nature neuroscience

The neurobiology of pair bonding

Larry J Young[1] & Zuoxin Wang[2]

A neurobiological model for pair-bond formation has emerged from studies in monogamous rodents. The neuropeptides oxytocin and vasopressin contribute to the processing of social cues necessary for individual recognition. Mesolimbic dopamine is involved in reinforcement and reward learning. Concurrent activation of neuropeptide and dopamine receptors in the reward centers of the brain during mating results in a conditioned partner preference, observed as a pair bond. Differential regulation of neuropeptide receptor expression may explain species differences in the ability to form pair bonds. These and other studies discussed here have intriguing implications for the neurobiology of social attachment in our own species.

Sexual attraction and the selective social attachments that often follow are two of the most powerful driving forces of human behavior, profoundly influencing art, music, literature and politics throughout history. The presence of strong, enduring relationships between sexual partners is widespread in nearly all societies, particularly in societies where monogamy is a predominant feature of the social organization. Whether humans have a biological propensity to practice monogamy (or perhaps more correctly, serial monogamy) is debatable; however, there is little doubt that the ability to form intense social attachments—or pair bonds—with a mate has a biological architecture with definable molecular and neural mechanisms. Studies using monogamous rodents as models for social attachment are providing insights into the biology of pair-bond formation.

The term 'monogamy' implies a social organization in which a male and female mate exclusively with each other, although extra-pair copulations are not unusual in monogamous species[1]. For this reason, the term 'monogamy' is used here to refer to a social organization in which each member of a mating pair displays selective (but not exclusive) affiliation and copulation, as well as nest sharing, with the partner; it also typically implies biparental care of offspring. Only 3–5% of mammals exhibit a monogamous social structure as defined by these criteria[2]. One group of species in particular, voles in the genus *Microtus*, has emerged as a valuable tool for investigating the neurobiological mechanisms of pair-bond formation[3,4]. Here we review recent discoveries concerning the molecular, cellular and neurobiological pathways that result in the development of a pair bond in the monogamous prairie vole (*Microtus ochrogaster*). These studies provide a framework for understanding the regulation and evolution of complex social behavior and may provide insights into the human social brain.

[1]Center for Behavioral Neuroscience, Department of Psychiatry and Behavioral Sciences, and Yerkes National Primate Research Center, Emory University, Atlanta, Georgia 30322, USA. [2]Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, Florida 32306, USA.
Correspondence should be addressed to L.J.Y. (lyoun03@emory.edu).

Published online 26 September 2004; doi:10.1038/nn1327

Peptidergic regulation of the pair bond

Like humans, voles display a remarkable diversity in social organization. For example, prairie voles form enduring pair bonds and are biparental, but montane (*Microtus montanus*) and meadow (*Microtus pennsylvanicus*) voles are nonmonogamous and typically do not display biparental care[5–7]. In nature, the majority of prairie voles that lose a mate never take on another partner[8].

In the laboratory, researchers study pair-bond formation using a partner-preference test. The testing apparatus consists of three chambers connected by tubes. The 'partner' and a novel 'stranger' are tethered in their own chambers, whereas the subject is free to move throughout the apparatus during a 3-h test. Pair bonding is inferred when subjects spend significantly more time in close proximity to the partner compared to the stranger (partner preference). In prairie voles, mating facilitates formation of partner preference, although cohabitation without mating may also result in partner-preference formation under some circumstances[9].

Two neuropeptides emerged initially as critical mediators of partner-preference formation in prairie voles: oxytocin and arginine vasopressin (AVP). Oxytocin also regulates mother-infant bonding in sheep[10], whereas AVP has been implicated in several male-typical social behaviors, including aggression, scent marking and courtship[11,12]. Infusion of oxytocin into the cerebral ventricles of female prairie voles accelerates pair bonding, as these females require only a brief cohabitation with a male, without mating, to form a partner preference[13]. Likewise, central AVP infusion facilitates pair-bond formation in male prairie voles without mating[14]. Administration of selective oxytocin receptor (OTR) and AVP receptor 1a (V1aR) antagonists prevents pair-bond formation in female and male prairie voles, respectively[13–16]. Although both peptides may facilitate pair-bond formation in either sex[16], oxytocin seems to be more important in females, whereas AVP is more critical in males[14,15,17]. The mechanism underlying this sex difference in behavioral response to oxytocin and AVP is unclear, because receptor densities in the brain are similar in males and females. Early social experience may also influence adult social behavior, as developmental studies suggest that neonatal oxytocin exposure enhances the likelihood of partner preference formation in adult male prairie voles[18]. Although other factors, including stress and stress hormones, also

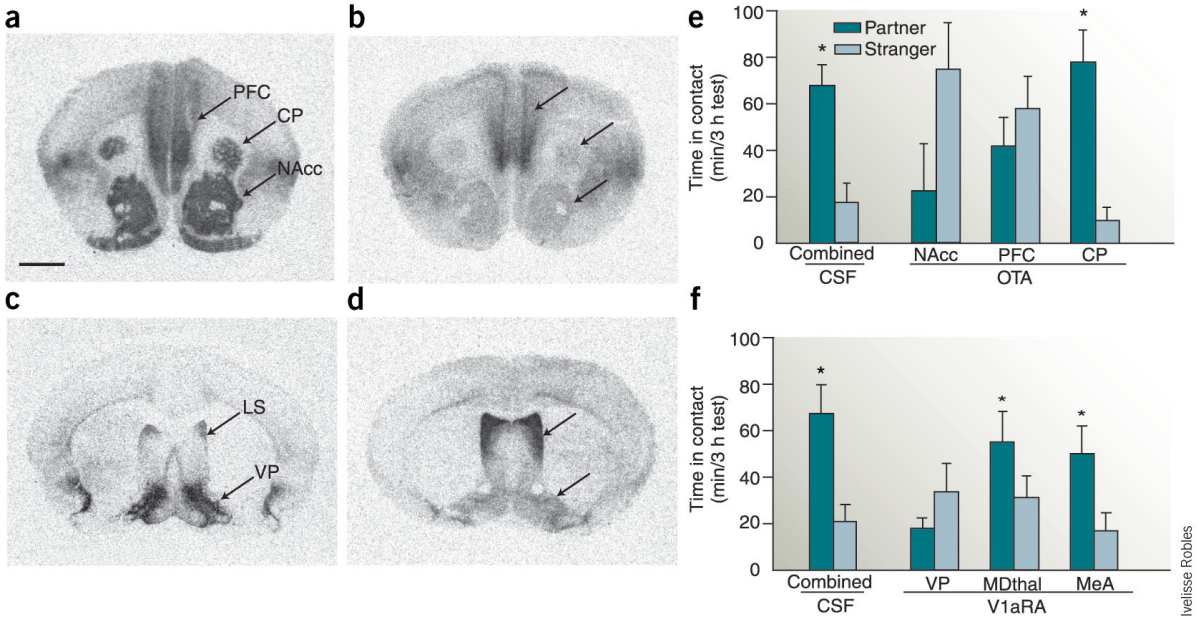

Figure 1 OTR and V1aR regulation of pair bonding in prairie voles. (**a**,**b**) Monogamous prairie voles (**a**) have higher densities of OTR in the nucleus accumbens (NAcc) and caudate putamen (CP) than do nonmonogamous montane voles (**b**). Both species have OTR in the prefrontal cortex (PFC). (**c**,**d**) Male prairie voles (**c**) have higher densities of V1aR in the ventral pallidum (VP) than do montane voles (**d**). (**e**) A selective OTR antagonist (OTA) infused bilaterally into the NAcc or PFC, but not the CP, blocks partner-preference formation in female prairie voles[24]. (**f**) Infusion of a selective V1aR antagonist (V1aRA) into the VP, but not into the mediodorsal thalamus (MDthal) or medial amygdala (MeA), prevents mating-induced partner-preference formation in male prairie voles[25]. Scale bar, 1 mm.

modulate partner-preference formation[19–21], for the sake of clarity we will restrict our focus to oxytocin and AVP, as well as their interactions with other neurotransmitter systems.

The first hypotheses about the neuroanatomical basis of pair-bond formation came from comparisons of OTR and V1aR distributions in the brains of monogamous and nonmonogamous vole species. Compared to nonmonogamous species, monogamous prairie voles have higher densities of OTR in the caudate putamen and nucleus accumbens (**Fig. 1a**,**b**)[22] and higher densities of V1aR in the ventral pallidum, medial amygdala and mediodorsal thalamus (**Fig. 1c**,**d**)[23]. Some of these regions are involved in pair-bond formation. For example, infusion of an OTR antagonist into the prefrontal cortex and nucleus accumbens of females, but not the caudate putamen, blocks mating-induced partner-preference formation (**Fig. 1e**)[24]. In males before mating, blocking V1aR neurotransmission in the ventral pallidum, but not the medial amygdala or mediodorsal thalamus, also inhibits partner-preference formation (**Fig. 1f**)[25]. Infusion of V1aR antagonist into the lateral septum, which expresses some V1aR in both species, also prevents mating-induced pair-bond formation in males[26].

Sex, reward and pair bonding

Results from anatomical and pharmacological studies indicate that the prefrontal cortex, nucleus accumbens and ventral pallidum are all critical brain regions in pair-bond formation. These regions are also involved in the mesolimbic dopamine reward system, suggesting that pair-bond formation uses the same neural circuitry as reward. Reward processing depends on the mesocorticolimbic dopaminergic system consisting of dopamine neurons in the ventral tegmental area and their projections to the nucleus accumbens, prefrontal cortex and other brain areas[27]. The ventral pallidum is a major target of the nucleus accumbens[28,29], and it further processes and relays stimuli from the nucleus accumbens to mediate locomotor responses to rewarding stimuli[30,31]. Dopamine release within this circuit is critically involved in natural reward (food intake and mating) as well as maladaptive (drug) reward[27,32,33]. Studies also implicate this circuit in conditioned reward learning, such as drug-induced place preferences[34], in which neutral stimuli become associated with rewarding stimuli.

Given that mating is rewarding in rodents[34–36] and facilitates pair-bond formation in voles, some researchers have hypothesized that pair bonding may be the result of conditioned reward learning, in which an association forms between the reinforcing properties of sex (unconditioned stimulus) and the specific olfactory signature of the partner (conditioned stimulus)[3,37]. For example, both male and female rats prefer to spend time in the chamber in which they copulated (a conditioned place preference)[38,39], and this sexual conditioning depends on D1-type and D2-type dopamine receptor activation in the nucleus accumbens[40].

Consistent with the hypothesis that pair bonding involves conditioned learning, dopamine within the nucleus accumbens is critical for partner preference formation in prairie voles (**Fig. 2**). The nucleus accumbens in voles contains dopamine terminals and receptors (**Fig. 2b**)[41,42] and mating results in an increase (51%) in extracellular dopamine in the nucleus accumbens of females (**Fig. 2c**)[43]. Mating also tends to increase dopamine turnover in the nucleus accumbens of males[42]. Systemic administration, or local injection into the nucleus accumbens, of haloperidol (a nonselective dopamine receptor antagonist) blocks mating-induced partner preferences, whereas apomorphine (a nonselective dopamine receptor agonist) facilitates partner preference without mating in both male and female prairie voles (**Fig. 2a**)[42,43].

The dopaminergic regulation of pair-bond formation in the nucleus accumbens is receptor subtype–specific: activation of D2, but

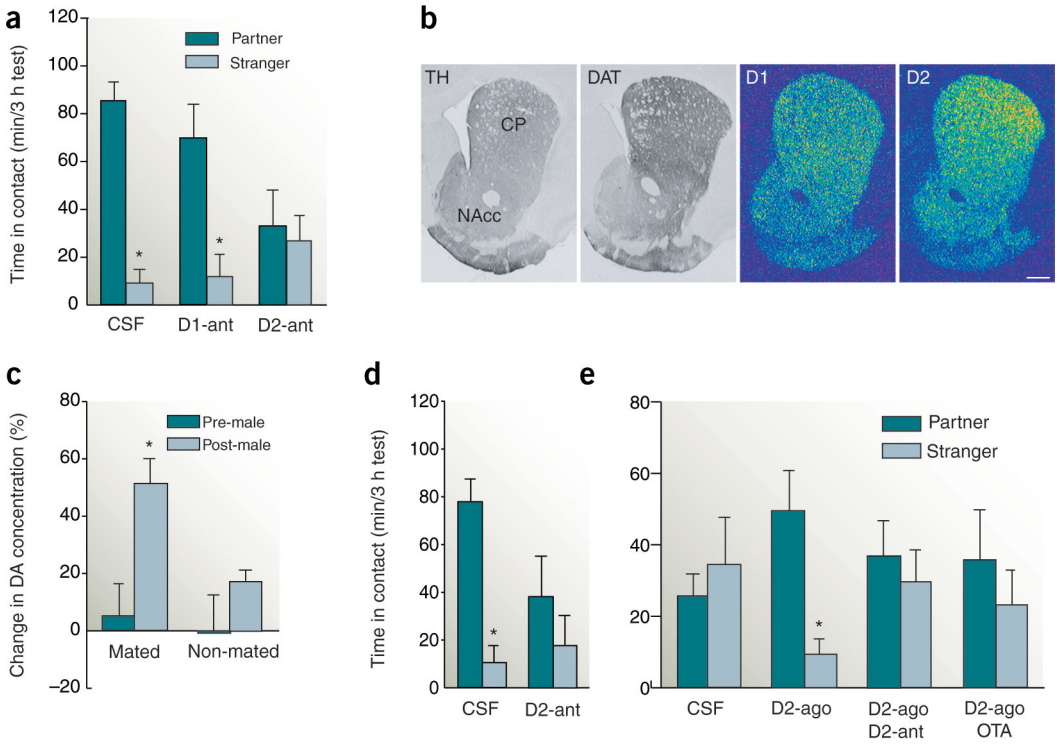

Figure 2 Dopamine regulates pair bonding in female prairie voles. (**a**) Females injected intraperitoneally with saline or saline containing a D1 receptor antagonist (D1-ant), but not a D2 antagonist (D2-ant), showed partner preferences after 24 h of cohabitation with mating, indicating the importance of D2 receptors in pair-bond formation[76]. (**b**) Photomicrographs of immunoreactive staining for tyrosine hydroxylase (TH) and dopamine transporter (DAT) as well as autoradiographic binding for D1 and D2 dopamine receptors in the nucleus accumbens (NAcc) and caudate-putamen (CP) of the prairie vole brain. Scale bar, 500 μm. (**c**) Estrus female voles that mated with a male showed a significant (51%) increase above the baseline in extracellular dopamine concentration in NAcc[43]. (**d**) Intra-NAcc administration of a D2 antagonist (D2-ant) blocked mating-induced partner preferences[43]. (**e**) Intra-NAcc administration of a D2 agonist (D2-ago) induced partner-preference formation after 6 h of cohabitation with a male in the absence of mating[44]. This behavior was blocked by coadministration of either the D2 antagonist (D2-ant) or the oxytocin receptor antagonist (OTA), suggesting that concurrent activation of both D2 and oxytocin receptors in NAcc is essential for pair-bond formation[44].

not D1, receptors in the nucleus accumbens of female prairie voles accelerates partner preferences without mating, whereas blockade of D2 receptors antagonizes this behavior (**Fig. 2d**)[43,44]. In males, D2 receptor activation also facilitates partner preference, but D1 receptor activation blocks partner preferences induced by mating or by D2 receptor activation[41]. Male prairie voles that have mated and pair bonded with a female for two weeks also show a significant increase in the density of D1, but not D2, receptors in the nucleus accumbens. No changes in dopamine receptor binding occur in other dopaminergic brain areas, including the caudate putamen[41]. As D1 activation in the nucleus accumbens prevents pair bonding in males[41], this increase in D1 receptor density may serve to prevent the formation of new pair bonds, thereby maintaining the current pair bond and stabilizing the monogamous social organization.

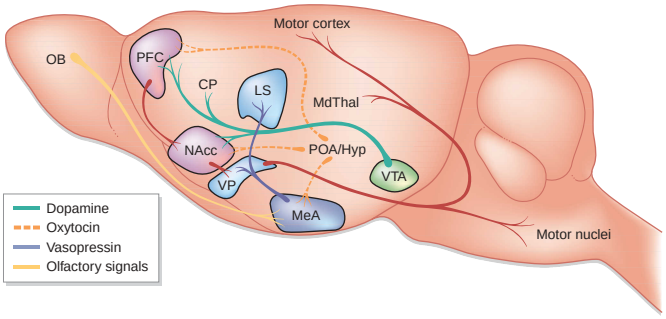

Figure 3 Sagittal view of a prairie vole brain illustrating a proposed neural circuit model for pair bonding. In this model, mating activates the VTA, resulting in increased dopamine activity in the prefrontal cortex (PFC) and nucleus accumbens (NAcc). Concurrently, olfactory signals from the mate are transmitted via the olfactory bulb (OB) to the medial nucleus of the amygdala (MeA). Oxytocin acts in the MeA, and AVP acts in the lateral septum (LS) to facilitate olfactory learning and memory. Mating also stimulates increased extracellular concentrations of oxytocin in the PFC and NAcc of females, and of vasopressin in the ventral pallidum (VP) of males. AVP fibers in the LS and VP originate from cell bodies in the MeA and bed nucleus of the stria terminalis (not shown). The source of oxytocin projections to the NAcc, MeA and PFC has not been defined (hence the dotted line), but they most likely originate from some population of cell bodies in the preoptic or hypothalamic area (POA/Hyp). Glutamatergic projections from the PFC to the NAcc are thought to be important in reinforcement and therefore potentially in pair bonding. The concurrent activation of the dopaminergic system and the oxytocin or AVP system in the NAcc or VP potentially results in the development of a conditioned partner preference. The VP is a major output relay of the NAcc and modulates motor output in response to reinforcing stimuli via projections to the mediodorsal thalamus (MdThal) and cortical and mesencephalic motor nuclei.

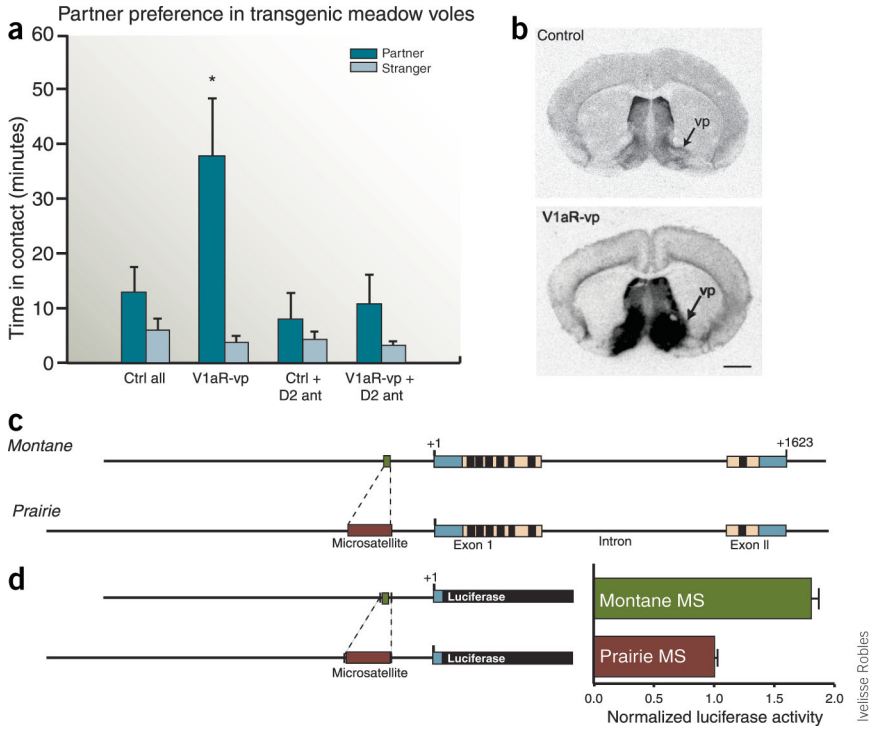

Figure 4 The molecular genetics of pair bonding. (**a**) Male meadow voles overexpressing the V1aR receptor in the ventral pallidum (V1aR-vp) showed enhanced mating-induced partner preferences compared to control animals (Ctrl all). Infusion of a D2 receptor antagonist (D2-ant) before mating abolished the partner preference in these males (V1aR-vp + D2-ant)[6]. (**b**) V1aR binding autoradiograms illustrating the increased expression of V1aR in the ventral pallidum (vp) in experimental males compared to control animals. (**c**) The structure of the *Avpr1a* gene of prairie and montane voles. The gene is highly homologous except for an expanded microsatellite sequence in the 5′ flanking region of the prairie vole gene. Yellow boxes indicate coding regions with the black bars representing the seven transmembrane domains. Gray indicates untranslated regions. The green and red boxes indicate the relative length and position of the microsatellite sequences in the montane and prairie vole genes, respectively. (**d**) The effect of the microsatellite sequence on expression as determined by a transcription reporter assay. The prairie vole promoter was spliced upstream of firefly luciferase. Exchanging only the prairie vole microsatellite sequence (prairie MS) with the montane vole sequence (montane MS) resulted in a significant alteration in luciferase expression in a rat A7r5 cell line.

Although mating-induced dopamine release in the nucleus accumbens is important for pair-bond formation in prairie voles, mating also induces dopamine release in the nucleus accumbens of other species of rodents, such as rats, which do not form pair bonds[35,36]. Why then does dopamine induce pair bonding only in monogamous prairie voles? The answer may lie in the interaction of the oxytocin, AVP and dopamine systems within the reward circuitry.

In female prairie voles, administration of an OTR antagonist into the nucleus accumbens blocks partner preferences induced by D2 receptor activation, whereas blockade of D2 receptors in the nucleus accumbens prevents partner preference formation induced by oxytocin[44] (**Fig. 2e**). These data indicate that dopamine and oxytocin are not acting sequentially, but rather that concurrent activation of both oxytocin and dopamine D2 receptors, and the interaction between these two systems in the nucleus accumbens, are necessary for pair-bond formation in females. Similar studies have not been done in males, but given that the D2 receptors in nucleus accumbens[42] and V1aR in the ventral pallidum[25,45] are important for pair bonding in males, and that these two areas are interconnected[28,29], it is likely that the dopamine and AVP systems also interact in the nucleus accumbens–ventral pallidum circuitry to influence pair-bond formation in males. The nature of the interaction of these systems in voles is not clear. Studies on drug tolerance and addiction suggest that these neuropeptides may modulate the role of dopamine in the reward circuitry[46]. Furthermore, dopamine administration induces central oxytocin release, whereas oxytocin administration increases central dopamine levels in the rat[47,48]. The interaction may also be indirect, with concurrent activation modulating downstream circuits involved in olfactory learning and conditioning, for example.

A neurobiological model for pair bonding

How might the oxytocin, AVP and dopamine systems interact to facilitate pair-bond formation? There are now several studies suggesting that both oxytocin and AVP are involved in the neural processing of sensory cues involved in social learning. In rodents, both neuropeptides are implicated in the processes required to identify the olfactory signatures of conspecifics (social recognition)[49]. Oxytocin knockout mice fail to recognize individuals to which they have been previously exposed[50], and infusions of oxytocin in the medial amygdala completely restore social recognition in these mice[51]. Selective V1aR antagonist or antisense V1aR administered into the lateral septum of rats also inhibits social recognition[52,53], whereas infusion of AVP or overexpression of the V1aR in this region enhances social recognition abilities[54]. V1aR knockout mice also exhibit a complete loss of social recognition[55]. However, both oxytocin and V1aR knockout mice perform normally in other olfactory and cognitive tasks, suggesting that this deficit is specific for social discrimination[50,55]. Given this role for oxytocin and AVP in social recognition and the interaction of these peptides with mesolimbic dopamine, a reasonable hypothesis is that pair bonding results from the convergence of social discrimination circuits and the reinforcing properties of the mesolimbic dopamine reward circuit (**Fig. 3**).

Mating in both males and females correlates with neural activity in several brain regions, including the ventral tegmental area (VTA), medial amygdala, preoptic area and hypothalamus[25,56]. Dopaminergic projections from the VTA release dopamine in the nucleus accumbens and prefrontal cortex, which has strong glutamatergic projections back to the nucleus accumbens[27]. Concurrently, olfactory cues from the partner are processed by the main and accessory olfactory bulbs, and subsequently by the medial amygdala and lateral septum, which are critical for social recognition. The medial amygdala and bed nucleus of the stria terminalis are major sources of AVP fibers projecting to the ventral pallidum and lateral septum[57], whereas oxytocin fibers in the nucleus accumbens most likely originate from neurons in the preoptic area or hypothalamus[58]. Activation of these areas during mating may result in local release of these peptides. Indeed, *in vivo* microdialysis shows that AVP is released in the male prairie vole ventral pallidum during mating (J.C. Morales and

L.J.Y., unpublished data), and vaginocervical stimulation increases central oxytocin release in sheep[59]. Thus, mating ultimately results in the concurrent activation of D2 receptors in the nucleus accumbens of both sexes, OTR in the prefrontal cortex and nucleus accumbens of females and V1aR in the ventral pallidum of males. As a result, the reinforcing, hedonic properties of mating may become coupled with the olfactory signatures of the mate, resulting in a conditioned partner preference, much in the same way as drugs of abuse result in conditioned place preferences. In this model, the basic mechanism of bonding is similar in males and females; the neuropeptides are simply modulating two different nodes of the same circuits. In nonmonogamous species, sexual activity can also result in conditioned preferences for nonsocial stimuli, including neutral odors placed on the sexual partner[60]. However, in nonmonogamous species, the dopamine system and the oxytocin and AVP systems are uncoupled because of the low densities of OTR and V1aR in this pathway.

We must stress that the study of the neurobiology of social bonding in voles is in its infancy, and the model described here draws heavily on neuroanatomical, behavioral and pharmacological data obtained from rat studies, particularly those focusing on conditioned learning, reinforcement and addiction. Our model is clearly limited in scope, and raises many more questions than it answers. For example, what is the nature of the interactions between the peptide and dopamine systems? How are other neurotransmitters such as glutamate and GABA involved in pair bonding? How do the circuits involved in olfactory processing converge on the reward circuits, and how does this result in olfactory conditioning? Is there a role for other structures such as the hippocampus and cortex? And finally, what types of molecular and synaptic changes take place to lead to the development of a permanent pair bond. Thus, although this admittedly is an oversimplified model, it provides a neurobiological framework in which to generate and test hypotheses regarding pair bonding.

The molecular basis of the pair bond

If our current model is correct, one would predict that pair-bonding behavior could be potentially induced in a nonmonogamous species by expressing OTR or V1aR in the nucleus accumbens or ventral pallidum. We tested this prediction using viral vector–mediated gene transfer to overexpress *Avpr1a*, the gene encoding V1aR, in the ventral pallidum of the nonmonogamous male meadow vole[6] (**Fig. 4a**,**b**). After cohabitation with a receptive female during which copulation occurred, these transgenic animals showed enhanced partner preference compared to controls. Pretreating virus-treated voles with a D2 receptor antagonist prevented partner preferences (**Fig. 4a**). This study has remarkable implications for the evolution of complex behavior, suggesting that mutations altering the expression pattern of a single gene can have a profound impact on complex social behaviors.

How did the differential patterns of V1aR and OTR expression emerge between monogamous and nonmonogamous species? Because researchers have studied this question most extensively with respect to *Avpr1a*, we will limit our discussion to this gene. The *Avpr1a* genes in the prairie vole and nonmonogamous montane vole are highly homologous[61]. However, approximately 660 base pairs upstream of the transcription start site, the prairie vole *Avpr1a* gene contains 500 base pairs of highly repetitive sequence, known as a microsatellite; in montane and meadow voles, this repetitive sequence is much shorter (**Fig. 4c**). Microsatellite sequences are highly unstable[62], and there are several examples of genes for which polymorphic microsatellites in the regulatory region result in differential levels of expression[63,64]. It is clear that the sequences proximal to the *Avpr1a* coding region determine the pattern of expression, as a transgenic mouse expressing a prairie vole *Avpr1a* gene that included 2.4 kb of upstream sequence expressed the *Avpr1a* gene in a pattern similar to that of the prairie vole[61]. The species-specific microsatellite also modulates gene expression in a cell type–specific manner. Replacing the prairie vole microsatellite with the shorter montane vole sequence increases reporter gene expression in a transcription reporter assay (**Fig. 4d**)[65]. Although the results, obtained in a cultured rat A7r5 cell line, are in the opposite direction from what one would predict from the species differences in ventral pallidal receptor binding, the effect is consistent with the higher level of V1aR expression in the septum of montane voles compared to prairie voles. As the effect of the microsatellite on expression is cell type–specific, it is likely that in other cell lines, and indeed in the brain itself, the prairie vole microsatellite might yield higher levels of transcription than the montane vole sequence. Together, these data suggest that expansion or contraction of this microsatellite in the 5′ flanking regulatory region of this gene could have been the molecular event that resulted in the altered expression of the V1aR gene in the preexisting reward circuit, resulting in the biological potential to develop conditioned partner preferences. We do not know, however, which selective pressures influenced the frequency of the microsatellite alleles, and consequently the monogamous social structure, in voles. The human V1aR gene (*AVPR1A*) has three highly polymorphic microsatellite sequences in the 5′ flanking region, and it has been suggested that variation in one of these sequences may be associated with autism[66,67].

Implications for human bonding

Undoubtedly there are numerous molecular and neurobiological pathways that could evolve to support pair-bond formation between mates, and different species may have achieved similar behaviors through a process of convergent evolution involving different circuits. We strongly emphasize that there are no hard data demonstrating common physiological mechanisms for pair-bond formation in voles and man. In addition, as with many human behaviors, the emergence of the neocortex and its ability to modify subcortical function cannot be ignored. Nevertheless, it is intriguing to consider the possibility that similar mechanisms may underlie the formation of pair bonds in both humans and rodents. Although it is not known whether human sexual intercourse results in central oxytocin or AVP release, plasma oxytocin levels are elevated at the time of orgasm in women, and similarly, plasma AVP concentrations increase during sexual arousal in men[68,69]. These changes may or may not reflect central peptide release; it is intriguing, however, to consider how aspects of human sexuality may reflect the influence of intercourse on pair bonding. For example, human females are 'hidden ovulators' and engage in sexual activity throughout the ovarian cycle. This regular sexual activity may serve to activate the circuits underlying bonding, thus strengthening the pair bond. Furthermore, in contrast to other mammalian species, human females have enlarged mammary tissues independent of lactation, and breast and nipple stimulation are an integral part of human sexuality. Nipple stimulation during lactation is one of the most potent stimuli for oxytocin release[70]. If oxytocin is involved in human social attachment, this aspect of sexual activity may thus serve to reinforce sexual bonding.

Human imaging studies also provide evidence consistent with the hypothesis that reward and neuropeptide circuits are involved in pair bonding in humans. When human subjects viewed photographs of individuals with whom they claimed to be romantically in love, their brain activity patterns (as measured by functional magnetic reso-

nance imaging, fMRI) looked remarkably similar to those observed after cocaine or μ-opioid infusions, with heavy activation of the VTA and striatal dopamine regions[71]. Many of the regions activated are rich in oxytocin, AVP or their respective receptors[72,73]. Similar patterns of activity occur when mothers view images of their own children, suggesting some overlap between the neural mechanisms of maternal attachment and those of romantic love[74]. In addition, the VTA and striatum show substantial activity (as measured by positron emission tomography, PET) during ejaculation in men, paralleling the activation pattern evoked by a heroin rush[75].

The work reviewed here has focused primarily on the neurobiology of mating-induced, heterosexual pair bonds. It is also intriguing to consider whether other types of social bonds, including familial bonds, close friendships or homosexual relationships might use some of the same neurobiological mechanisms.

The pair bond is an integral aspect of human sexuality with important implications for both psychological and physical health. In the last few years, the neurobiological mechanisms underlying pair bonding in voles have provided valuable insights into the social brain. The convergence of mechanisms underlying reward, conditioning and the neural processing of social cues seems to result in the motivation to maintain selective contact with one's partner. It is unclear whether the same mechanisms are involved in rodent and human pair bonding, but it is likely that in both cases, the social brain and reward circuits are both involved, perhaps giving credence to the adage, "love is an addiction."

ACKNOWLEDGMENTS

The authors acknowledge A.Z. Murphy, E.A.D. Hammock, M.M. Lim, B. Aragona and T. Curtis for discussion and comments during the writing of this manuscript. The authors especially thank C.S. Carter and T.R. Insel for their pioneering work, which laid the foundation for neurobiological studies of social bonding. Much of this work was supported by National Institute of Mental Health grants to L.J.Y. and Z.X.W.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

Received 23 June; accepted 10 August 2004
Published online at http://www.nature.com/natureneuroscience/

1. Wolff, J.O., Mech, S.G., Dunlap, A.S. & Hodges, K.E. Multi-male mating by paired and unpaired female prairie voles (*Microtus ochrogaster*). *Behaviour* **139**, 1147–1160 (2002).
2. Kleiman, D. Monogamy in mammals. *Q. Rev. Biol.* **52**, 39–69 (1977).
3. Insel, T.R. & Young, L.J. The neurobiology of attachment. *Nat. Rev. Neurosci.* **2**, 129–136 (2001).
4. Carter, C.S., DeVries, A.C. & Getz, L.L. Physiological substrates of mammalian monogamy: the prairie vole model. *Neurosci. Biobehav. Rev.* **19**, 303–314 (1995).
5. Insel, T.R., Preston, S. & Winslow, J.T. Mating in the monogamous male: behavioral consequences. *Physiol. Behav.* **57**, 615–627 (1995).
6. Lim, M.M. *et al.* Enhanced partner preference in promiscuous species by manipulating the expression of a single gene. *Nature* **429**, 754–757 (2004).
7. Wang, Z.X. & Insel, T.R. Parental behavior in voles. *Adv. Study Behav.* **25**, 361–384 (1996).
8. Getz, L.L. & Carter, C.S. Prairie-vole partnerships. *Am. Sci.* 84, 56–62 (1996).
9. Williams, J., Catania, K. & Carter, C. Development of partner preferences in female prairie voles (*Microtus ochrogaster*): the role of social and sexual experience. *Horm. Behav.* **26**, 339–349 (1992).
10. Kendrick, K.M. *et al.* Neural control of maternal behavior and olfactory recognition of offspring. *Brain Res. Bull.* **44**, 383–395 (1997).
11. Goodson, J.L. & Bass, A.H. Social behavior functions and related anatomical characteristics of vasotocin/vasopressin systems in vertebrates. *Brain Res. Rev.* **35**, 246–265 (2001).
12. Ferris, C.F., Albers, H.E., Wesolowski, S.M., Goldman, B.D. & Luman, S.E. Vasopressin injected into the hypothalamus triggers a stereotypic behavior in golden hamsters. *Science* **224**, 521–523 (1984).
13. Williams, J.R., Insel, T.R., Harbaugh, C.R. & Carter, C.S. Oxytocin administered centrally facilitates formation of a partner preference in prairie voles (*Microtus ochrogaster*). *J. Neuroendocrinol.* **6**, 247–250 (1994).
14. Winslow, J., Hastings, N., Carter, C.S. & Harbaugh, C. & Insel, T.R. A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature* **365**, 545–548 (1993).
15. Insel, T.R. & Hulihan, T. A gender-specific mechanism for pair bonding: Oxytocin and partner preference formation in monogamous voles. *Behav. Neurosci.* **109**, 782–789 (1995).
16. Cho, M.M., DeVries, A.C., Williams, J.R. & Carter, C.S. The effects of oxytocin and vasopressin on partner preferences in male and female prairie voles (*Microtus ochrogaster*). *Behav. Neurosci.* **113**, 1071–1079 (1999).
17. Cushing, B. & Carter, C.S. Peripheral pulses of oxytocin increase partner preferences in female, but not male, prairie voles. *Horm. Behav.* **37**, 49–56 (2000).
18. Bales, K. & Carter, C.S. Developmental exposure to oxytocin facilitates partner preferences in male prairie voles (*Microtus ochrogaster*). *Behav. Neurosci.* **117**, 854–859 (2003).
19. DeVries, A.C., DeVries, M.B., Taymans, S.E. & Carter, C.S. Stress has sexually dimorphic effects on pair bonding in prairie voles. *Proc. Natl. Acad. Sci. USA* **93**, 11980–11984 (1996).
20. DeVries, C.A., DeVries, M.B., Taymans, S. & Carter, C.S. Modulation of pair bonding in female prairie voles (*Microtus ochrogaster*) by corticosterone. *Proc. Natl. Acad. Sci. USA* **92**, 7744–7748 (1995).
21. Devries, A.C., Guptaa, T., Cardillo, S., Cho, M. & Carter, C.S. Corticotropin-releasing factor induces social preferences in male prairie voles. *Psychoneuroendocrinology* **27**, 705–714 (2002).
22. Insel, T.R. & Shapiro, L.E. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. *Proc. Natl. Acad. Sci. USA* **89**, 5981–5985 (1992).
23. Insel, T.R., Wang, Z. & Ferris, C.F. Patterns of brain vasopressin receptor distribution associated with social organization in microtine rodents. *J. Neurosci.* **14**, 5381–5392 (1994).
24. Young, L.J., Lim, M., Gingrich, B. & Insel, T.R. Cellular mechanisms of social attachment. *Horm. Behav.* **40**, 133–148 (2001).
25. Lim, M.M. & Young, L.J. Vasopressin-dependent neural circuits underlying pair bond formation in the monogamous prairie vole. *Neuroscience* **125**, 35–45 (2004).
26. Liu, Y., Curtis, J.T. & Wang, Z.X. Vasopressin in the lateral septum regulates pair bond formation in male prairie voles (*Microtus ochrogaster*). *Behav. Neurosci.* **115**, 910–919 (2001).
27. Wise, R.A. Brain reward circuitry: insights from unsensed incentives. *Neuron* **36**, 229–240 (2002).
28. Heimer, L., Zahm, D.S., Churchill, L., Kalivas, P.W. & Wohltmann, C. Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience* **41**, 89–125 (1991).
29. Klitenick, M., Deutch, A., Churchill, L. & Kalivas, P.W. Topography and functional role of dopaminergic projection from the ventral messencephallic tegmentum to the ventral pallidum. *Neuroscience* **50**, 371–386 (1992).
30. Koob, G.F. & Swerdlow, N.R. The functional output of the mesolimbic dopamine system. *Ann. N.Y. Acad. Sci.* **537**, 216–227 (1988).
31. Kalivas, P.W., Churchill, L. & Klitenick, M.A. The circuitry mediating the translation of motivational stimuli into adaptive motor responses. in *Limbic Motor Circuits and Neuropsychiatry* (eds. Kalivas, P.W. & Barnes, C.D.) 237–288 (CRC Press, Boca Raton, Florida, USA, 1993).
32. Di Chiara, G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav. Brain Res.* **137**, 75–114 (2002).
33. Koob, G.F. & Nestler, E.J. The neurobiology of drug addiction. *J. Neuropsychiatry Clin. Neurosci.* **9**, 482–497 (1997).
34. Kelley, A.E. & Berridge, K.C. The neuroscience of natural rewards: relevance to addictive drugs. *J. Neurosci.* **22**, 3306–3311 (2002).
35. Becker, J.B., Rudick, C.N. & Jenkins, W.J. The role of dopamine in the nucleus accumbens and striatum during sexual behavior in the female rat. *J. Neurosci.* **21**, 3236–3241 (2001).
36. Pfaus, J.G. *et al.* Sexual behavior enhances central dopamine transmission in the male rat. *Brain Res.* **530**, 345–348 (1990).
37. Insel, T.R. Is social attachment an addictive disorder. *Physiol. Behav.* **79**, 351–357 (2003).
38. Paredes, R. & Alonso, A. Sexual behavior regulated (paced) by the female induces conditioned place preference. *Behav. Neurosci.* **111**, 123–128 (1997).
39. Everitt, B.J. Sexual motivation: a neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses of male rats. *Neurosci. Biobehav. Rev.* **14**, 217–232 (1990).
40. Pfaus, J. & Phillips, A. Role of dopamine in anticipitory and consummatory measures of sexual behavior in the male rat. *Behav. Neurosci.* **105**, 727–743 (1991).
41. Aragona, B.J., Liu, Y., Cameron, A., Perlman, G. & Wang, Z.X. Opposite modulation of social attachment by D1- and D2-type dopamine receptor activation in nucleus accumbens shell. *Horm. Behav.* **44**, 37 (2003).
42. Aragona, B.J., Liu, Y., Curtis, T.J., Stephan, F.K. & Wang, Z.X. A critical role for nucleus accumbens dopamine in partner preference formation of male prairie voles. *J. Neurosci.* **23**, 3483–3490 (2003).
43. Gingrich, B., Liu, Y., Cascio, C., Wang, Z. & Insel, T.R. Dopamine D2 receptors in the nucleus accumbens are important for social attachment in female prairie voles (*Microtus ochrogaster*). *Behav. Neurosci.* **114**, 173–183 (2000).
44. Liu, Y. & Wang, Z.X. Nucleus accumbens dopamine and oxytocin interact to regulate pair bond formation in female prairie voles. *Neuroscience* **121**, 537–544 (2003).
45. Pitkow, L.J. *et al.* Facilitation of affiliation and pair-bond formation by vasopressin receptor gene transfer into the ventral forebrain of a monogamous vole. *J. Neurosci.* **21**, 7392–7396 (2001).
46. Kovacs, G.L., Sarnyai, Z. & Szabo, G. Oxytocin and addiction: a review. *Psychoneuroendocrinology* **23**, 945–962 (1998).

47. Pfister, H.P. & Muir, J.L. Influence of exogenously administered oxytocin on central noradrenaline, dopamine and serotonin levels following psychological stress in nulliparous female rats (*Rattus norvegicus*). *Int. J. Neurosci.* **45**, 221–229 (1989).
48. Melis, M.R., Argiolas, A. & Gessa, G.L. Apomorphine increases plasma oxytocin concentration in male rats. *Neurosci. Lett.* **98**, 351–355 (1989).
49. Ferguson, J.N., Young, L.J. & Insel, T.R. The neuroendocrine basis of social recognition. *Front. Neuroendocrinol.* **23**, 200–224 (2002).
50. Ferguson, J.N., Young, L.J., Hearn, E.F., Insel, T.R. & Winslow, J.T. Social amnesia in mice lacking the oxytocin gene. *Nat. Genet.* **25**, 284–288 (2000).
51. Ferguson, J.N., Aldag, J.M., Insel, T.R. & Young, L.J. Oxytocin in the medial amygdala is essential for social recognition in the mouse. *J. Neurosci.* **21**, 8278–8285 (2001).
52. Everts, H.G.J. & Koolhaas, J.M. Differential modulation of lateral septal vasopressin receptor blockade in spatial-learning, social recognition, and anxiety-related behaviors in rats. *Behav. Brain Res.* **99**, 7–16 (1999).
53. Landgraf, R. *et al.* V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities and anxiety-related behavior in rats. *J. Neurosci.* **15**, 4250–4258 (1995).
54. Landgraf, R. *et al.* Viral vector mediated gene transfer of the vole V1a vasopressin receptor in the rat septum: improved social discrimination and affiliative behavior. *Eur. J. Neurosci.* **18**, 403–411 (2003).
55. Bielsky, I.F., Hu, S-B., Szegda, K.L., Westphal, H. & Young, L.J. Profound impairment in social recognition and reduction in anxiety in vasopressin V1a receptor knockout mice. *Neuropsychopharmacology* **29**, 483–493 (2004).
56. Pfaus, J.G. & Heeb, M.M. Implications of immediate-early gene induction in the brain following sexual stimulation of female and male rodents. *Brain Res. Bull.* **44**, 397–407 (1997).
57. De Vries, G. & Buijs, R. The origin of vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. *Brain Res.* **273**, 307–317 (1983).
58. Wang, Z.X., Zhou, L., Hulihan, T.J. & Insel, T.R. Immunoreactivity of central vasopressin and oxytocin pathways in microtine rodents: a quantitative comparative study. *J. Comp. Neurol.* **366**, 726–737 (1996).
59. Kendrick, K.M., Keverne, E.B., Baldwin, B.A. & Sharman, D.F. Cerebrospinal fluid levels of acetylcholinesterase, monoamines and oxytocin during labor, parturition, vaginocervical stimulation, lamb separation and suckling in sheep. *Neuroendocrinology* **44**, 149–156 (1986).
60. Pfaus, J., Kippin, T. & Centeno, S. Conditioning and sexual behavior: a review. *Horm. Behav.* **40**, 291–321 (2001).
61. Young, L.J., Nilsen, R., Waymire, K.G., MacGregor, G.R. & Insel, T.R. Increased affiliative response to vasopressin in mice expressing the vasopressin receptor from a monogamous vole. *Nature* **400**, 766–768 (1999).
62. Li, Y.C., Korol, A.B., Fahima, T. & Nevo, E. Microsatellites within genes: structure, function, and evolution. *Mol. Biol. Evol.* **21**, 991–1007 (2004).
63. Lesch, K.P. *et al.* Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**, 1527–1531 (1996).
64. Michelhaugh, S.K., Fiskerstrand, C., Lovejoy, E., Bannon, M.J. & Quinn, J.P. The dopamine transporter gene (SLC6A3) variable number of tandem repeats domain enhances transcription in dopamine neurons. *J. Neurochem.* **79**, 1033–1038 (2001).
65. Hammock, E.A.D. & Young, L.J. Functional microsatellite polymorphisms associated with divergent social structure in vole species. *Mol. Biol. Evol.* **21**, 1057–1063 (2004).
66. Wassink, T.H. *et al.* Examination of AVPR1a as an autism susceptibility gene. *Mol. Psychiatry* published online (2004).
67. Kim, S. *et al.* Transmission disequilibrium testing of arginine vasopressin receptor 1A (AVPR1A) polymorphisms in autism. *Mol. Psychiatry* **7**, 503–507 (2002).
68. Carmichael, M.S. *et al.* Plasma oxytocin increases in the human sexual response. *J. Clin. Endocrinol. Metab.* **64**, 27–31 (1987).
69. Murphy, M.R., Seckl, J.R., Burton, S., Checkley, S.A. & Lightman, S.L. Changes in oxytocin and vasopressin secretion during sexual activity in men. *J. Clin. Endocrinol. Metab.* **65**, 738–741 (1987).
70. Christensson, K., Nilsonn, B.A., Stock, S., Matthiesen, A.S. & Unvas-Moberg, K. Effect of nipple stimulation on uterine activity and on plasma levels of oxytocin in full term, healthy, pregnant women. *Acta Obstet. Gynaecol. Scand.* **68**, 205–210 (1989).
71. Bartels, A. & Zeki, S. The neural basis for romantic love. *Neuroreport* **11**, 3829–3834 (2000).
72. Loup, F., Tribollet, E., Dubois-Dauphin, M. & Dreifuss, J.J. Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. *Brain Res.* **555**, 220–232 (1991).
73. Jenkins, J.S., Ang, V., Hawthorn, J., Rossor, M.N. & Iversen, L.L. Vasopressin, oxytocin and neurophysins in the human brain and spinal cord. *Brain Res.* **291**, 111–117 (1984).
74. Bartels, A. & Zeki, S. The neural correlates of maternal and romantic love. *Neuroimage* **21**, 1155–1166 (2004).
75. Holstege, G. *et al.* Brain activation during human male ejaculation. *J. Neurosci.* **23**, 9185–9193 (2003).
76. Wang, Z.X. *et al.* Dopamine D2 receptor-mediated regulation of partner preferences in female prairie voles: a mechanism for pair bonding. *Behav. Neurosci.* **113**, 602–611 (1999).