diseases may be reduced by such bonds [1,2]. On the contrary, the inability to form and maintain these positive bonds is a characteristic of various psychological disorders [3]. Therefore, positive social relationships are instrumental to human health and efforts have been put forward to better understand bonding and its underlying neural mechanisms.

Neurobiological studies focusing on understanding the bonding in humans have shown that bonds between spouses as well as between parents and their children involve reward, motivation, and emotion circuits [4,5•,6,7]. These findings are similar to observations in

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Conflict of interest statement

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other mammalian species displaying monogamous life strategies—highlighting the importance of social bonds to well-being and the similarity of neural mechanisms across monogamous species [e.g., 8,9,10]. Consequently, these observations spurred the interest to develop appropriate animal models to study the neurobiological mechanisms underlying pair bonding.

As pair bond formation and the associated behaviors (e.g., mate guarding and bi-parental care) are only displayed by 3–5 % of mammals [11,12], there are very few appropriate animal models. Here we will focus on the prairie vole (*Microtus ochrogaster*) that has been used to study the neurobiological mechanisms of pair bonding [13]. We will discuss the role of the neurochemicals oxytocin (OT) and dopamine (DA) in pair bond formation. Then, we will discuss some recent findings highlighting the importance of OT and DA during bond disruption and in mediating social buffering effects on stress responses.

The prairie vole model

The prairie vole is a socially monogamous rodent species. Social monogamy is defined here as long-term selective association between a male and female adult that are not necessarily sexually exclusive [14]. This species displays three unique patterns of social behaviors, namely partner preference (pair bonding) between mates, selective aggression toward conspecific strangers (mate guarding), and bi-parental care of offspring—making it an ideal model to study the neurobiology of social behaviors associated with the monogamous life strategy [13]. In the laboratory, mating-induced pair bonding is assessed by a 3-hour preference test between the familiar partner and a conspecific stranger. Twenty-four hour mating induces partner preference formation, whereas 6-hour cohabitation without mating does not induce such preferences in both male and female prairie voles [15,16]. In female prairie voles, a longer than 24-hour cohabitation period without mating can also result in partner preference formation [15]. These valid behavioral paradigms have provided tools for the study of pair bond formation and its underlying neurochemical mechanisms [13]. Furthermore, recent studies have shown that pair bond disruption induces physiological and behavioral stress responses, whereas partner reunion causes social buffering by reducing bond disruption-induced stress responses, indicating the utility of this animal model for the study of pair bond disruption and function as well as the underlying mechanisms [17••,18••]. Indeed, a variety of neuropeptides, neurochemicals, and hormones have been implicated in pair bonding in prairie voles [13,14,19]. In this review, we will focus on the neurochemical OT and DA and discuss their roles in pair bond formation, bond disruption, and social buffering.

Pair bond formation

OT has been implicated in learning and memory, individual recognition, as well as prosocial and affiliative behaviors [2]. Thus, it is reasonable to expect that OT is also involved in pair bonding. Early neurochemical studies using voles have illustrated the presence of OT receptors (OTR) in many brain areas important for social behaviors. Furthermore, there are striking species differences in the distribution pattern of OTR in the brains of prairie voles and other vole species, such as montane (*M. montanus*) and meadow (*M. pennsylvanicus*)

voles that are promiscuous and do not display mating-induced pair bonding [20,21]. Peripheral or central (intracerebroventricular, icv) administration of an OTR antagonist impairs mating-induced partner preference, whereas administration of OT induces this behavior without mating, suggesting that OT is both necessary and sufficient for pair bond formation in prairie voles [22–24]. Several brain areas have been identified for OT regulation of pair bonding. In adult female prairie voles, for example, pharmacological activation of OTR in the nucleus accumbens (NAcc) facilitates partner preference, whereas OTR blockade impairs this behavior induced by mating or by OT administration [25]. In the NAcc, selective partial knockdown of OTR disrupts partner preference, whereas over-expression of OTR by adeno-associated viral vector-mediated gene transfer (AAV-OTR) facilitates partner preference formation without mating [21,26]. Such OTR over-expression in the NAcc of juvenile female voles also results in an accelerated partner preference as adults [27]. Interestingly, epigenetic events are involved in NAcc OTR-mediated pair bonding in prairie voles [28••,29•]. Specifically, mating facilitates H3 acetylation on the OTR gene promoter region in the NAcc, which, in turn, increases the OTR expression and enhances partner preference formation. Further, OT in the medial prefrontal cortex (mPFC) of females [8] and lateral septum (LS) of males [30] has also been implicated in the regulation of pair bonding in prairie voles.

The mesocorticolimbic DA system is well known for its role in regulating motivated behaviors [31]. This system, particularly DA in the NAcc, has also been implicated in pair bonding. In prairie voles, DA is released in the NAcc during mating, and intra-NAcc administration of a non-selective DA receptor (DAR) antagonist inhibits mating-induced partner preference [32,33]. Further, NAcc DA regulates pair bonding in a receptor-specific manner: D2R antagonism inhibits mating-induced partner preference, whereas D2R agonism facilitates partner preference without mating in male prairie voles [32–35]. Conversely, D1R activation in the NAcc impairs partner preference induced by mating or by D2R activation [35]. This receptor-specific DA regulation of pair bonding is due to opposing effects of D1R/D2R on the activity of the cyclic adenosine monophosphate (cAMP) signaling cascade and associated G-proteins [13]. Furthermore, this DA effect is site-specific, it influences pair bonding behavior only when the DAR manipulation is in the NAcc shell, but not in the NAcc core or caudate putamen [35]. Finally, it has been shown that DA and OT interact in the regulation of pair bonding. In the NAcc, for example, OTR blockade inhibits partner preference induced by D2R activation, whereas D2R, but not D1R, antagonism inhibits partner preference induced by OT treatment [25].

Pair bond disruption

In humans, disruption of social bonds can manifest in stress-related diseases, disorders, and behaviors [1,3]. These findings are similar to observations in prairie voles. Data from early studies indicate that social isolation, in particular separation from cage mates, leads to increased physiological and behavioral stress responses including altered cardiovascular functions, elevated activity of the hypothalamic-pituitary-adrenal (HPA) axis, and increased anxiety-like and depression-like behaviors in prairie voles [36–40]. Similarly, separation from a bonded partner elevates plasma corticosterone and increases anxiety-like and depression-like behaviors in prairie voles [17••,18••,41•]. After 4 weeks of mate separation,

male prairie voles no longer display partner preference, indicating disrupted pair bonding [17••]. Chronic social isolation (4 weeks) leads to increases in OTR expression in the paraventricular nucleus of the hypothalamus (PVN) and in plasma levels of OT in female voles [42•]. In male voles, bond separation results in an increased OTR expression in the PVN [17••]. Therefore, disrupted brain OT system may be involved in the physiological and behavioral responses to bond disruptions. Interestingly, OT treatment prevents alterations in cardiovascular consequences and depression-like behaviors induced by social isolation in female prairie voles [43].

Exposure to psychostimulant drugs, such as amphetamine (AMPH), also disrupts pair bonding in prairie voles [44,45,46••]. Three days of repeated exposure to AMPH is rewarding to prairie voles as it induces conditioned place preference (CPP). Such AMPH experience does not alter mating and locomotor activity but impairs mating-induced partner preference and selective aggression, indicating disrupted bonding behaviors in prairie voles [44,45,46••]. Interestingly, such AMPH exposure increases D1R expression in the NAcc in male prairie voles, which is responsible for the impaired pair bonding, as D1R blockade can restore mating-induced partner preference in AMPH-treated voles [45]. In females, AMPH exposure decreases D2R density in the NAcc and OTR expression in the mPFC [46••]. OT administration into the mPFC can restore partner preference in AMPH-treated female voles [46••]. Finally, voluntary alcohol consumption is found to alter partner preference in prairie voles in a sexual dimorphic manner. Alcohol consumption inhibits partner preference formation in males, but facilitates the same behavior in female prairie voles [47••].

Pair bond-facilitated social buffering

Social attachments can act as a protective buffer against many negative consequences of stressful events [48]. In recent studies, prairie voles have also been used as an animal model to study the functional significance of pair bonding in ameliorating negative consequences from stressful experience on the brain and behavior. For example, unlike their sexually naïve counterparts, pair-bonded male voles do not display AMPH-induced CPP, indicating that pair bonding experience decreases the rewarding properties of AMPH, which is mediated by D1Rs in the NAcc [49]. In another study, interacting with a familiar social partner can protect against alcohol relapse in prairie voles although the neurochemical underpinning is still unknown [50••].

Several recent studies have generated some interesting data illustrating the anxiolytic effects of brain OT in mediating social buffering on stress responses in prairie voles. In a study in female prairie voles [51••], 1-hour immobilization increases anxiety-like behavior and plasma corticosterone in females that recovered alone but not in females that recovered with the male partner. This social buffering effect by the male partner on the female's biobehavioral stress response is accompanied by increased OT release in the PVN. Further, intra-PVN administration of OTR antagonist blocks the effects of the social buffering, whereas administration of OT reduces behavioral and hormonal responses to immobilization in females that recovered alone. Together, these data demonstrate that the PVN OT mediates social buffering effects on the stress response in female prairie voles [51••]. In a subsequent study, it was found that the anxiolytic effects of OT on the female's biobehavioral responses

to stress are due to recruitment of GABAergic neurons, in particular activation of GABAa receptors, in the PVN [52•]. It is interesting to note that during the recovery period, male partners display augmented social approaching, sniffing, and grooming toward the distressed females—behaviors that are believed to play a role in consoling the distressed female [51••]. In humans and greater apes, consoling distressed individuals following stressful events represents critical behavior for stress coping [53,54].

The consolation behavior toward distressed partners is further studied in prairie voles [55]. Voles (both males and females) display increased partner-directed grooming toward familiar mates that have experienced a stressor (i.e., light foot shocks). This enhanced grooming is specific as it is only directed toward stressed mates but not stressed strangers or an unstressed mate. This behavior is mediated by OT in the anterior cingulate cortex and is associated with decreased anxiety-like behavior displayed by the distressed cage-mate. These data illustrate the role of brain OT in partner's consolation behavior in mediating social buffering effects on stress responses.

In addition to the involvement of OT in mediating pair bond formation, pair bond disruption, and social buffering, OT has also been implicated in behavioral variations that have been observed in free-living prairie voles. In particular, male prairie voles with high, but not low, OTR density in the NAcc display social monogamy [56]. Interestingly, there are also variations in vasopressin receptor expression that play a role in male social behavior [57•, 58,59].

Conclusion and future direction

The evidence reviewed here highlights the utility of the prairie vole model to study the neurobiological mechanisms underlying pair bond formation, bond disruption, and social buffering. Data have shown that the neurochemicals OT and DA work in concert to regulate pair bond formation wherein epigenetic events are also involved. Such epigenetic events include the increase in OTR expression facilitating partner preference formation. Factors (such as social isolation, bond separation, and AMPH exposure) that lead to pair bond disruption also cause a dysregulation of the OT and DA systems. Interestingly, an increased activity in the brain OT system is involved in the regulation of social buffering of pair bonding on stress responses.

Previous studies have also implicated various other neurochemicals (such as vasopressin, GABA, and corticotropin releasing factor) in pair bonding and stress response behaviors [2,13,17••,18••]. Therefore, cutting-edge technologies such as optogenetics, epigenetics, and gene manipulations should be used in the prairie vole research to investigate the neurochemical circuitry including the neurochemical interactions across various brain regions underlying pair bond formation, bond disruption, as well as social buffering. In particular, epigenetic events have been observed in the prairie vole NAcc, which play a role in the OT regulation of pair bonding. Although not being examined in voles, optogenetic manipulation, especially manipulations of the OT and DA systems in the NAcc and prefrontal cortex (PFC), alter social behaviors including increases in social interactions [60••,61••]. Literature has indicated that neurochemicals such as OT and DA interact in

selected brain regions including the NAcc and PFC (see Figure 1) in the regulation of pair bond formation in prairie voles [62]. Thus, it will be interesting to apply the above-mentioned cutting edge techniques to examine OT and DA interactions and their functional roles in the regulation of pair bonding, bond disruption, and social buffering. Furthermore, these approaches should also be used to further assess bonding behavior outside the laboratory setting in semi-natural and field studies to further enrich our knowledge about the evolutionary significance of the pair bond.

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Highlights

- The prairie vole model can be used to study the neurobiological mechanisms of pair bonding, bond disruption, and social buffering.
- Oxytocin and dopamine interact to regulate pair bond formation.
- Pair bond disruption causes the dysregulation of oxytocin and dopamine.
- Social buffering depends on the oxytocin system.

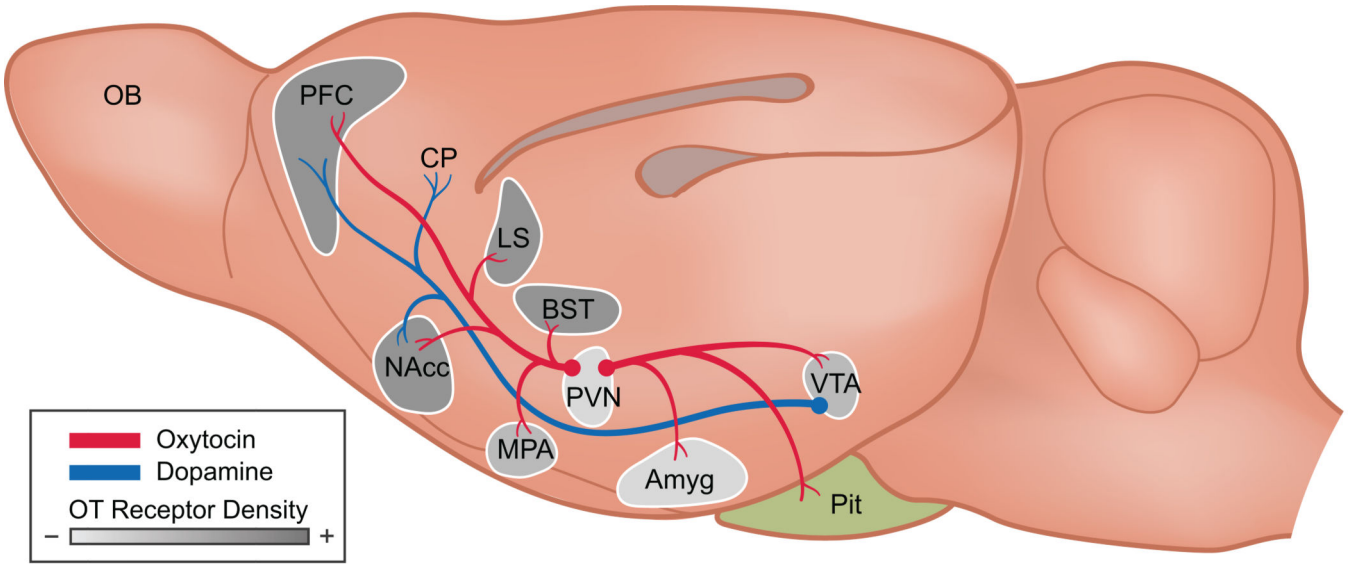

Figure 1.

Schematic illustration of oxytocin (OT) and dopamine (DA) neurocircuitry involved in pair bonding, bonding disruption, and social buffering in prairie voles. OT receptor densities are illustrated in each of the OT projection areas including the prefrontal cortex (PFC), nucleus accumbens (NAcc), lateral septum (LS), bed nucleus of the stria terminalis (BST), medial preoptic area (MPA), amygdala (Amyg), and ventral tegmental area (VTA), while both DA D1-type and D2-type receptors are present in the NAcc, PFC, and caudate putamen (CP).