Chapter 16 Neural Regulation of Social Behavior in Rodents

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Social behavior arises from a complex interplay of numerous and often-competing sensory stimuli, the physiological and motivational states of the participants, and the ages and genders of the individuals involved. Overlying the internal responses to a social encounter are a variety of external factors, such as the context in which the encounter occurs, the time of year, environmental conditions, and the outcomes of previous social interactions. To further complicate the situation, each individual in a social encounter must be able to adjust its own actions depending on the responses of other animals. Given such complexity, a detailed understanding of the neural basis of social behavior would seem next to impossible. Nonetheless, considerable progress has been made. By examining individual components of social behavior while controlling for other variables, researchers have begun to parcel out the contributions of specific brain regions and neurochemicals to specific aspects of social behavior.

A comprehensive survey of the hormonal and neural control of all of the different types of rodent social behavior is beyond the scope of a single book chapter. Here, we will concentrate on the neuroanatomical and neurochemical substrates that underlie rodent social structures, with a particular focus on social bonds. Behavior, like all other aspects of a species' natural history, is subject to natural selection. Since the ultimate test of a behavioral repertoire is reproductive success, it is perhaps appropriate to focus on mating systems in addressing the neural control of social behavior. By focusing on mating systems we are able to place a variety of social behaviors into a firm ecological context, since behaviors such as aggression likely derive from the mating system.

Rodents are a diverse group of creatures that inhabit a wide variety of ecological niches. As might be expected of such diversity, rodents display a wide range of mating systems. Males and females of many species often have different mating strategies (Waterman, chap. 3, Solomon and Keane, chap. 4, this volume). However, some environmental conditions require extensive cooperation between the sexes for reproductive success (Kleiman 1977). In these cases, the mating strategies of the two sexes may converge and a monogamous mating system may arise. Only about 3% of mammalian species have been categorized as being monogamous (Kleiman 1977). Within the rodent order, monogamy has arisen several times (Kleiman 1977), in some cases within genera in which other species are not monogamous. This polyphyletic origin to mating systems has presented opportunities for detailed comparative studies of the neural control of social behaviors and how the brains differ between closely related species with different social structures.

Comparative Models

Over the past two decades much research on social behavior has focused on two genera: *Microtus* and *Peromyscus*. Species within *Microtus* or *Peromyscus* often display very similar nonsocial behaviors, such as activity and feeding patterns (Madison 1985), but differ significantly in social interactions and mating systems (Dewsbury 1987; Bester-

Meredith et al. 1999). Most species exhibit a promiscuous mating system. Promiscuous species show little in the way of social ties, typically defend individual territories, and the female usually is the sole caretaker of pups. A few species, however, display characteristics of monogamy such as shared parental care, shared nests even beyond the breeding season, and selective aggression against strangers but not toward the partner. These animals form strong pair bonds with their mate, which are manifested by a preference for social contact with the partner even when other conspecifics are available.

Such species differences in social behavior have been exploited in comparative studies that allow differences in social organization to be correlated with neuroanatomical and neurochemical differences between species. Similarities in nonsocial behaviors suggest that differences found in the brain are more likely to be related to social behavior. Studies using *Peromyscus* and *Microtus* have identified a number of brain regions and neurochemical systems that are critically involved in the central control of socially relevant behaviors but that differ between species with differing mating systems. Although we will concentrate on these genera, we are in no way minimizing the contributions arising from studies using other rodent species. In many cases, work on rats, hamsters, and other species of mice (numerous strains derived from *Mus musculus*) has laid the groundwork for studies in *Peromyscus* and *Microtus,* and we will refer often to such work to provide context for findings in these latter species.

Research in Juveniles

Species differences associated with social behavior arise early in development, even among closely related species. In general, pups of promiscuous species such as the meadow voles (*M. pennsylvanicus*) and montane voles (*M. montanus*) show more rapid development when compared to pups from monogamous pine voles (M. *pinetorum*) and prairie voles (*M. ochrogaster*) (McGuire and Novak 1984; Nadeau 1985; McGuire and Novak 1986; Prohazka et al. 1986). Relative to monogamous species, promiscuous vole species display more advanced neuromuscular development at five days of age, and become independent earlier. Pups from promiscuous vole species eat solid food as early as 8 days of age and wean at 13–14 days, while pups of monogamous vole species are not weaned until about 1 week later (McGuire and Novak 1984). Similarly, among *Peromyscus,* pups of a promiscuous species, the white-footed mouse (*P. leucopus*), open their eyes earlier and wean earlier than do pups of monogamous California mice (*P. californicus*) (reviewed by Layne [1968]).

Behavioral differences reflecting the various social structures also are reflected to some extent in the play behavior of juvenile rodents (Pellis et al. 1989). This is not surprising, since juvenile play behavior may serve to prepare relevant brain circuitry for appropriate adult social behavior (Cooke et al. 2000). In fact, rats (*Rattus norvegicus*) that are deprived of opportunities to engage in play when young display deficits in social behavior as adults (van den Berg et al. 1999). Young prairie voles, which are highly social as adults, display a greater propensity for intimate contact and mutual grooming than do young meadow voles, which are rather asocial as adults (Wilson 1982a). Juveniles of highly social vole species also exhibit more complex play behavior (Pellis and Iwaniuk 1999), and the structure of play differs from that of asocial species (Pellis et al. 1989; Pierce et al. 1991). In play fighting, a passive defense posture is adopted by social species, while a more aggressive defense posture is adopted by nonsocial species (Pellis et al. 1989). Interestingly, the differences in play appear to reflect differences in precopulatory behavioral patterns of adults of each species (Pellis et al. 1989; Pierce et al. 1991).

The differences in juvenile behaviors suggest that there are differences in the central nervous system early in development among rodents with differing social systems. Indeed, several studies have shown that brain development may be delayed in monogamous voles. Allometric relationships are ratios between pairs of measures of an animal, and these ratios may change during development. Vole species with differing mating systems display different allometric relationships between brain mass and body mass during development. Promiscuous vole species switch from an immature allometric growth pattern to an adult pattern earlier in development than do the monogamous voles (Gutierrez et al. 1989), suggesting that brain development is delayed in monogamous voles. These species differences in brain growth may be attributable to the proliferation of new cells. Indices of cell proliferation in the cerebrum suggest that the brains of monogamous pine voles are still undergoing considerable mitotic activity at 5 days postnatally. At the same age, however, mitotic activity is significantly reduced in meadow voles and in other non-pair-bonding species such as rats and mice (Gutierrez et al. 1989). In the same study, monogamous vole species were also found to display a greater increase in cell proliferation in the cerebellum between 2 and 5 days of age compared to that in promiscuous voles, again suggesting that brain development is delayed in monogamous species. This difference may account for the more advanced neuromuscular development displayed by promiscuous vole pups (Prohazka et al. 1986).

In addition to differences in brain growth, the development of neurochemical systems differs between species with differing social systems. For example, brain derived neu-

rotrophic factor (BDNF) is important for the proliferation of neurons as well as for their survival and growth. In some brain areas the promiscuous meadow vole displays adult patterns of BDNF expression at about 2 weeks of age, while the monogamous prairie vole does not show adult patterns until at least 3 weeks of age (Liu, Fowler et al. 2001). It is interesting to note that the timing of the switch to adult patterns of BDNF expression to some extent parallels the timing of weaning and independence in each species. Monogamous prairie voles and promiscuous montane voles also differ in temporal and regional expression of the gene for receptors that bind the neurochemicals vasopressin or oxytocin (Wang and Young 1997; Wang, Young et al. 1997), which, in adults, are critical for social memory and/or for the formation of social attachments in monogamous species (Dantzer et al. 1988; Williams et al. 1994; Wang et al. 1998).

Collectively, these observations demonstrate clear species differences in the ontogeny of the brain that may be important for species-specific social structures. However, it is not clear whether such differences are driven by nature or nurture. This issue typically is addressed in cross-fostering studies. Monogamous California mice, cross-fostered as pups to promiscuous white-footed mice, display some behavior patterns typical of their foster parents as adults (Bester-Meredith and Marler 2001; Bester-Meredith and Marler 2003), and the behavioral differences are correlated with changes within the brain (Bester-Meredith and Marler 2001; Bester-Meredith and Marler 2003). In studies in which pups of a promiscuous vole species were cross-fostered to monogamous parents or in-fostered to conspecific, promiscuous parents, the fostered pups showed a slight preference for the species to which it was fostered (McGuire and Novak 1987) and displayed parental behaviors at a level closer to that of their fostering parents (McGuire 1988). These results suggest that, at minimum, environmental factors can interact with genetics to influence the social behavior of rodents.

Research in Adults

Research in juveniles has provided important information about the development of brain structures and systems that are critical for social function. However, in some cases, the behavioral manifestations of developmental differences seen in juveniles do not occur until sexual maturity. Thus a thorough understanding of the neural control of social behavior also requires examination of the central nervous system in adults.

The formation and maintenance of social attachments between individuals appears to involve primarily two brain circuits (fig. 16.1). The first circuit is comprised of portions of the amygdala, the bed nucleus of the stria terminalis (BST), and the lateral septum. This circuit may serve as a recognition circuit, allowing appropriate social responses to be displayed upon encountering another individual. The second circuit is centered on the nucleus accumbens and includes the ventral tegmental area, ventral pallidum, certain thalamic nuclei, and portions of the cortex (Insel 2003). This circuit may serve to convey incentive value in social interactions. Examination of these two brain circuits illustrates several ways in which species differences in the central nervous system are correlated with species-specific social and mating systems.

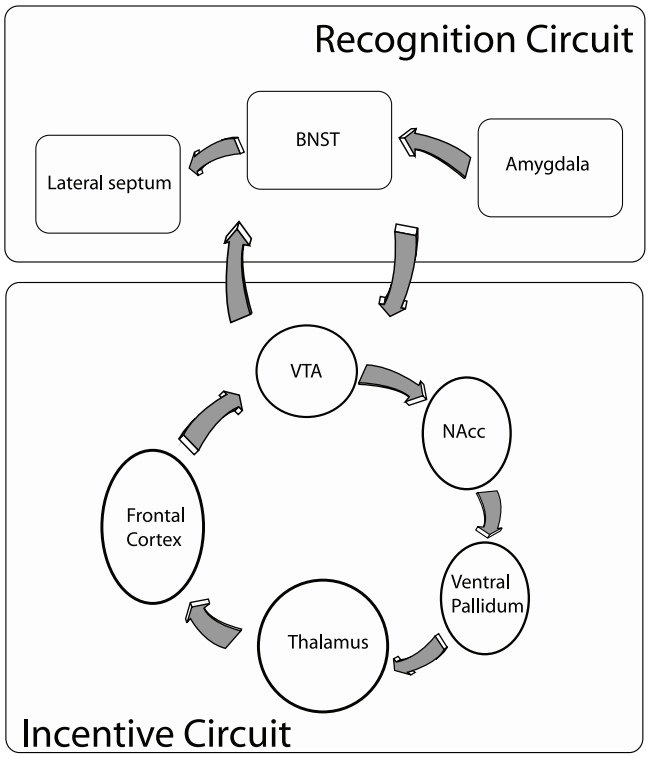

Figure 16.1 The regulation of social attachment appears to involve primarily two brain circuits. The recognition circuit may mediate the ability to distinguish individuals and thus allow context-appropriate social behaviors to be expressed. Information about the identity of another individual from the recognition circuit may modify (or even initiate) responses within the incentive circuit. Feedback from the incentive circuit may then dictate the direction (approach or avoidance, aggressive or nonaggressive, other behaviors) and intensity of the interactions. The incentive circuit was adapted from Insel 2003. BNST—bed nucleus of the stria terminalis, VTA—ventral tegmental area, Nacc—nucleus accumbens.

The Amygdala-BST-Lateral Septum Circuit

In humans, social interactions can elicit a range of emotional responses. Whether rodents experience analogous "feelings" is unknown, but human responses suggest that

a good place to start examining rodent social behavior is the amygdala, the "emotional brain." The amygdala has been implicated in a variety of socially relevant functions including sexual behavior, affiliative behavior, social memory, fear, and learned helplessness (Dominguez et al. 2001; also see Kling and Brothers 1992 for extensive review). Damage to the amygdala can alter the structure of play behavior by juvenile rats (Daenen et al. 2002) and, in fact, in adults, the amygdala is reduced in size in animals that were deprived of play as pups (Cooke et al. 2000). Lesions targeting particular subnuclei of the amygdala show that the medial portion of the amygdala is involved in mediating affiliative behavior in voles (Kirkpatrick et al. 1994). The findings from lesion studies are supported by observations that the amygdala is activated during the early stages of social attachment formation (Curtis and Wang 2003; Cushing et al. 2003). Interestingly, when female voles are exposed to males, the rate at which new cells are added to the amygdala increases (Fowler et al. 2002). Whether these new cells play a role in social behavior is currently being investigated.

The amygdala is an important site for the integration of a variety of sensory inputs. Among the sensory input reaching the amygdala is pheromonal information from the vomeronasal organ (VNO). Such information is important in mediating maternal behavior, pair bonding, and sexual behavior. For example, male mice in which the VNO is impaired fail to increase testosterone levels after exposure to a female and display deficits in sexual behavior (reviewed by Keverne 2002). Under natural circumstances female voles do not experience estrous cycles and require 24 to 48 hours of exposure to a male to induce sexual receptivity (Carter et al. 1987). Such reproductive activation does not occur in females from which the VNO has been removed (Lepri and Wysocki 1987; Curtis et al. 2001). Further, even if sexual receptivity is artificially induced and mating occurs, normally monogamous prairie voles do not form pair bonds after VNO lesions (Curtis et al. 2001), suggesting that pheromonal input is important in mate recognition. The importance of VNO input also is apparent after mating. For example, maternal behavior by female rats in which VNO input has been eliminated can be altered to such an extent that pup survival is compromised (Brouette-Lahlou et al. 1999).

The involvement of the amygdala in social behavior appears to be mediated, at least in part, via projections to the lateral septum, either directly or indirectly via the BST (Caffe et al. 1987). Consistent with inclusion in this pathway, the BST and lateral septum also have been implicated in a number of rodent social behaviors (Wang, Smith et al. 1994; Liu et al. 2001b). But how is information conveyed within the amygdala-BST-lateral septum circuit? The neuropeptide vasopressin has been shown to affect a variety of social behaviors.

Vasopressin and social behavior

Vasopressin is probably most widely known for its peripheral effects. Vasopressin synthesized within the hypothalamus is released via the pituitary and acts as a potent vasoconstrictor, and plays a critical role in body fluid regulation via effects at the level of the kidney. However, in addition to its peripheral effects, vasopressin can also act within the brain. For example, centrally administered vasopressin induces grooming and changes in core body temperature (Drago et al. 1997). Within the central nervous system the majority of vasopressin innervation is found in the amygdala-BST-lateral septum circuit (de Vries and Miller 1998). This extrahypothalamic vasopressin system is sexually dimorphic in rodents. Castration of neonatal male rats produces a pattern of vasopressin innervation similar to that seen in females (de Vries and Miller 1998), suggesting that this dimorphism is regulated by perinatal exposure to gonadal hormones (Wang et al. 1993; de Vries and Miller 1998; Axelson et al. 1999).

Central administration of vasopressin also produces effects on social behavior, such as facilitation of maternal behavior in rats (Pedersen et al. 1982), and induction of selective aggression (Winslow et al. 1993), paternal behavior (Wang, Ferris et al. 1994), and the formation of partner preferences (Winslow et al. 1993; Cho et al. 1999) in monogamous voles. In some cases, the effects of central vasopressin are species-specific. For example, in monogamous prairie voles, central administration of vasopressin induces aggression (Young et al. 1997), whereas the same treatment in promiscuous montane voles does not alter aggression (Young et al. 1997). If vasopressin contributes to social behavior, one might then expect that the vasopressin systems would differ among species with differing social structures. Indeed, there appear to be relationships between the density of vasopressin innervation and/or number of vasopressin receptors and species-specific social structures. The distributions of vasopressin fibers in the brain differ between monogamous and promiscuous species within both *Microtus* and *Peromyscus*. However, between genera, the distribution of vasopressin fibers differs in opposite directions. Males of a monogamous *Peromyscus* species, the California mouse, display a higher density of vasopressin immunoreactive staining in the BST than does the promiscuous white-footed mouse (Bester-Meredith et al. 1999; Bester-Meredith and Marler 2001). In *Microtus,* the opposite pattern is found: monogamous species display less vasopressin innervation in BST than do promiscuous species (Wang 1995). Vasopressin receptor densities also differ between species with differing social structures (fig. 16.2). Again, however, although there are species differences within each genus, a consistent correlation between vasopressin receptors and social structure is not found. For example, in the lateral septum, mo-

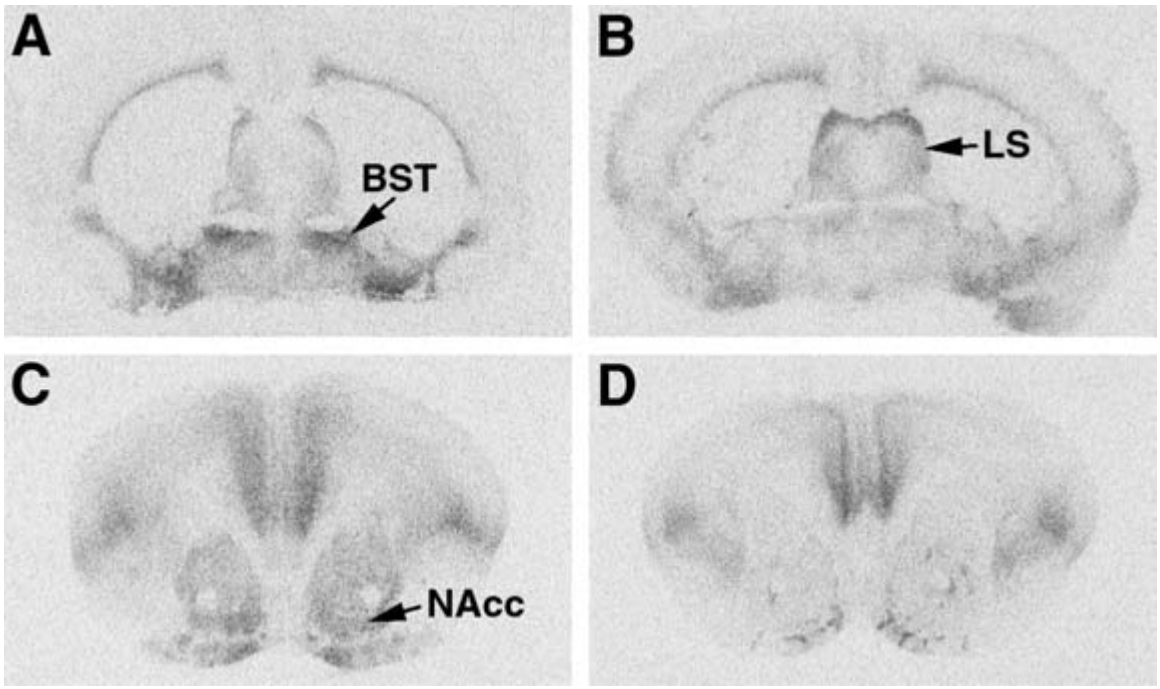

Figure 16.2 Although structurally very similar, the brains of monogamous and nonmonogamous voles differ in the densities and distribution patterns of receptors for many neurotransmitters. Panels A and B show the densities of vasopressin receptors in the bed nucleus of the stria terminalis (BST) and lateral septum (LS) in monogamous prairie voles (A) and nonmonogamous montane voles (B). Such differences in vasopressin receptor density have been correlated with species-specific social structures and patterns of aggression. Panels C and D show the densities of oxytocin receptors in nucleus accumbens (NAcc) in prairie (C) and montane (D) voles. Oxytocin receptor activation plays a critical role in pair bond formation by monogamous voles.

nogamous *Peromyscus* species have a higher density of vasopressin receptors than do promiscuous species (Insel et al. 1991; Bester-Meredith et al. 1999), exactly opposite to the pattern seen for vasopressin receptors in the lateral septum in monogamous and promiscuous *Microtus* species (Insel et al. 1994). There is a consistent correlation between vasopressin receptor densities and mating system in only one brain region, the ventral pallidum (Bester-Meredith et al. 1999), and this region has recently become the focus of several studies (cf. Pitkow et al. 2001).

Vasopressin and aggression

It has been suggested that one aspect of mating systems, species-specific aggression patterns, actually may be a better predictor of vasopressin innervation than is the mating system per se (Bester-Meredith et al. 1999). Within species, differential vasopressin innervation has been associated with individual differences in aggressiveness (Compaan et al. 1993; Everts et al. 1997). In rats, there is a negative correlation between individual aggression and vasopressin fiber density in the lateral septum (Everts et al. 1997). The negative correlation between aggression and vasopressin fiber density is also seen in other species. Aggressive mice have a lower density of vasopressin fibers in the BST than do nonaggressive mice (Compaan et al. 1993), and parental male prairie voles, which are more aggressive than are sexually naive males, have lower vasopressin fiber density in the lateral septum relative to virgin males (Bamshad et al. 1993). Interestingly, no change in vasopressin fiber density is seen in male meadow voles after the birth of pups (Bamshad et al. 1993). This difference may reflect the fact that, after mating, monogamous prairie voles display extensive parental and nest- and mate-guarding behaviors that are not seen in promiscuous meadow voles.

Consistent with our basic premise that many social behaviors derive from the mating system, in some species mating can produce fundamental changes in social behaviors, including aggression. Male prairie voles are very different animals before and after mating (Winslow et al. 1993; Insel et al. 1995; Gammie and Nelson 2000). Sexually naive male prairie voles display little aggression when exposed to a novel male (Winslow et al. 1993). However, after 24 hours of mating, these males become less fearful and more aggressive (Insel et al. 1995). Even the pattern of agonistic behavior changes: attack bites are added to the pre-mating repertoire of defensive and threat-type behaviors (Insel et al. 1995). The transition from defense to attack appears to be mediated by vasopressin. Blockade of vasopressin receptors prior to mating blocks mating-induced aggression, while treatment with vasopressin induces aggression in the absence of mating (Winslow et al. 1993). Changes in aggres-

sion after mating are not limited to males. Sexually experienced breeder female prairie voles display more aggression and less affiliative behavior than do sexually naive females (Bowler et al. 2002), and postpartum female common voles (*M. arvalis*) become more aggressive toward males as pups develop (Heise and Lippke 1997). Whether the increases in aggression in females are attributable to mating or to gestational or postpartum changes are unknown, but changes in vasopressin gene expression after the birth of pups are known to occur (Wang et al. 2000).

The importance of vasopressin in mediating aggressive behavior suggests involvement of the amygdala-BST-lateral septum circuit. This notion is supported by studies in a variety of species. For example, agonistic behavior activates the amygdala-BST-lateral septum circuit in male Syrian hamsters (*Mesocricetus auratus;* Kollack-Walker and Newman 1995) and female house mice (*Mus musculus;* Gammie and Nelson 2001). Similarly, in a resident/intruder test, previously mated male prairie voles had elevated expression of the *c-fos* gene in the amygdala, BST, and lateral septum (Wang, Hulihan et al. 1997). Since *c-fos* expression is an indicator of neuronal activation, these observations suggest that this circuit is activated during aggression in voles as well. These results show a consistent pattern of involvement of this circuit associated with aggression, regardless of species or gender. Interestingly, in monogamous voles, activation of this system occurred only in response to a stranger, not after reexposure to the familiar partner, suggesting that aggression can be modified by familiarity (Wang, Hulihan et al. 1997).

Vasopressin and social recognition

It is apparent that the amygdala-BST-lateral septum circuit is important for a variety of social behaviors, suggesting a common factor that is involved in all of these behaviors. The ability to respond appropriately in social encounters depends to a large extent on being able to recognize individuals. We suggest that the amygdala-BST-lateral septum circuit is critical for social recognition. How important is social recognition in structuring interactions between rodent conspecifics? Although few rodent social systems appear to be structured on a hierarchical basis, for those, such as mole-rats (*Cryptomys damarensis*) that display such a social system (Gaylard et al. 1998), individual recognition likely is an important attribute. Individual recognition seems to be necessary in species that form pair bonds.

Rodents can distinguish among individuals. Evidence from Syrian hamsters suggests that the loser of an aggressive encounter can identify the individual that defeated him (Lai and Johnston 2002). Prairie voles with lesions of the amygdala have deficits in mate recognition (Demas et al. 1997), suggesting that the amygdala is involved in social recognition. Mice with impaired VNO function display deficits in the ability to discriminate sex (Stowers et al. 2002), and this structure also plays an important role in social recognition in rats (Bluthe and Dantzer 1993). Experiments in rats also suggest that the lateral septum plays an important role, mediated by vasopressin, in social memory (Dantzer et al. 1988; Bluthe and Dantzer 1993; Everts and Koolhaas 1999). The lateral septum may be critical for mate recognition in monogamous voles as well. In a number of studies on pair bonding, neurochemical manipulations have been tested for effect both before and after the formation of pair bonds. In most cases, treatments after pair bond formation are ineffective at blocking the expression of pair bonds. The single exception appears to be the effects of vasopressin in the lateral septum. Vasopressin infused into the lateral septum, presumably mimicking natural release from cells in the BST, facilitates partner preference formation by prairie voles (Liu et al. 2001b). However, administration of a vasopressin receptor blocker into the lateral septum, either before or after pair bond formation, impairs the ability of prairie voles to express a partner preference (Liu et al. 2001a). One possible explanation for these results is that the treatment interferes with mate recognition.

If the suggestion that the amygdala-BST-lateral septum circuit plays a fundamental role in organizing rodent social interactions by mediating individual identification is valid, this circuit then should interact with other brain regions involved in specific social behaviors. Further, connections within and arising from this circuit should be able to influence social interactions by modifying behaviors to ensure that responses are appropriate for the social context. An important test of such hypotheses is to show that this circuit can influence behaviors mediated by other brain regions. Flank-marking by Syrian hamsters occurs in response to stimuli associated with conspecifics (Johnston 1992) and the frequency and location of flank-marking may be modified by individual recognition (Ferris and Delville 1994). This behavior appears to be mediated via the anterior hypothalamus since injections of vasopressin into this area stimulate flank-marking (Ferris et al. 1999). Of interest here is that the anterior hypothalamus receives afferent input from the lateral septum, and stimulation of the septum also gives rise to flank marking (Irvin et al. 1990). These results show that the extrahypothalamic vasopressin can affect social behavior via connections to other brain regions.

Of course, the vasopressin system does not regulate behavior in the absence of other neurochemical systems. For example, in the lateral septum vasopressin interacts with oxytocin to regulate pair bond formation (Liu et al. 2001b). Within both the anterior hypothalamus and the ventrolateral hypothalamus, vasopressin enhances aggression, and

these effects are antagonized by serotonin (Delville et al. 1996; Ferris et al. 1997) or galanin (Ferris et al. 1999). In addition to direct effects on behavior, vasopressin effects may modify, or be modified by, the effects of other neurotransmitter systems. Cells immunoreactive for tyrosine hydroxylase, an enzyme involved in the biosynthesis of catecholamines, are found in the BST of Siberian hamsters (*Phodopus sungorus;* Shi and Bartness 2000). Noradrenergic projections from the brainstem interact with vasopressin within the BST to modulate fear responses (Onaka and Yagi 1998) and norepinephrine within the olfactory bulbs interacts with vasopressin to mediate social recognition (Dluzen et al. 1998). Finally, vasopressin release in the lateral septum may modulate the release of dopamine (Ishizawa et al. 1990), and activation of vasopressin receptors in the ventral pallidum may modify responses associated with the mesolimbic dopamine system (Pitkow et al. 2001).

Dopamine and social behavior

There is a long history of research into the effects of central dopamine on behavior. Such research has implicated dopamine in responses to stress (Dunn 1988; Abercrombie et al. 1989), in mediating conditioned preferences (Kivastik et al. 1996) and the rewarding effects of food intake (Azzara et al. 2001), and in the control of mating behavior (Becker et al. 2001). More recently, researchers have begun to examine the role of dopamine in mediating social behavior (Mitchell and Gratton 1992; Mermelstein and Becker 1995; Tidey and Miczek 1996; Keer and Stern 1999; Lorrain et al. 1999) and, in particular, in pair bond formation (Gingrich et al. 2000; Aragona et al. 2003a). To date, much of this latter work has been directed toward the role of nucleus accumbens dopamine in social attachment. Mating induces dopamine release in the nucleus accumbens (Gingrich et al. 2000) and facilitates pair bond formation in prairie voles (Williams et al. 1992), suggesting a connection between dopamine release and pair bonding. Dopamine released within the nucleus accumbens is thought to be involved in reward processing, and indeed has been found to be of critical importance in the formation and maintenance of pair bonds in both sexes of prairie voles (Gingrich et al. 2000; Aragona et al. 2003a). Early work in this system identified activation of one kind of dopamine receptor, the D_2 subtype, as being a critical step in pair bond formation (Wang et al. 1999; Gingrich et al. 2000). These studies, together with a later report (Aragona et al. 2003a), also produced evidence for gender-specific effects of dopamine on pair bonding; the same doses of dopamine agonists that induced a preference for the familiar partner in female voles were ineffective in males. In addition, more recent work has provided details that make it apparent that D_2 receptor activation is just one aspect in a complex set of neurochemical interactions within nucleus accumbens during the formation and maintenance of pair bonds.

As mentioned previously, mating induces dopamine release in the nucleus accumbens in voles, and such release is shown to be important in pair bond formation (Wang et al. 1999; Gingrich et al. 2000; Aragona et al. 2003a). However, mating also induces dopamine release in the nucleus accumbens in species that do not form pair bonds (Pfaus et al. 1990; Mermelstein and Becker 1995). Why, then, does dopamine induce pair bonds in only some species? The answer may lie in interactions between dopamine and other neurochemical systems. For many years it has been known that oxytocin plays a critical role in the formation of bonds between adults (Williams et al. 1994), just as it does in the formation of bonds between mother and offspring (Carter 1998). In both *Microtus* and *Peromyscus,* monogamous and promiscuous species differ in the distribution of oxytocin receptors within the brain (fig. 16.2; Insel et al. 1991; Insel and Shapiro 1992). Within nucleus accumbens, monogamous vole species display a much higher density of oxytocin receptors than do promiscuous species (Insel and Shapiro 1992), and activation of these receptors acts in concert with the D_2 dopamine receptors to produce pair bonds. When either D_2 or oxytocin receptors are blocked no pair bonds are formed (Liu and Wang 2003). Thus the combination of mating-induced dopamine release with species-specific patterns of oxytocin activation may partially explain the variety of rodent mating systems.

There also is indirect evidence for a connection between oxytocin/dopamine interactions and pair bonding. Auto- and allogrooming play important roles in many social interactions and may facilitate the transfer of socially relevant information (Ferkin et al. 2001). Like pair bond formation, grooming behavior is to some extent mediated by an interaction of dopamine and oxytocin in the nucleus accumbens (Drago et al. 1986). It was found that non-pair-bonded male prairie voles groomed more frequently than did pair-bonded males (Wolff et al. 2002), providing further evidence of oxytocin-dopamine interaction in pair-bonding.

The nucleus accumbens contains more than just D_2 and oxytocin receptors: other dopamine receptor subtypes are expressed as well. The D_1 dopamine receptor subtype was originally described as playing no role in pair bonding (Wang et al. 1999). This is probably true in terms of pair bond *formation,* but increasing evidence suggests that D_1 dopamine receptors may be critical for pair bond *maintenance*. Male prairie voles that remain with their female partner for 2 weeks display an important change within the nucleus accumbens (Aragona et al. 2003b). In these voles, the density of D_1 dopamine receptors is substantially greater than that seen in non-pair-bonded voles. Further, activa-

tion of D_1 dopamine receptors impairs the formation of pair bonds induced either by mating or by D_2 receptor activation (Aragona et al. 2003b). The increase in D_1 receptors in pair-bonded animals may prevent the formation of a second pair bond, which in turn may serve to maintain a monogamous life strategy. It would be interesting to examine whether a similar reorganization occurs in species that display serial monogamy or whether there are sex differences in species such as Mongolian gerbil (*Meriones unguicalatus*) that appear to display sex-specific types of social bonds (Starkey and Hendrie 1998). Finally, it also would be of interest to learn whether there are individual differences in the regulation of D_1 receptor expression in pair-bonded voles. Although considered to be a monogamous species, some prairie voles can form a second pair bond (Pizzuto and Getz 1998). Differences in the ability to increase D_1 receptors may account for the small percentage of monogamous voles that form new pair bonds after losing a mate.

Corticosterone and social behavior

Vasopressin, oxytocin, and dopamine all have been implicated in social attachment in voles and, although there are sex differences in sensitivity to these neurochemicals, the direction of effects is similar in both sexes. This is not the case when the effects of the stress hormone corticosterone are examined. Monogamous prairie voles display basal circulating levels of corticosterone that are as much as ten times higher than those found in promiscuous vole species or in rats (Hastings et al. 1999). Nonetheless these voles are capable of further, stress-induced increases in corticosterone (Taymans et al. 1997). Interestingly, the effects of stress on pair bonding are sexually dimorphic in monogamous voles. In males, the effects of stress, presumably including increased circulating corticosterone, enhance the formation of pair bonds (DeVries et al. 1996). Conversely, adrenalectomy, which reduces circulating corticosterone, inhibits pair bonding (DeVries et al. 1996). In females, the opposite pattern is found; adrenalectomy enhances pair bonding, whereas stress reduces pair bond formation (DeVries et al. 1995; DeVries et al. 1996).

How might corticosterone affect pair bond formation? One possibility may be via interaction with the vasopressin system. Adrenalectomy reduces the density of vasopressin receptors in the lateral septum and BST, an effect that is reversed by hormone replacement (Watters et al. 1996). Corticosterone actions are mediated by two types of glucocorticoid receptors, high-affinity Type I receptors and low-affinity Type II receptors, and activation of the two receptor subtypes can produce differing effects (de Kloet et al. 1993). Interestingly, hormone replacement using aldosterone, which acts primarily on Type I receptors, reversed adrenalectomy effects on vasopressin receptor density only in the BST. Dexamethasone treatment, which acts on Type II receptors, restored vasopressin receptor densities in both the lateral septum and the BST (Watters et al. 1996). These results show that changes in circulating corticosterone levels have the potential to significantly alter vasopressin-induced responses. Given the sexual dimorphism in the extrahypothalamic vasopressin system, it is possible that the sex- specific effects of corticosterone are secondary to its effects on vasopressin activity.

Corticosterone also can interact with the dopamine system. Glucocorticoid receptors are found on dopamine cells within the ventral tegmental area (VTA). It has been shown that stress alters excitatory glutamate receptors on dopaminergic cells in the VTA (Saal et al. 2003). Importantly, the stress-induced changes in VTA were blocked by glucocorticoid receptor antagonists (Saal et al. 2003). Since the VTA is the primary source of dopamine input to the nucleus accumbens (Schoffelmeer et al. 1995), these results suggest that glucocorticoid receptor activation in VTA could impact dopamine release in nucleus accumbens. Direct effects of glucocorticoid receptor activation within nucleus accumbens also are possible. For example, there is a direct correlation between corticosterone levels and dopamine transporter (DAT) activity in the shell portion of nucleus accumbens (Sarnyai et al. 1998), the subregion most strongly implicated in pair bonding (Aragona et al. 2003b). Since corticosterone levels are lower in voles that are paired (DeVries et al. 1995; DeVries et al. 1997), it is possible that DAT activity also is decreased, reducing clearance of dopamine from the synapse, and thus potentiating the effects of released dopamine. The net result of this decrease in DAT function may alter the rewarding aspects of contact with the partner. Sex differences in the distribution of glucocorticoid receptors, in the basal levels of D_1 receptors, or in the glucocorticoid/DAT interaction could explain the sex differences in responses to glucocorticoid in pair bond formation. In males the potentiated dopamine effect may be rewarding, and in females, aversive. Thus interaction between the corticosterone and dopamine systems may in part explain the sex-specific effects of stress on pair bond formation.

Synthesis

A recent review (Insel 2003) outlined a circuit that may mediate the rewarding aspects of social interaction. This circuit, involving the mesolimbic dopamine system, may be critical to an assessment of the incentive value associated with another individual, but may not account for one important aspect of social behavior, the recognition of an-

other individual. In this regard, interplay between the vasopressin and dopamine systems may have an important impact on social behavior: the dopamine incentive system dictates the intensity of the interaction, the vasopressin recognition circuit dictates with whom the individual interacts. Are there direct connections between the recognition and incentive circuits? The answer appears to be yes. For example, there are projections from both lateral septum (Zahm et al. 2001) and BST (Georges and Aston-Jones 2002) to the VTA, a major source of dopamine to nucleus accumbens as well as to other brain regions associated with social attachment. In fact, electrical stimulation of the BST activates the vast majority of dopamine neurons in the VTA (Georges and Aston-Jones 2002). The amygdala and prefrontal cortex also may control dopamine release via direct inputs to nucleus accumbens (Carr and Sesack 2000; Howland et al. 2002). Similarly, there are efferent projections from the dopamine incentive circuit to the amygdala-BST-lateral septum circuit (cf. Hurley et al. 1991). We propose that the extrahypothalamic vasopressin system interacts with the mesolimbic dopamine reward circuit by mediating social recognition and thus modifying responses within the reward pathway.

How might these two systems interact? It is well established that nucleus accumbens dopamine is elevated in response to novelty, including exposure to another individual (Damsma et al. 1992; Noguchi et al. 2001). However, when a familiar situation is encountered, dopamine release in the nucleus accumbens, especially in the shell portion, is attenuated relative to that in earlier encounters (Bassareo et al. 2002). It is unlikely that the individuals comprising a pair remain together at all times. Evidence for sex-specific predation risk, even in monogamous species (Sommer 2000), suggests that members of a pair are at times separated. Social recognition has the potential to most greatly affect nucleus accumbens dopamine during reunion after a separation, and it is in this circumstance that a recognition circuit based on the vasopressin system may play a role in pair bonding. Since pair-bonded animals have more D_1 receptors in the nucleus accumbens and activation of these receptors interferes with pair bonding, dopamine release at the wrong time within the nucleus accumbens could disrupt an existing attachment. However, recognition of the partner via the amygdala-BST-lateral septum circuit may inhibit dopamine release in the nucleus accumbens, thus precluding activation of the D_1 receptors and preserving the pair bond. Such recognition would not be afforded to strangers, and the novelty-induced elevation of nucleus accumbens dopamine would then activate the increased D_1 receptors, producing an aversive response to an unfamiliar individual. Such a response could in turn feed back on the extrahypothalamic vasopressin system to produce aggression toward the stranger. In addition, the fact that D_1 activation may produce an aversive response could also activate the hypothalamic-pituitary-adrenal axis, altering circulating levels of corticosterone. Corticosterone can alter function in both the vasopressin and dopamine systems, in conjunction with the fact that the corticosterone system differs in monogamous species from that in nonmonogamous species, suggesting that feedback via the corticosterone system may play a critical role in coordinating the actions of the incentive and recognition systems during social encounters. Certainly, these scenarios need to be tested in further studies.

Future Directions

Research over the past few decades has provided a strong understanding of the basic neuroanatomical substrates underlying social behavior in rodents and has begun to reveal how various neurochemical systems interact to mediate social interactions. Nonetheless, there is considerable work still to be done. Even within species, there are often subtle differences in social behavior between populations (Roberts et al. 1998; Cushing et al. 2001; Wolff and Dunlap 2002) that may be influenced by local environmental conditions. Exactly how such differences are mediated is unknown, but the fact that there are population-specific patterns of behavior suggests a genetic basis. The role of genetics in producing different social structures is just beginning to be examined. Young et al. (1999) have shown that differences in the promoter region of the vasopressin receptor gene can produce species-specific patterns of receptor expression that are correlated with social structure. In fact, expression of the vasopressin receptor gene from monogamous voles in mice can affect the social behavior of the mouse (Young et al. 1999). This line of research has the potential to provide considerable insight into the evolution of rodent social structure.

Although much is known about the effects of vasopressin, oxytocin, dopamine, and corticosterone, little is known about how these chemicals interact with each other and with other neurochemical systems to mediate social responses. For example, studies on stress responses and drug addiction have shown that neurotransmitters such as glutamate and GABA can significantly affect the activities of the mesolimbic dopamine system (Enrico et al. 1998; Takahata and Moghaddam 1998). What role such neurochemicals may play in social behaviors such as pair bonding has barely been addressed.

Finally, there is considerable work yet to be done examining the role of perinatal and exogenous influences on the central control of social behavior. Elevated stress hormones during development, perinatal exposure to vasopressin, or

oxytocin, or to altered gonadal hormone levels all have been shown to impact social behaviors (Axelson et al. 1999; Stribley and Carter 1999; Catalani et al. 2000; Lonstein and De Vries 2000a; Kramer et al. 2003). Even substances consumed by the dam can affect the social behavior of offspring (Kelly and Tran 1997). Given the recent evidence that a variety of manmade chemicals in the environment can mimic the effects of endogenous substances, the study of social behavior in rodents may become even more important by providing a means to study the effects of anthropogenic substances on biologically important behaviors.

Summary

Social behavior in rodents is regulated by complex interactions between a number of brain regions and by a variety of neurotransmitter systems within the central nervous system. The combined behavioral output of these systems must be capable of responding appropriately to a wide variety of stimuli, not the least of which are the responses of the individuals with which an animal interacts. Research over the past 20 years has provided a basic framework upon which our current understanding of the neural basis of social behavior rests. Two loosely defined systems appear to interact to modulate a large percentage of social interactions. The first system may be defined as a "recognition circuit," and is responsible for distinguishing between individuals such that appropriate behavioral responses, in some cases based on past interactions, may be displayed. The second circuit, an "incentive circuit," may serve to determine the intensity of the interaction. Together these circuits may act to determine the valence and/or intensity of the interaction, that is, approach or avoidance, aggressive versus passive behavior, and so forth. Ongoing research is attempting to elaborate central changes underlying the formation and maintenance of social bonds, the effects of perinatal influences on adult social behavior, and the role of genetics in determining species- and individual-specific social behaviors.