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Neuropeptidergic regulation of pair-bonding and stress buffering: Lessons from voles

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ABSTRACT

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Interpersonal attachment is a critical component of the human experience. Pair-bonding ameliorates the severity of several mental and physical diseases. Thus, a better understanding of how the central nervous system responds to and encodes social-buffering during stress is a valuable research enterprise. The prairie vole (*Microtus ochrogaster*), as a laboratory animal model, provides the gold standard for the investigation of the neurobiology underlying attachment. Furthermore, emerging research in voles, additional laboratory rodents, transgenic mice, primates, and humans has provided novel insight into the neurochemical mechanisms underlying the therapeutic effects of social bonds reducing anxiety, depression, and drug abuse liability. In the present review, we highlight the work from this burgeoning field and focus on the role(s) of the neuropeptides oxytocin (OT), vasopressin (AVP), and corticotrophin releasing hormone (CRH) mediating stress buffering. Together, the data suggest that OT underlies social bonding to reduce stress-induced psychological illness while AVP and CRH facilitate arousal to enhance autonomic reactivity, increasing susceptibility to adverse mental and physical health.

Introduction

Stable social relationships are necessary for maintaining human health. Conversely, breaking bonds can create severe emotional and physical distress including passive-stress coping states involving anxiety, depression, and vulnerability to drugs of abuse. However, we know little regarding how the brain changes and responds to social attachment and partner loss. Thus, in order to better understand the adverse psychological manifestations caused by breaking pair-bonds, the establishment of an animal model that exhibits strong face validity to human attachment is necessary to investigate basic neurobiological mechanisms underlying the effects of social-buffering modulating the stress response. Because male and female prairie voles (*Microtus ochrogaster*) form enduring social pair-bonds after mating and extended cohabitation, these rodents provide an innovative animal model system to investigate the neurobiology of social attachment and partner loss. While a laundry list of neurotransmitters, peptides, molecules, and genes in the central nervous system (CNS) has been implicated in attachment behavior in voles (Young and Wang, 2004), here we focus primarily on the role of neuropeptides modulating bonding behavior and stress.

Coping represents a psychological state where an individual consciously establishes a set of specific goals to reduce physiological harm during stressful life experiences (Lazarus and Folkman, 1984, Lazarus, 1999). Due to the extreme frequency of adverse life events that people endure during life, several definitions and conceptual frameworks have been proposed. There is a vast literature in which the term "coping", as it pertains to stress, is classified. Here, we focus on the role of sociality within the context of stress social buffering. Social-buffering is a phenomenon whereby socio-sexual interactions protect an individual from adverse physiological and psychological consequences of stress during challenging situations (Lazarus and Folkman, 1984, Lazarus, 1999). This phenomenon is well known in humans, however — only recently, has it begun to be characterized in laboratory animals.

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Because mating induces arousal associated with anxiolytic-like states accompanied by sedation and calmness, it was originally hypothesized that sexual activity reduces anxiety because of central oxytocin (OT) release. In support of this hypothesis, in 1989, Flannery & Wieman found that OT was released in the paraventricular nucleus of the anterior hypothalamus (PVN) of male rats courting a sexually-receptive female. These anxiolytic effects of sexual activity were blocked by central administration of an OT receptor antagonist administered directly after mating but had no effects in non-mated male rats. This work demonstrated a critical role of central OT underlying anxiolytic effects associated with mating and social-buffering of the stress response. Later work revealed that exogenous central infusions of OT, but not vasopressin (AVP), reduced stress-induced corticosterone (CORT) release and anxiety-like behavior in female rats (Windle et al., 1997). These data suggested that central OT represents a potent anxiolytic, ameliorating both CORT release and anxiety-like states, and thus may play a significant role in buffering physiological responses to stressful life experiences.

In this review, we begin by discussing previous work examining the role of central OT and related neuropeptides (*e.g.*, AVP and CRH) involved in the stress response. We then focus on more recent studies investigating the direct role of OT and its interactions with other peptidergic systems, classical neurotransmitters, and genes underlying social-buffering of stress in voles and expand the review to include information from similar studies using other laboratory rodents, primates, and humans. We conclude by discussing recent work utilizing OT as a potential therapeutic to alleviate stress-induced psychopathology.

Neuropeptides, attachment, and the molecular genetics of sociality

The functional significance of long-term pair-bonding has been documented cross-culturally in humans. Individuals living in stable paired relationships live longer than their unpaired, single, counterparts — across demographic groups (House et al., 1988; Lillard and Waite, 1995). A significant number of humans grieving the loss of a family member or intimate partner experience long, and sometimes short — but intense — periods of post-traumatic stress, major depression, panic attacks, and generalized anxiety (Byrne and Raphael, 1999; Kristensen et al., 2012; Onrust and Cuijpers, 2006; Zivin and Christakis, 2007). Social-buffering serves as a potent anxiolytic, while social isolation, separation, or loss of a familiar conspecific predicts poor mental and physical health (Cohen and Wills, 1985; Flannery and Wieman, 1989; Heinrichs et al., 2003; Karelina and DeVries, 2011; Maulik et al., 2010; Smith and Wang, 2012; Smith et al., 2013), increasing the risk of developing debilitating psychological diseases (Byrne and Raphael, 1997; Elwert and Christakis, 2008a, 2008b; Kristensen et al., 2012; Onrust and Cuijpers, 2006; Rozenzweig et al., 1997; Zivin and Christakis, 2007). Previous clinical research has associated these mental health issues with dysregulation in OT, AVP, and CRH (Dinan et al., 1999; Meyer-Lindenberg et al., 2011; Pitman et al., 1993; Purba et al., 1996; Raadsheer et al., 1994). Thus, elucidating neuropeptidergic mechanisms underlying social-buffering of stress should be an important focus in biomedical research (Hostetler and Ryabinin, 2013).

Neuropeptides and dopamine promote pair-bond formation and maintenance

The prairie vole is a socially monogamous rodent that lives predominantly in the grasslands of the central United States. Adaptation to this harsh environment, with limited access to food and water resources, may have contributed to the evolution of a socially monogamous life strategy in this species (Carter et al., 1995). Pair-bonding behavior in prairie voles has been extensively studied in the field and laboratory settings. After 24 h of cohabitation, with successful mating, male prairie voles exhibit partner preference toward their female partner but not a stranger (Figs. 1A–C; Dewsbury, 1975; Dewsbury, 1987; Getz and Carter, 1996; Getz et al., 1981; Getz et al., 1993; Gray and Dewsbury, 1973; Williams et al., 1992) and become highly aggressive toward unfamiliar male and female conspecifics (Aragona et al., 2006; Gobrogge et al., 2007, 2009; Insel et al., 1995; Wang et al., 1996, 1997; Winslow et al., 1993). Bonded males can retain their partner preference even after two weeks of separation from a female partner (Insel et al., 1995; Bosch et al., 2009). Field work demonstrates that over 75% of prairie voles maintain their bond throughout life (Getz and Carter, 1996; Getz et al., 2003) even when a female partner dies or abandons their male partner 80% of males never bond again (Getz et al., 1993).

In prairie voles, mating increases AVP (Wang et al., 1994) and CRH (Bosch et al., 2009) mRNA expressed in neurons of the bed nucleus of the stria terminalis (BNST) yet decreases AVP processes in the lateral septum (LS) (Bamshad et al., 1994) — brain areas where OT acts to reduce stress. Female prairie voles, on-the-other-hand, exposed to olfactory cues display differences in the density of OT receptors (OTRs) in the accessory olfactory bulb (Witt et al., 1991) and exhibit a significantly higher density of OTRs in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc) compared to promiscuous montane voles (Fig. 1D). Intra-cerebro-ventricular (ICV) infusion of an AVP or OT receptor antagonist reduces partner preference while AVP or OT receptor activation enhances partner preference without mating, in both male (Cho et al., 1999; Winslow et al., 1993) and female (Cho et al., 1999) prairie voles. Site-specific manipulation of neuropeptides in select brain nuclei supports these correlative anatomical findings. For example, micro-infusion of AVP in the LS of sexually naïve males enhances partner preference in the absence of mating (Lim and Young, 2004; Liu et al., 2001). OT release in the NAcc increases when females mate with male prairie voles (Ross et al., 2009a), and OT micro-infusion into the NAcc increases partner preference in the absence of mating. Partner preference can be blocked with concurrent micro-injection of an OTR antagonist in the NAcc (Fig. 1E) and prelimbic cortex (PLC), in the absence of mating (Liu and Wang, 2003; Young et al., 2001). Further, male vole bond formation is facilitated via stress-induced HPA axis activity (DeVries et al., 1996). Sexually naïve males receiving intra-cerebro-ventricular (ICV), or intra-NAcc infusion with CRH display partner preference that can be blocked by co-infusion with a CRH receptor antagonist (DeVries et al., 2002; Lim et al., 2007).

Behavioral genetics of partner preference formation and social memory

Neurogenetic research, employing viral-vector-mediated gene transfer methods, has substantiated the role of OT in the NAcc and AVP in the ventral pallidum (VP) in the facilitation of partner preference in both sexes. OTR over-expression in the NAcc of sexually inexperienced female prairie voles enhanced partner preference formation (Fig. 1F; Ross et al., 2009b) but had no effect in female meadow voles. Thus, NAcc OTR density correlates positively with affiliation and partner preference in monogamous but not polygamous voles (Ross et al., 2009b). Viral vector expression of AVP receptors (V1aRs) in the VP enhanced partner preference in the absence of mating in male prairie voles (Pitkow et al., 2001). Remarkably, V1aR over-expression in the VP of promiscuous male meadow voles recapitulated a socially monogamous life strategy (Lim et al., 2004).

Neurobiobehavioral consequences of stress-induced bereavement

Behavioral manifestations and neurochemistry accompanied by partner loss

Because partner loss in humans activates an entire suite of mental and physical health problems (Shear and Shair, 2005), the socially monogamous prairie vole has been utilized to investigate mechanisms associated with bereavement (*i.e.*, bond loss). Several laboratories have demonstrated depressive-like symptomology, by using the prairie