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Genetics of Aggression in Voles

Kyle L. Gobrogge¹ and Zuoxin Wang

Abstract

Prairie voles (*Microtus ochrogaster*) are socially monogamous rodents that form pair bonds—a behavior composed of several social interactions including attachment with a familiar mate and aggression toward conspecific strangers. Therefore, this species has provided an excellent opportunity for the study of pair bonding behavior and its underlying neural mechanisms. In this chapter, we discuss the utility of this unique animal model in the study of aggression and review recent findings illustrating the neurochemical mechanisms underlying pair bonding-induced aggression. Implications of this research for our understanding of the neurobiology of human violence are also discussed.

I. INTRODUCTION

Mating induces aggression in several organisms throughout the animal kingdom. Within species, patterns of inter- and intrasexual aggression vary as a function of monogamy, parental investment, and group structure. In the wild, the appropriate coordination of social behavior is necessary for survival and reproductive success. How organisms make decisions about which behavior to display in the natural environment remains an important area of biological investigation. To address these questions, previous work has relied on using traditional laboratory rodents. However, these animals do not readily display certain types of social behaviors and thus are not appropriate for some investigations. For example, laboratory rats and mice do not exhibit strong social bonds between mates, and males typically do not display paternal behavior or female-directed aggression. Because mating naturally induces pair bonding, aggression, and biparental behavior in the socially monogamous prairie vole (*Microtus ochrogaster*), this species represents a unique animal model to study the underlying neural mechanisms regulating social behavior associated with a monogamous life strategy.

In this chapter, we begin by describing the prairie vole model and reviewing the neural correlates of pair bonding behavior. We focus on the neuropeptides arginine vasopressin (AVP) and oxytocin; neurotransmitters dopamine (DA), gamma-aminobutyric acid (GABA), and glutamate; and steroid hormones testosterone and estrogen in the regulation of aggression. We highlight the molecular genetics underlying courtship and aggression associated with monogamous pair bonding in voles and humans. Finally, we speculate on the potential for translation, of aggression studies in prairie voles, for research examining the etiology of violence in human populations—with a particular emphasis on the interactions between drug abuse and social behavior.

¹Present address: Department of Neurobiology, Harvard Medical School, Boston, Massachusetts, USA

II. THE PRAIRIE VOLE MODEL

Voles are microtine (*Microtus*) rodents that are taxonomically and genetically similar, yet show remarkable differences in their social behavior (Young and Wang, 2004; Young *et al.*, 2008, 2011a). These animals have provided an excellent opportunity for comparative studies examining social behaviors associated with different life strategies. For example, prairie (*M. ochrogaster*) and pine (*M. pinetorum*) voles are highly social and monogamous, whereas meadow (*M. pennsylvanicus*) and montane (*M. montanus*) voles are asocial and promiscuous (Dewsbury, 1987; Insel and Hulihan, 1995; Jannett, 1982). In the laboratory, prairie and pine voles are biparental, with both parents equally caring for their young, while meadow and montane voles are primarily maternal and males do not stay in the natal nest after female parturition (McGuire and Novak, 1984, 1986; Oliveras and Novak, 1986). Following mating, prairie voles develop pair bonds between mates (Fig. 6.1A; Young and Wang, 2004) and males even display aggression selectively toward conspecific strangers but not toward their familiar partner (Fig. 6.1B; Aragona *et al.*, 2006; Gobrogge *et al.*, 2007, 2009; Winslow *et al.*, 1993)—behaviors that are not exhibited by promiscuous meadow or montane voles (Insel *et al.*, 1995; Lim *et al.*, 2004). Interestingly, these vole species do not differ in their nonsocial behavior (Tamarin, 1985), further indicating associations between species-specific social behavior and life strategy (Carter *et al.*, 1995; Insel *et al.*, 1998; Wang and Aragona, 2004; Young and Wang, 2004; Young *et al.*, 1998). Therefore, prairie voles represent a unique model system to dissect the neural mechanisms underlying ethologically relevant social behavior.

One behavioral index of pair bonding is selective aggression, which is more prominent in male than in female prairie voles. It has been suggested that selective aggression is a behavioral trait associated with mate guarding that is important for pair bonding (Carter *et al.*, 1995). Selective aggression is studied using a resident–intruder test (RIT) (Fig. 6.1C; Gobrogge *et al.*, 2007, 2009; Winslow *et al.*, 1993; Wang *et al.*, 1997a). A conspecific intruder is introduced into the male resident cage and their behavioral interactions are videotaped for 5–10 min (Aragona *et al.*, 2006; Gobrogge *et al.*, 2007, 2009; Wang *et al.*, 1997a; Winslow *et al.*, 1993). Subject's behavioral interactions with the intruder are recorded and the frequency of aggressive behaviors including attacks, bites, chases, defensive/offensive upright postures, offensive sniffs, threats, and retaliatory attacks are calculated as a composite score (Gobrogge *et al.*, 2007, 2009) as well as the duration of affiliative side-by-side physical contact (Gobrogge *et al.*, 2007, 2009; Winslow *et al.*, 1993). It is important to note that both offensive and defensive types of aggression are critical components of selective aggression in male prairie voles (Wang *et al.*, 1997a; Winslow *et al.*, 1993).

Selective aggression is associated with mating, as cohabitation in the absence of mating does not induce this behavior in male prairie voles (Insel *et al.*, 1995; Wang *et al.*, 1997a; Winslow *et al.*, 1993). Selective aggression is also enduring (Aragona *et al.*, 2006; Gobrogge *et al.*, 2007, 2009; Insel *et al.*, 1995) and lasts for at least 2 weeks after partner preference formation (Aragona *et al.*, 2006; Gobrogge *et al.*, 2007, 2009), even in the absence of continuous exposure to a partner (Insel *et al.*, 1995). Importantly, males display aggression not only toward conspecific males (Fig. 6.1B; Aragona *et al.*, 2006; Gobrogge *et*

al., 2007, 2009; Insel *et al.*, 1995; Wang *et al.*, 1997a; Winslow *et al.*, 1993) but also toward sexually receptive females (Fig. 6.1B and C; Gobrogge *et al.*, 2007, 2009). This selective aggression functions to maintain monogamous pair bonds as males reject potential female mates (Fig. 6.1B and C; Aragona *et al.*, 2006; Gobrogge *et al.*, 2007, 2009; Wang *et al.*, 1997a). Together, these reliably expressed and measurable agonistic behaviors make the prairie vole an excellent model for investigation of the neural mechanisms underlying naturally occurring aggression associated with monogamy. It should be mentioned that although female aggression has been less studied in voles, female prairie voles exhibit similar aggressive behavior as males and this behavior is influenced by a female's social and sexual experience (Bowler *et al.*, 2002).

III. NEURAL CORRELATES

With considerable overlap of brain areas involved in several forms of social (Newman, 1999) and agonistic (Table 6.1) behaviors, there is a significant amount of ambiguity regarding which brain areas may be involved in the regulation of selective aggression. Using a neuronal activation marker of an immediate early gene, *c-fos*, previous studies in voles have examined neuronal activity associated with aggression (Wang *et al.*, 1997a), maternal (Katz *et al.*, 1999) and paternal behavior (Kirkpatrick *et al.*, 1994), mating (Curtis and Wang, 2003; Lim and Young, 2004), anxiety (Stowe *et al.*, 2005), spatial learning (Kuptsov *et al.*, 2005), chemosensory processing (Hairston *et al.*, 2003; Tubbiola and Wysocki, 1997), social experience (Cushing *et al.*, 2003a; Kramer *et al.*, 2006), or pharmacological challenges (Curtis and Wang, 2005b; Cushing *et al.*, 2003b; Gingrich *et al.*, 1997). Within these studies, however, typically only one type of behavior was investigated. Little focus was aimed at examining other forms of social behavior, including affiliation or general social olfactory processing. Consequently, there is considerable overlap in brain-behavior relationships among these studies leading to ambiguity as to which brain areas regulate selective aggression. Nevertheless, in an early study, male prairie voles displayed aggression toward a male intruder following 24 h of mating, but not following 24 h of cohabitation with a female without mating (Wang *et al.*, 1997a). However, despite their differences in sociosexual experience and in aggressive behavior, both types of male exposure led to equal levels of Fos-ir (immunoreactivity) expression in some brain areas, such as the bed nucleus of the stria terminalis (BNST). Males that mated for 24 h and displayed high levels of aggression toward either a male or a female intruder showed increased levels of Fos-ir expression in the medial amygdala (MeA; Wang *et al.*, 1997a), compared to males that cohabitated with a female without mating, implicating the MeA as a brain area associated with the display of mating-induced selective aggression (Fig. 6.1D and E).

In a more recent study, several brain areas including the BNST, medial preoptic area (MPOA), paraventricular nucleus (PVN), and lateral septum (LS) showed higher levels of Fos expression in pair bonded males that had experienced an RIT compared to pair bonded males not exposed to a social intruder (Gobrogge *et al.*, 2007). However, no group differences in Fos expression across these brain areas were found among males that were exposed to different social stimuli or displaying different patterns of social behavior, including aggression or affiliation toward intruders. These data suggest that the increased neuronal activation in these brain regions is probably due to olfactory stimulation or general

arousal associated with exposure to a conspecific, but such a response is nonselective. A unique pattern of Fos expression was found in the anterior hypothalamus (AH), in which exposure to a conspecific stranger, either male or female, induced a significant increase in AH-Fos over those reexposed to their familiar partner (Fig. 6.1D and E; Gobrogge *et al.*, 2007). This increase in Fos staining may indicate a stimulus-specific response. The AH appears to be more responsive to chemosensory, tactile, and/or visual cues associated with conspecific strangers, but not familiar partners (Gobrogge *et al.*, 2007). These data indicate that the increased neuronal activation in the AH may be involved in aggressive behavior displayed by pair bonded male prairie voles (Gobrogge *et al.*, 2007). This notion is corroborated by previous research documenting a critical role of the hypothalamus in regulating aggression across several mammalian species. For example, the ventromedial hypothalamus (VMH) in mice (Choi *et al.*, 2005; Lin *et al.*, 2011) and AH in rats (Veening *et al.*, 2005) is responsive to conspecific chemosensory cues, which elicit aggressive behavior. Electrical stimulation applied directly to the AH induces attack toward conspecifics in rats (Kruk, 1991) and other animals (Albert and Walsh, 1984; Siegel *et al.*, 1999). Interestingly, in humans, surgical lesioning of the AH reduces physical violence (Ramamurthi, 1988; Sano *et al.*, 1966). In summary, data from vole studies demonstrate that activation of the MeA and AH is associated with the display of selective aggression (Gobrogge *et al.*, 2007; Wang *et al.*, 1997a).

IV. NEURAL CIRCUITRY

To directly evaluate the neural circuitry programming selective aggression, we performed a series of tract tracing experiments focusing on the AH and MeA. Intra-AH injections of an anterograde tracer, biotinylated dextran amine (BDA), resulted in BDA-ir staining in several brain regions. The AH projected to areas involved in processing chemosensory cues including the MeA; areas important for regulating social behavior including the LS, BNST, MPOA, VMH, and dorsal raphe (DR); and areas coordinating motor output, such as the periaqueductal gray (Gobrogge and Wang, 2009). The AH also projected to brain areas implicated in evaluating incentive salience including the medial prefrontal cortex (mPFC), nucleus accumbens (NAcc), and ventral pallidum (VP), as well as areas involved in memory formation and consolidation including hippocampal regions CA3 and the dentate gyrus (Gobrogge and Wang, 2009). Further, site-specific injections of a retrograde tracer, fluorogold (FG), into the LS, NAcc, or MeA resulted in FG-ir staining in the AH, indicating reciprocal connections between the AH and regions involved in motivation and chemosensory communication (Gobrogge and Wang, 2009).

Fos-ir staining was also used to assess neuronal activation, in this circuit, associated with the display of pair bonding behavior. Males displaying aggression toward an unfamiliar female showed a significantly higher density of Fos-ir in the AH and MeA relative to males displaying affiliation toward their female partner (Fig. 6.1D and E), replicating our previous findings (Gobrogge *et al.*, 2007; Wang *et al.*, 1997a). Interestingly, we identified a MeA-AH-LS circuit that was activated when males were displaying aggression and a DR-AH circuit that was recruited when males were displaying affiliation (Gobrogge and Wang, 2009). The identification of these two neural circuits indicates a specific neuronal

framework associated with the choice between affiliation (DR-AH circuit) and aggression (MeA-AH-LS circuit) in pair bonded male prairie voles.

V. NEUROCHEMICAL REGULATION OF SELECTIVE AGGRESSION

Previous work has primarily focused on partner preference formation and documented a growing list of neurochemicals, including oxytocin (OT), AVP, corticotropin releasing hormone, DA, GABA, and glutamate, as well as their interactions in the regulation of pair bonding behavior (Aragona *et al.*, 2003; Curtis and Wang, 2005a,b; Carter *et al.*, 1995; DeVries *et al.*, 1995; Gingrich *et al.*, 2000; Lim and Young, 2004; Liu and Wang, 2003; Lim *et al.*, 2004; Liu *et al.*, 2001; Smeltzer *et al.*, 2006; Wang *et al.*, 1998, 1999; Williams *et al.*, 1992, 1994; Winslow *et al.*, 1993). Importantly, data from several studies indicate a select subset of neurochemicals in the regulation of selective aggression.

A. Neuropeptides

Comparative approaches have been utilized in studies examining neuroendocrine mechanisms regulating social behavior in voles (Insel, 2010). Studies have focused on examining the central AVP system, a nine amino acid neuropeptide with diverse forebrain projections, across monogamous and promiscuous vole species. AVP is an antidiuretic hormone and has been shown to stimulate three structurally distinct receptors V1a, V1b, and V2, each activating very specific second messenger systems (Michell *et al.*, 1979). Classically, AVP was first described as a primary homeostatic factor controlling kidney water reabsorption, blood volume/pressure, and vasodilatation in the peripheral nervous system. AVP and its receptors have been shown to be widely expressed in the central nervous system (Thibonnier, 1992), within specific brain regions (Johnson *et al.*, 1993).

The V1a AVP receptor subtype (V1aR), in particular, has been extensively studied in the regulation of social behavior (Insel *et al.*, 1994) including aggression (Albers *et al.*, 2006; Cooper *et al.*, 2005; Ferris *et al.*, 2006; Winslow *et al.*, 1993). V1aRs are directly coupled to stimulatory (s) Gq-11 proteins (Thibonnier *et al.*, 1993). Stimulation of these G-proteins leads to activation of adenylate cyclase, cAMP, protein kinase C, and phospholipases C, A₂, and D (Raggenbass *et al.*, 1991; Thibonnier, 1992; Thibonnier *et al.*, 1992, 1994) enhancing calcium influx through L-type calcium channels (Son and Brinton, 2001). Such activation enhances learning and memory in the aging brain (Deyo *et al.*, 1989; Yamada *et al.*, 1996) via direct effects on gene expression (Murphy *et al.*, 1991).

Because AVP regulates species-specific social behaviors such as aggression (Ferris *et al.*, 1984; Ryding *et al.*, 2008), it was hypothesized that the organization of central AVP systems may differ between monogamous and promiscuous vole species (Bamshad *et al.*, 1993b; Insel and Shapiro, 1992). To test this hypothesis, the distribution pattern of AVP cells, fibers, and receptors were mapped in the vole brain. In all vole species examined, AVP-ir neurons were found in several brain regions, including the PVN and SON (supraoptic nucleus) of the hypothalamus, the BNST, MeA, AH, and MPOA (Bamshad *et al.*, 1993b; Gobrogge *et al.*, 2007; Wang, 1995; Wang *et al.*, 1996). AVP-ir fibers were localized in the LS, lateral habenular nucleus, diagonal band, BNST, MPOA, and MeA (Bamshad *et al.*, 1993b; Wang *et al.*, 1996). Overall, AVP distribution patterns were highly conserved

between monogamous and promiscuous vole species (Wang, 1995; Wang *et al.*, 1996). Dramatic species differences in the distribution patterns and regional densities of V1aRs, however, were observed between vole species exhibiting different life strategies (Hammock and Young, 2002). For example, prairie voles have higher densities of V1aRs in the BNST, VP, central and basolateral nuclei of the amygdala, and accessory olfactory bulb, whereas montane voles exhibit a higher density of V1aRs in the LS and mPFC (Insel *et al.*, 1994; Lim *et al.*, 2004; Smeltzer *et al.*, 2006; Wang *et al.*, 1997c; Young *et al.*, 1997). Further, prairie and pine voles exhibit similar patterns of V1aR binding, which differ from that of promiscuous meadow and montane voles (Insel *et al.*, 1994; Lim *et al.*, 2004). Species differences in V1aR distribution are stable across the lifespan (Wang *et al.*, 1997b,c) and are receptor-specific, as no species differences are found in either the benzodiazepine or opiate receptor systems (Insel and Shapiro, 1992). In addition, monogamous prairie and promiscuous meadow voles differ in central AVP activity during mating and reproduction (Bamshad *et al.*, 1993a; Wang *et al.*, 1994). Because of these anatomical and functional differences, central AVP was thought to underlie selective aggression in male prairie voles (Winslow *et al.*, 1993).

Among the neuropeptides underlying aggression (Miczek *et al.*, 2007; Siever, 2008), AVP, and its homolog vasotocin, have been found to regulate several forms of aggression across species (Caldwell *et al.*, 2008; Ritters and Panksepp, 1997) and diverse taxa (Backstrom and Winberg, 2009; Goodson, 2008). In humans, central AVP correlates with aggressive behavior (Coccaro *et al.*, 1998) and mediates anger (Thompson *et al.*, 2004). Thus, the central AVP system may have evolved to be primed by a wide variety of experiences to induce aggression, when appropriate, in social animals (Donaldson and Young, 2008). Because central AVP underlies territorial aggression in other rodents (Ferris *et al.*, 1984), AVP was proposed to regulate mating-induced aggression in prairie voles. In a pharmacological study, injections of a V1aR antagonist (V1aR Ant) into the lateral ventricle of male prairie voles blocked selective aggression induced by mating whereas injections of AVP-induced aggression toward an intruder in the absence of mating (Winslow *et al.*, 1993). These effects were neuropeptide specific, as intracerebroventricular (ICV) infusion of an OT receptor antagonist had no effect on mating-induced aggression (Winslow *et al.*, 1993). Importantly, developmental exposure to either AVP in male prairie voles (Stribley and Carter, 1999) or OT in female prairie voles (Bales and Carter, 2003) facilitates aggression in adulthood. Together, these data highlight a critical role of neuropeptide regulation of prairie vole aggression. However, the action site and release dynamics of neuropeptides in the regulation of selective aggression were unclear.

In a more recent study, it was found that the display of selective aggression was associated with increased neuronal activation in the AH, specifically in neurons expressing AVP (Fig. 6.2A and B; Gobrogge *et al.*, 2007). In a previous study in Syrian hamsters (*Mesocricetus auratus*), aggression has also been shown to be associated with an increase in AVP-ir/Fos-ir double-labeled cells in the nucleus circularis (NC), medial SON (mSON), and surrounding areas ventral to the fornix in the AH (Delville *et al.*, 2000). Our data, combined with previous results from other species, suggest that the AH may be a brain area in which AVP regulates selective aggression. Indeed, AH-AVP has been implicated in various forms of

aggressive behavior. In Syrian hamsters, for example, blockade of V1aRs in the AH diminished offensive aggression (Caldwell and Albers, 2004; Ferris and Potegal, 1988) whereas intra-AH administration of a V1aR agonist enhanced aggressive behavior (Caldwell and Albers, 2004; Ferris *et al.*, 1997). More recently, the density of V1aRs in the AH has been found to increase significantly in Syrian hamsters after their display of offensive aggression (Albers *et al.*, 2006).

Because selective aggression was associated with neuronal activation in the AH, specifically in AVP-containing neurons (Fig. 6.2A and B; Gobrogge *et al.*, 2007), we tested the hypothesis that selective aggression is associated with AH-AVP release. *In vivo* brain microdialysis, with ELISA, was performed on male prairie voles that were pair bonded for 2 weeks. Pair bonded males displayed significantly higher levels of aggression toward novel females but more side-by-side affiliation with their familiar female partner (Gobrogge *et al.*, 2009). ELISA analysis indicated that exposure to a stranger female, compared to a familiar partner, increased AH-AVP release (Fig. 6.2C), which is further confirmed by correlation analyses indicating that AH-AVP release was coupled positively with aggression and negatively with affiliation (Gobrogge *et al.*, 2009). Moreover, intra-AH administration of AVP at a high (500 ng/side), but not a low (5 ng/side), dose in sexually naïve males induced aggression toward a novel female, and this effect was mediated by V1aR as concurrent administration of a 10-fold higher dose of a V1aR Ant blocked AVP-induced aggression (Fig. 6.2D; Gobrogge *et al.*, 2009). Further, intra-AH infusions of a V1aR Ant (5 µg/side), in pair bonded males, blocked aggression and facilitated social affiliation toward novel females (Fig. 6.2D; Gobrogge *et al.*, 2009). Thus, AH-AVP is both necessary and sufficient to regulate mating-induced selective aggression in male prairie voles.

Prior research has shown that the social environment has a significant impact on signaling and structural components of AVP systems in the brain. In marmoset monkeys, for example, prefrontal V1aR increases during fatherhood (Kozorovitskiy *et al.*, 2006). In hamsters, several social and drug paradigms have been shown to directly alter the AH-AVP system to regulate offensive aggression (Ferris *et al.*, 1989; Grimes *et al.*, 2007; Harrison *et al.*, 2000b; Jackson *et al.*, 2005). In a previous study in male prairie voles, cohabitation with a female significantly increased the number of AVP mRNA labeled cells in the BNST (Wang *et al.*, 1994). Because social isolation increases the density of V1aRs in the AH to regulate offensive aggression in golden hamsters (Albers *et al.*, 2006), we tested the hypothesis that the density of AH-V1aR changes with pair bonding experience to engage selective aggression. Pair bonded males showed higher densities of V1aR binding, site specifically, in the AH (Fig. 6.2E), with no change in OT receptor binding, demonstrating that pair bonding experience induces a neural plastic reorganization of V1aRs in a region- and receptor-specific manner (Gobrogge *et al.*, 2009). To determine whether this increase in V1aR density in the AH, following pair bonding, was directly related to the emergence of aggression toward novel females, we used viral vector mediated gene transfer to artificially elevate V1aR density in the AH. Males that received intra-AH infusions of the AAV-V1aR displayed higher levels of aggression toward a novel female compared to control males that received infusions of the *LacZ*-gene (Fig. 6.2F; Gobrogge *et al.*, 2009). Similar viral vector mediated increases in V1aR expression in the VP in voles (Lim *et al.*, 2004; Pitkow *et al.*,

2001) and LS in mice (Bielsky *et al.*, 2005) enhanced affiliation. In male rats, intermale aggression correlates with AVP release in the LS while AVP release in the BNST is inversely related to aggression levels (Veenema *et al.*, 2010). Together, these data support the notion that region-specific AVP functioning regulates specific types of social behaviors, and multiple brain regions serve as a circuit in which AVP coordinates a range of adaptive behaviors important for reproductive success.

B. Dopamine

Anatomically, central DA is divided into three distinct pathways: nigrostriatal, incertohypothalamic, and mesocorticolimbic. DA cell bodies projecting from the substantia nigra synapse in the dorsal striatum and comprise the nigrostriatal path (Swanson, 1982). Incertohypothalamic paths extend from DA cell bodies of the A12–14 cell groups and project to the MPOA and PVN (Cheung *et al.*, 1998). The mesocorticolimbic path represents DA cell bodies originating in the ventral tegmental area (VTA; Fig. 6.3C) projecting to the mPFC and NAcc (Fig. 6.3C; Carr and Sesack, 2000; Swanson, 1982). In addition, DA cells in the AH (Fig. 6.3B) project to forebrain areas including the striatum, LS, NAcc, and mPFC (Alcaro *et al.*, 2007; Lindvall and Stenevi, 1978; Maeda and Mogenson, 1980).

DA preferentially binds to two families of receptors: D1-like and D2-like. Both types of DA receptors are found in the mPFC, NAcc, LS, and MeA (Boyson *et al.*, 1986). D1-like receptors are directly coupled to both stimulatory (s) G α and G α_{olf} proteins (Neve *et al.*, 2004). Stimulation of these G-proteins leads to activation of adenylate cyclase, cAMP, and protein phosphatase-1 inhibitor DARPP-32 (Neve *et al.*, 2004). Conversely, D2-like receptors couple to inhibitory (i) G α proteins and, when activated, downregulate adenylate cyclase, cAMP, and protein phosphatase-1 inhibitor DARPP-32 (Neve *et al.*, 2004). D1-receptor stimulation plays a critical role in calcium influx, via L-type calcium channels, which is important for cellular long-term potentiation facilitating learning and memory in the aging brain (Deyo *et al.*, 1989; Yamada *et al.*, 1996) through direct influences on gene expression (Murphy *et al.*, 1991).

Because mesocorticolimbic DA underlies partner preference formation (Aragona and Wang, 2009; Aragona *et al.*, 2003; Gingrich *et al.*, 2000; Gobrogge *et al.*, 2008; Wang *et al.*, 1999), studies focused on examining the potential role of central DA regulating selective aggression (Gobrogge *et al.*, 2008). Pair bonded male prairie voles have significantly higher levels of DA D1-type receptors (D1Rs), but not D2-type receptors (D2Rs), in the NAcc (Fig. 6.3D and E; Aragona *et al.*, 2006). Males that cohabitated with a female for 24 h, with or without mating, did not exhibit an increase in D1Rs in the NAcc, supporting the idea that upregulation of NAcc D1Rs, after pair bonding, may directly regulate selective aggression. To test this notion, pair bonded male prairie voles were injected with a D1R antagonist (D1R Ant) into the NAcc. NAcc-D1R, not D2R (D2R Ant), antagonism was sufficient to block selective aggression in pair bonded male prairie voles (Fig. 6.3F; Aragona *et al.*, 2006). In other work, both brief and extended cohabitation with unfamiliar conspecifics in female prairie voles significantly increased the number of DA-ergic cells in the BNST and MeA (Cavanaugh and Lonstein, 2010) and blocking D2Rs, during development, decreased aggression-related behavior including infanticide in adult female, but not male, prairie voles

(Hostetler *et al.*, 2010). Further, pair bonded male prairie voles—displaying aggression toward either male or female intruders, had a significantly higher density of cells in the AH that were double-labeled for tyrosine hydroxylase-ir (TH—rate-limiting enzyme in DA biosynthesis) and Fos-ir than males not exposed to a social stimulus or males that were re-exposed to their familiar female partner (Fig. 6.3A and B), implicating AH-DA involvement in selective aggression (Gobrogge *et al.*, 2007).

C. Steroid hormones

Physical aggression is significantly more common in males than females and these behavioral sex differences have been observed across many species (Gatewood *et al.*, 2006). Research describing biological contributions underlying these sex differences has focused primarily on steroid hormones (Gatewood *et al.*, 2006). Several studies have examined the role of androgens in the development of aggressive behavior, both organizationally (e.g., treatment with prenatal testosterone) and activationally (e.g., treatment with postnatal testosterone). Previous research has found that prenatal androgen exposure increases the behavioral expression of adult aggression (Michard-Vanhee, 1988; Vale *et al.*, 1972). Although organizational and activation influences of androgen on aggression have been noted, some inconsistent results have been reported. For example, castration in male rats (Koolhaas *et al.*, 1990) and male prairie voles (Demas *et al.*, 1999) has no effect on aggression. Thus, circulating testosterone, alone, cannot solely contribute to the expression of aggressive behavior in all rodent species. However, these findings do not rule out the possible effects of testosterone having organizational influences on other neurochemical systems in the brain—which, together, may regulate aggression in adulthood. Thus, neurochemical–steroid hormone interactions—underlying aggression—have also been examined. For example, AVP administered directly into the MeA facilitates territorial aggression in male rats and is sufficient to block the effects of castration on reducing aggression (Koolhaas *et al.*, 1990). Further, castration (Bermond *et al.*, 1982), but not ovariectomy (Kruk *et al.*, 1984), decreases the excitability of neurons in the AH—blocking electrically induced aggression, which in castrates can be reversed by testosterone treatment (Bermond *et al.*, 1982). Therefore, circulating testosterone may be acting as a potent neuromodulator—interacting with neurochemicals, like AVP, to regulate aggression.

Additional evidence demonstrating steroid hormone–neurotransmitter interactions exists in research investigating central DA. For example, 75% of TH-ir expressing cells in the hamster posterior MeA contain androgen receptors, are DA-ergic (i.e., they do not co-label with DA beta hydroxylase), and are highly influenced by gonadal hormones compared to TH-ir cells found in the anterior MeA (Asmus and Newman, 1993; Asmus *et al.*, 1992). Interestingly, this same group of TH-ir cells is found in the posterior MeA and BNST in male prairie voles, which appears to be influenced by testosterone (Northcutt *et al.*, 2007) and activated after mating and social experience (Northcutt and Lonstein, 2009). Together, these data suggest interactions between steroid hormones and central DA, in areas such as the MeA, in processing chemosensory cues related to social communication.

D. Classical neurotransmitters

In addition to the effects of neurotransmitters and hormones on aggression, neuromodulators such as GABA and glutamate have also been shown to be involved in the display of agonistic behavior. For example, microinjection of a GABA antagonist (Adams *et al.*, 1993; Roeling *et al.*, 1993) with concurrent treatment of a glutamate agonist (Haller *et al.*, 1998) in the AH facilitates attack behavior in rodents—with higher doses having greater behavioral effects. Further, reverse microdialysis infusion with a glutamate agonist and a GABA-A antagonist into the AH of rats, recently having experienced an agonistic encounter, also facilitates aggression (Haller *et al.*, 1998). Finally, it is worth mentioning that neuromodulators in the VTA, which provides the major source of DA projections to the NAcc (Fig. 6.3C) and mPFC, are also involved in pair bonding behavior. Glutamate and GABA receptor blockade in the VTA, which alters DA activity in the NAcc, induces partner preference formation in the absence of mating in male prairie voles (Curtis and Wang, 2005b).

VI. MOLECULAR GENETICS OF SELECTIVE AGGRESSION

Monogamous male prairie voles carry several repetitive microsatellite DNA sequences in the promoter region of the V1aR gene that are not found in promiscuous male voles (Hammock and Young, 2002, 2004; Young, 1999). These genetic differences directly contribute to species differences in social organization (Landgraf *et al.*, 2003; Lim *et al.*, 2004; Pitkow *et al.*, 2001). Further, mice carrying a transgene coding for the prairie vole V1aR exhibit central V1aR patterns similar to prairie voles and, when injected with AVP, display enhanced social affiliation (Young *et al.*, 1999). Male voles injected in the VP, with a virus expressing V1aR, display enhanced partner preference in the absence of mating (Lim *et al.*, 2004; Pitkow *et al.*, 2001). Interestingly, individual variability in the genetic sequences coding V1aRs has revealed remarkable within species differences in the strength of monogamous pair bonds in prairie voles (Hammock and Young, 2005; Ophir *et al.*, 2008).

Because prairie voles carry varying lengths of DNA to code V1aRs (Hammock and Young, 2005), this genomic predisposition enables their brain to dynamically express V1aRs after sociosexual experience. This genetic loading distinguishes prairie voles from traditional laboratory rodents that lack this genetic makeup. Future work would benefit from comparing aggression levels between male prairie voles carrying long versus short versions of the promoter region encoding the V1aR gene. In humans, polymorphisms in the promoter region encoding V1aR are associated with differences in sociosexual bonding behaviors (Prichard *et al.*, 2007; Walum *et al.*, 2008) including altruism (Israel *et al.*, 2008) and deficits in social communication observed in individuals with autistic spectrum disorders (Israel *et al.*, 2008; Kim *et al.*, 2002; Meyer-Lindenberg *et al.*, 2008). To date, no study has examined potential associations between the V1aR gene and patterns of aggression in humans. Thus, it would be interesting to examine polymorphisms in the V1aR gene in patients with a lifetime history of pathological violence, as the V1aR system may harbor susceptibility genes underlying extreme forms of aggression, increasing the prevalence of homicide and suicide in human populations.

VII. DRUG-INDUCED AGGRESSION

The prairie vole has been established as an animal model for depression related to social separation (Bosch *et al.*, 2009; Grippo *et al.*, 2007). Further, chronic metal ingestion—a potential model for autism—produces social avoidance in male, but not female, prairie voles exposed to unfamiliar same-sex conspecific strangers (Curtis *et al.*, 2010), suggesting a developmental mechanism underlying the social deficits associated with autistic spectrum disorders in humans. Recently, prairie voles have also been utilized to examine the effects of drugs of abuse on pair bonding behavior (Gobrogge *et al.*, 2009; Liu *et al.*, 2010; Young *et al.*, 2011b).

Drug addiction is a significant problem for many humans because drug abuse has such a powerful control over social behavior essential for survival (Kelley and Berridge, 2002; Nesse and Berridge, 1997; Panksepp *et al.*, 2002). In humans, substance abuse has been associated with weapon-related violence and homicide (Hagelstam and Hakkanen, 2006; Madan *et al.*, 2001; Spunt *et al.*, 1998), intimate partner aggression, including partner-directed physical and psychological aggression (Chermack *et al.*, 2008; O'Farrell and Fals-Stewart, 2000), sexual (El-Bassel *et al.*, 2001), and child abuse (Haapasalo and Hamalainen, 1996; Mokuau, 2002; Walsh *et al.*, 2003). Collectively, drug-related violence leads to family system dysfunction and incarceration (Krug *et al.*, 2002), creating significant societal concerns. While aggression research in humans has provided valuable information regarding relationships between drug abuse and violence, animal models have been used to examine neural mechanisms underlying drug-induced aggression.

Drug use can override neurobiological programs to activate maladaptive forms of agonistic behavior, engaging inappropriate types of physical aggression (Swartz *et al.*, 1998) such as domestic violence (Moore *et al.*, 2008) and intimate partner homicide (Farooque *et al.*, 2005). As a result, chronic drug abuse can cause permanent neural reorganization (Nestler and Aghajanian, 1997; White and Kalivas, 1998), impairing the adaptive—social brain (Panksepp *et al.*, 2002), leading to the display of maladaptive social behavior (Wise, 2002). Multiple studies have demonstrated that aggression may be altered shortly after drug exposure and that the directionality of these effects depends on drug, dose, and individual differences between subjects.

Repeated exposure to several drugs of abuse, during adolescence or adulthood, persistently enhances agonistic behaviors, specifically those associated with offensive aggression. For example, Syrian hamsters treated during adolescence with cocaine (DeLeon *et al.*, 2002a; Harrison *et al.*, 2000a; Jackson *et al.*, 2005; Knyshevski *et al.*, 2005a,b; Melloni *et al.*, 2001) or anabolic-androgenic steroids (AASs) (DeLeon *et al.*, 2002b; Harrison *et al.*, 2000b; Melloni and Ferris, 1996; Melloni *et al.*, 1997) display enhanced offensive aggression in adulthood. Interestingly, these drug experiences reorganize AVP (Grimes *et al.*, 2007; Harrison *et al.*, 2000b; Jackson *et al.*, 2005), DA (Ricci *et al.*, 2009; Schwartz *et al.*, 2009), and GABA (Schwartz *et al.*, 2009) signaling in the AH.

For example, when compared with nonaggressive sesame oil-treated control males, aggressive AAS-treated males exhibit significant neuroplastic changes in the AH including

increased AVP-ir fiber density and AVP content (Harrison *et al.*, 2000b), an increase in TH-ir cell and fiber density (Ricci *et al.*, 2009), enhanced DA-D2R expression (Schwartzter *et al.*, 2009), a higher number of GAD₆₇-ir cells (Schwartzter *et al.*, 2009), and decreased GABA_A receptor expression (Schwartzter *et al.*, 2009). Further, pharmacological blockade of D2 (Schwartzter and Melloni, 2010a,b), but not D5 (Schwartzter and Melloni, 2010b), DA receptors in the AH abolishes these effects. Together, results from this work suggests that AVP and DA signaling facilitates aggression by GABA inhibition in the AH of AAS-treated male Syrian hamsters.

As noted above, previous work has shown that exposure to drugs of abuse, such as cocaine, enhances male–male aggression by reorganizing the AH-AVP system in hamsters (Jackson *et al.*, 2005). Therefore, we tested the hypothesis that amphetamine (AMPH), another commonly abused psychostimulant, would act in a similar fashion in affecting male-to-female aggression in prairie voles. Because our recent data revealed that repeated AMPH treatment—(1 mg/ kg) for 3 consecutive days—induces a conditioned place preference (Aragona *et al.*, 2007) and blocks mating-induced partner preference (Fig. 6.4A; Liu *et al.*, 2010), this treatment regimen was used. To examine the selectivity of AMPH-induced aggression, males treated with saline or AMPH were tested for aggression toward an unfamiliar female or a familiar female (that cohabitated with a male across a wire mesh screen for 24 h without mating). Compared with saline-treated controls, AMPH-treated males displayed significantly higher levels of aggression toward either familiar or unfamiliar females (Fig. 6.4B), indicating that AMPH exposure induces generalized aggression, rather than being selective to novel females. This AMPH treatment also induced an increase in the density of AVP-V1aR binding in the AH, but not MPOA, relative to saline control males (Fig. 6.4C). Further, intra-AH infusions of CSF containing the V1aR Ant, but not CSF alone, diminished AMPH-induced aggression toward novel females (Fig. 6.4D). These data suggest that repeated exposure to AMPH can induce female-directed aggression and that this behavior is mediated by AH-AVP. Interestingly, these behavioral effects coincide with upregulation of D1Rs in the NAcc (Liu *et al.*, 2010) and V1aRs in the AH (Gobrogge *et al.*, 2009)—which both facilitate aggression toward novel females (Aragona *et al.*, 2006; Gobrogge *et al.*, 2009); indicating that drugs of abuse can hijack neuroplasticity evolved to maintain monogamous pair bonds.

VIII. CONCLUSIONS AND FUTURE DIRECTIONS

Prairie voles have provided an excellent model system to study the neurobiology of ethologically meaningful aggression associated with monogamous pair bonds. Aggression can be easily manipulated under laboratory conditions and reliably expressed following mating and social cohabitation. Several brain areas: MeA, AH, and NAcc, work in a neural circuit to regulate selective aggression via AVP and DA. Commonly abused drugs, like AMPH, can usurp these neurochemical circuits to engage maladaptive social behavior impairing monogamous pair bonds.

Although male-to-male aggression has been studied in a variety of mammals, we know surprisingly little about male-to-female aggression and its underlying neuromechanisms. Interestingly, pair bonded male prairie voles naturally display aggression toward conspecific

females but not toward their female partner and, therefore, selective aggression allows for investigation of the neurobiology of male-to-female aggression. Data have demonstrated that this form of selective aggression is mediated by elevated AVP release and increased V1aR expression in the AH—priming male prairie voles to respond aggressively to novel females. In addition, data have also shown that the same AH-AVP system mediates generalized, female-directed aggression induced by AMPH. Together with previous research from other animals (Ferris *et al.*, 1989, 1997; Grimes *et al.*, 2007; Harrison *et al.*, 2000b; Jackson *et al.*, 2005; Veenema *et al.*, 2006), these data demonstrate a unique point of convergence in the mammalian brain (Choi *et al.*, 2005; Motta *et al.*, 2009). The AH-AVP system is highly conserved and functions to control different forms of aggression to maintain a wide range of resources important for reproductive success. These highly evolved neuropeptide systems appear to be extremely vulnerable to drugs of abuse, as our data show that hypothalamic AVP controls both naturally occurring as well as drug-facilitated female-directed aggression, suggesting that psychostimulant drugs, like AMPH, are capable of switching adaptive (functional) forms of aggression (e.g., mate guarding) to aberrant (dysfunctional) forms of violent behavior (e.g., partner-directed aggression). Together, these data demonstrate the utility of the prairie vole model for evaluation of the effects of drug abuse on neural systems controlling adaptive forms of aggression—such as mate guarding.

Finally, because other neurochemicals, such as DA (Aragona *et al.*, 2006) and serotonin (Villalba *et al.*, 1997), also regulate selective aggression in prairie voles, offensive aggression related to drug experience (Tidey and Miczek, 1992) and AVP/5-HT interactions mediate aggression in other rodents (Ferris *et al.*, 1997; Veenema *et al.*, 2006), future studies should examine potential neurochemical interactions in the regulation of selective aggression. By understanding the basic neuroendocrinology of pair bonding in prairie voles, we may eventually be able to better clarify the neural chemistry of mental health deficits associated with aberrations in social behavior in patients suffering from drug addiction or pathological violence.

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Figure 6.1.

Neural correlates of selective aggression. (A) After 24 h, but not 6 h, of mating, male and female prairie voles display significantly more time in side-by-side physical contact with an opposite sex familiar partner than with a stranger. (B) Sexually naïve male prairie voles (Naïve) do not display aggression toward a stranger female, whereas 2 weeks of sexual and social experience (Paired) induces selective aggression toward both male and female strangers but not toward familiar female partners. (C) Photo depicts a pair bonded male prairie vole (left) preparing to attack a—sexually receptive—stranger female prairie vole (right). (D) Stereological estimates reveal a significantly higher density of Fos-ir cells in the anterior hypothalamus (AH) and medial amygdala (MeA) of pair bonded males displaying aggression toward a stranger female (Stranger) compared to males displaying affiliation toward their familiar female partner (Partner). (E) Photomicrographs showing Fos-ir (dark nuclear staining) in the AH and MeA from pair bonded males re-exposed to their familiar female partner (Partner) or to a stranger female (Stranger). F: fornix; OT: optic tract. Bars indicate means±standard error of the mean. Bars with different Greek letters differ significantly from each other. * $p<0.05$. Scale bar=100 μ m. Adapted from Aragona and Wang (2009), Gobrogge and Wang (2009), Gobrogge *et al.* (2007), Wang *et al.* (1997a), Winslow *et al.* (1993), and Young *et al.* (2011a).

Figure 6.2.

Vasopressin (AVP) regulation of selective aggression. (A) Pair bonded male prairie voles that display aggression toward female or male strangers exhibit a significantly higher density of AVP-ir/Fos-ir double-labeled cells in the AH relative to pair bonded males re-exposed to their female partner or to males not exposed to any social stimulus (Control). (B) Photomicrograph of AVP-ir cell bodies and fibers (brown cytoplasmic staining), Fos-ir (dark nuclear staining), or AVP-ir/Fos-ir double labeled cells (insert) in the anterior hypothalamus (AH). (C) *In vivo* brain microdialysis reveals a significant increase in AH-AVP release in pair bonded male prairie voles displaying aggression toward a stranger female compared to males reexposed to their female partner. (D) Intra-AH AVP microinfusion, in sexually naïve males (Naïve), is sufficient to induce aggression toward a stranger female compared to control males infused with cerebral spinal fluid (CSF). AH-AVP-induced aggression is blocked with concurrent administration of AVP with a V1aR Ant. Pair bonded males (Paired) display aggression toward stranger females, which is blocked by intra-AH infusion of a V1aR Ant. (E) Pair bonded males (Paired) exhibit a significantly higher density of AVP-V1a receptor (V1aR) binding in the AH relative to sexually naïve males (Naïve). (F) Sexually naïve males infused with an adeno-associated virus expressing the *V1aR* gene (AAV-*V1aR*) in the AH exhibit enhanced aggression toward stranger females relative to males infused with the *LacZ*-gene (Control). F, fornix; OT, optic tract. Bars indicate means $\pm$ standard error of the mean. Bars with different Greek letters differ significantly from each other. * $p < 0.05$. Scale bars=100 μ m, insert scale bars=10 μ m. Adapted from Aragona *et al.* (2006), Gobrogge *et al.* (2007, 2009), and Young *et al.* (2011a).

Figure 6.3.

Dopamine (DA) regulation of selective aggression. (A) Pair bonded male prairie voles that display aggression toward female or male strangers exhibit a significantly higher density of TH-ir/Fos-ir double-labeled cells in the AH relative to pair bonded males re-exposed to their female partner or to males not exposed to any social stimulus (Control). (B) Photomicrograph of TH-ir cell bodies and fibers (brown cytoplasmic staining), Fos-ir (dark nuclear staining), or TH-ir/Fos-ir double labeled cells (insert) in the anterior hypothalamus (AH). (C) Photomicrograph of TH-ir fibers in the nucleus accumbens (NAcc) and neurons in the ventral tegmental area (VTA). (D, E) Pair bonded males (Paired) exhibit a significantly higher density of DA D1-like (D1R), but not D2-like (D2R), receptor binding in the NAcc compared to sexually naïve males (Naïve). (F) Pair bonded males, infused with CSF in the NAcc, display aggression toward a stranger female but not toward their female partner. Concurrent infusion of CSF with a DA D1R antagonist (D1R Ant), but not D2R antagonist (D2R Ant), in the NAcc is sufficient to attenuate pair bonding-induced aggression toward a stranger female. F, fornix; OT, optic tract. Bars indicate means $\pm$ standard error of the mean. Bars with different Greek letters differ significantly from each other. * p <0.05. Scale bars=100 μ m, insert scale bars=10 μ m. Adapted from Aragona *et al.* (2006), Gobrogge *et al.* (2007, 2009), and Young *et al.* (2011a).

Figure 6.4.

Drug experience impairs pair bonding behavior. (A) Pair bonded (Intact) and saline treated (0.0) male prairie voles, receiving 3-day—once daily; repeated injections, spend significantly more time in physical side-by-side contact with their familiar female partner than with an unfamiliar stranger female. Pair bonded males injected (i.p., intraperitoneal) with 1.0 or 5.0 mg/kg amphetamine (AMPH) spent equal amounts of time in physical side-by-side contact with their female partner as with a stranger female. (B, C) Repeated AMPH exposure, in sexually naïve males, increases aggression toward both familiar and unfamiliar females and enhances the density of vasopressin (AVP) receptor (V1aR) expression in the anterior hypothalamus (AH) but not in the medial preoptic area (MPOA). (D) Site-specific microinfusion of an AVP-V1aR antagonist (V1aR Ant) into the AH, of males receiving 3-day repeated AMPH exposure (i.p.), significantly decreases AMPH-induced aggression toward novel females relative to males receiving intra-AH infusions of cerebral spinal fluid (CSF). Bars indicate means±standard error of the mean. Bars with different Greek letters differ significantly from each other. * $p < 0.05$; ** $p < 0.01$. Adapted from Gobrogge *et al.* (2009), Liu *et al.* (2010), and Young *et al.* (2011a).

Table 6.1

Summary of Brain Areas Implicated in Aggression

Brain area	Species	References
Anterior hypothalamus (AH)	Human	Sano <i>et al.</i> (1966), Ramamurthi (1988)
	Prairie vole	Gobrogge <i>et al.</i> (2007, 2009), Gobrogge and Wang (2009)
	Rat	Veening <i>et al.</i> (2005), Kruk (1991), Bermond <i>et al.</i> (1982), Kruk <i>et al.</i> (1984), Adams <i>et al.</i> (1993), Roeling <i>et al.</i> (1993), Haller <i>et al.</i> (1998), Veenema <i>et al.</i> (2006), Motta <i>et al.</i> (2009)
	Syrian hamster	Delville <i>et al.</i> (2000), Ferris and Potegal (1988), Caldwell and Albers (2004), Ferris <i>et al.</i> (1997, 1989), Albers <i>et al.</i> (2006), Harrison <i>et al.</i> (2000b), Jackson <i>et al.</i> (2005), Grimes <i>et al.</i> (2007), Ricci <i>et al.</i> (2009), Schwartz <i>et al.</i> (2009), Schwartz and Melloni (2010a,2010b)
Lateral septum (LS)	Rat	Veenema <i>et al.</i> (2010)
Medial amygdala (MeA)	Human	Ramamurthi (1988)
	Prairie vole	Wang <i>et al.</i> (1997a), Gobrogge and Wang (2009)
	Rat	Koolhaas <i>et al.</i> (1990)
Nucleus accumbens (NAcc)	Prairie vole	Aragona <i>et al.</i> (2006)
Ventromedial hypothalamus (VMH)	Mouse	Choi <i>et al.</i> (2005), Lin <i>et al.</i> (2011)

Brain structures involved in aggression, across species, with corresponding references to ground brain area acronyms used throughout the chapter.