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**Acknowledgements**
*My sincere thanks to Mitchell Glickstein for his encouragement, suggestions, and revision of the manuscript and to Jeffrey J. Hutsler for reading and commenting on the manuscript. This work has been supported by a Jacob Javits Neuroscientist Investigator Award, NIH Grant No. NS-22897, USA.*

# Neuroendocrine bases of monogamy

Larry J. Young, Zuoxin Wang and Thomas R. Insel

**A number of studies have implicated the neurohypophyseal peptides oxytocin and vasopressin in the central mediation of complex social behaviors, including affiliation, parental care and territorial aggression. Research on a monogamous rodent, the prairie vole (*Microtus ochrogaster*), suggests that these neuropeptides are also involved in the control of several behaviors associated with monogamy, including pair bonding, paternal care and mate guarding. Comparative studies using several species of vole have identified species-specific patterns of oxytocin- and vasopressin-receptor expression in the brain that appear to be associated with a monogamous versus non-monogamous social structure. Molecular studies suggest that changes in the regulation of oxytocin- and vasopressin-receptor gene expression underlie these species differences in receptor distribution and might provide a mechanism for the evolution of monogamy in voles.**

*Trends Neurosci.* (1998) 21, 71–75

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MONOGAMY AS A FORM of social organization is found in ~3% of mammals, with a higher percentage reported in primates[1]. Monogamy in rodents is characterized by an adult male and female pair sharing a nest and home range, preferential (if not exclusive) copulating with the mate, males participating in parental care, and vigorous defending of the nest against intruders[2,3]. Alternative forms of social organization include polygamy, defined as cohabitation with multiple mates, and promiscuity, characterized by an apparent absence of long-term social relationships. Over the past several years, the neuroendocrine mechanisms underlying the behavioral components of monogamy have been investigated in a group of mouse-like rodents (voles) native to North America. Here we summarize recent research on the neuroendocrine basis of monogamy in rodents and discuss possible genetic mechanisms involved in the evolution of monogamy in voles.

## Microtine rodents: a comparative model for studying monogamy

North American microtine rodents (voles) present an excellent opportunity for the investigation of the

 0166 - 2236/98/$19.00 PII: S0166-2236(97)01167-3

**TABLE 1. Comparison of social behavior of the prairie vole and the montane vole**

| Behavior | Prairie vole | Montane vole |
|---|---|---|
| Mating system | Monogamous | Promiscuous |
| Parental care | Biparental | Maternal |
| Partner preference | High | Low |
| 'Selective' aggression | High | Low |
| Social contact | High | Low |

neural substrates underlying monogamy and social attachment. Species within the genus *Microtus* exhibit diverse forms of social organization ranging from minimally parental and promiscuous to biparental and monogamous social structures (Table 1). For example, the prairie vole (*Microtus ochrogaster*), which is highly social, forms lasting pair bonds after mating[4]. Pair-bonded males prefer the company of the mate and exhibit 'selective' aggression towards other members of the species. The breeding pair nests together: both parents provide extensive, prolonged parental care, and the offspring remain in the parental nest for several weeks beyond weaning. By contrast, the montane vole (*Microtus montanus*), which is relatively asocial, nests typically in isolated burrows and breeds promiscuously[5,6]; breeding partners do not form a pair bond after mating, males are not parental, and females abandon the offspring in the second or third postnatal week.

Remarkably, the behavioral differences between these species that have been described in field studies can be demonstrated in the lab. When several individuals are placed in a large cage, prairie voles spend more than 50% of the time in close physical contact with each other, whereas montane voles spend less than 5% of the time in close proximity to other individuals[7]. Experimental paradigms have been developed to study quantitatively various behavioral components of monogamy, such as partner-preference formation, mate guarding and paternal care. In addition, prairie voles and montane voles have been compared using various physiological and anatomical measures to investigate the neural hormones of monogamy. This search has implicated two neuroendocrine hormones, oxytocin (OT) and vasopressin (AVP), that show conspicuous differences in monogamous and non-monogamous voles.

**TABLE 2. Effects of central administration of oxytocin and vasopressin on social behavior**

| Behavior | Oxytocin | Vasopressin | Refs |
|---|---|---|---|
| **Effects in rodents** | | | |
| Affiliative behavior | +++ | ? | 8 |
| Sexual behavior | +++ | ? | 9,10 |
| Maternal behavior | +++ | + | 11,12 |
| Social memory | ++ | +++ | 13,14 |
| Territorial behavior | ? | +++ | 15 |
| Male aggression | ? | +++ | 16 |
| **Effects in monogamous voles** | | | |
| Partner preference in females | +++ | – | 17,18 |
| Partner preference in males | – | +++ | 19 |
| 'Selective' aggression | – | +++ | 19 |
| Paternal care | ? | +++ | 20 |

+++, marked effect; ++, moderate effect; +, some effect; –, no effect; ?, effect unknown.

## Oxytocin and vasopressin: hormonal substrates of monogamy

The central pathways that contain OT and AVP have been implicated in the control of a number of social behaviors in rodents, including sexual behavior, maternal behavior, affiliation, social memory, territorial behavior and aggression (Table 2). Specifically, it has been suggested that OT released in the brain at parturition could facilitate the dramatic shift from avoidance of infants to nurturing behavior in female rats and sheep[21,22]. In addition, chronic intracerebroventricular infusion of OT increases social contact in the male rat[8]. Both OT and AVP appear to facilitate the consolidation of memory of socially familiar individuals[13,14,23]. In hamsters, AVP plays a direct role in the expression of territorial aggression in males[15,16]. Because each of these behaviors is a component of monogamy, these neuropeptides are good candidates for influencing pair-bond formation in the monogamous prairie vole.

Prairie voles usually form pair bonds as a consequence of mating. Mating in this species involves 15–30 bouts of copulation during a 24 h period. Because vagino–cervical stimulation in other mammals results in central OT release[24], it seems likely that the intense mating of the prairie vole could stimulate OT release and facilitate the social attachment of the female vole to her mate. Indeed, in females that do not mate, intracerebroventricular infusion of OT[18], but not AVP[17], facilitates the formation of a pair bond, when measured by a partner preference test (Fig. 1). Conversely, intracerebroventricular injection of a specific OT-receptor antagonist, d($CH_2$)$_5$[Tyr(Me)$_2$,Thr$^4$Tyr-$NH_2^9$] ornithine vasotocin, before mating prevented the formation of a partner preference[18]. These results suggest that OT, released in response to mating behavior, is sufficient and necessary for the female to form a preference for her mate.

In the male prairie vole, mating also facilitates the formation of a partner preference[19] as well as paternal behavior[25]. However, in contrast to females, OT appears to have little effect on partner-preference formation in males[19]: mating and the subsequent emergence of these behaviors is associated with a decrease in immunocytochemical staining of AVP fibers in the lateral septum[25] and an increase in AVP mRNA in the cells projecting to the lateral septum[26]. This is consistent with a synaptic release of AVP that is accompanied by increased AVP synthesis (Fig. 2). In the male prairie vole, central administration of AVP facilitates the formation of a partner preference, aggression towards strangers[19] and paternal care[20] in the absence of mating (Figs 1,2). Furthermore, a specific vasopressin-receptor antagonist, d($CH_2$)$_5$ [Tyr(Me)]AVP, blocks the formation of a partner preference and aggression even in males experiencing extended mating bouts. The site of action of the AVP released by the fibers in the lateral septum is unclear: few AVP receptors are found in this region in the prairie vole[27], suggesting that diffusion into adjacent areas that are rich in receptors might be required for the facilitation of these behaviors.

The mechanisms underlying this gender dimorphism in the neuroendocrine control of monogamous behaviors are uncertain: there are no sex differences in the distribution or density of either OT or AVP receptors in prairie voles[27,28] and there do not appear to be sex differences in the distribution of OT-immunoreactive cells. However, there are dramatic sex differences in AVP fibers in the lateral septum, with immunoreactive staining in males far exceeding that in females[29].

Subsequent studies suggest that stress and adrenal corticosterone might also modulate the formation of partner preferences in a sexually dimorphic manner. In female prairie voles, adrenalectomy facilitates the formation of a preference for a familiar partner after only 1 h of cohabitation without mating, and corticosterone treatment reverses this effect[30]. By contrast, stress appears to facilitate partner preference in males[31]: males forced to swim before being placed with a female develop a preference for the familiar female in the absence of mating. The interactions of the neurohypophyseal peptides and stress might play an important role in the formation of pair bonds, but the nature of this interaction has yet to be elucidated.

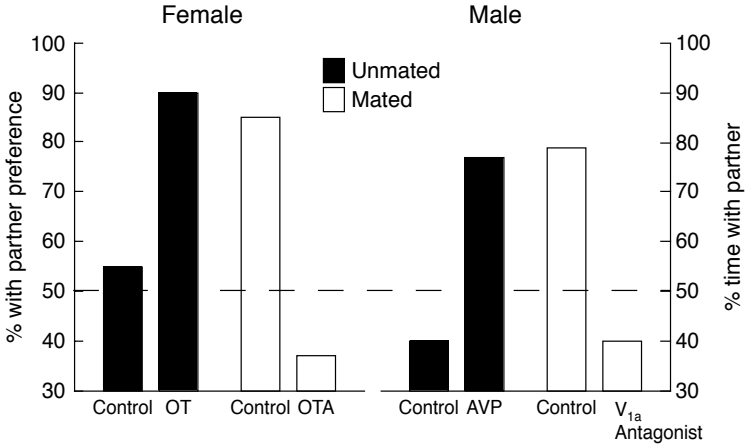


**Fig. 1.** ***Effects of intracerebroventricular oxytocin (OT) and vasopressin (AVP) on partner-preference formation in prairie voles.*** *Oxytocin facilitates the formation of partner preferences in unmated females towards male cagemates when compared with controls, whereas the oxytocin receptor antagonist (OTA) blocks the formation of preferences in mated females[20]. Similar results are found in male prairie voles following administration of AVP or an antagonist of the AVP receptor subtype $V_{1a}$ (Ref. 19). These effects are gender-specific: OT has little effect in males and vasopressin does not facilitate partner preference formation in females.*

## Neuroendocrine correlates of monogamy

The pharmacological data demonstrate a role for OT and AVP in monogamous behavior in prairie voles. In non-monogamous species, such as montane voles, central administration of OT or AVP is associated with a different behavioral response[32,33]. For example, whereas intracerebroventricular infusion of AVP into a male prairie vole increased aggression toward intruders, the identical treatment in a male montane vole did not affect aggression, but increased autogrooming[33]. Because these species share similar OT and AVP immunoreactive patterns[29] but respond differently to exogenous peptide, the neuroendocrine differences between monogamous and non-monogamous species probably reside post-synaptically rather than pre-synaptically.

The behavioral actions of OT and AVP are mediated by related, seven-transmembrane domain, G-protein-coupled receptors that are located in specific brain regions that are known to modulate social behaviors[34]. The distribution and concentration of OT receptors and AVP receptors of the subtype $V_{1a}$ have been determined using radioligand–receptor autoradiography. A comparison of the neuroanatomical distribution of the OT and AVP receptors in the prairie vole and montane vole reveals striking species differences (Fig. 3)[27,28]. Comparison of other vole species supports the suggestion that the pattern of OT and AVP receptor binding is associated with social organization: for example, the monogamous pine vole (*Microtus pinetorum*) shares similar receptor distributions with the prairie vole, whereas the receptor distributions of the promiscuous meadow vole (*Microtus pennsylvanicus*) are similar to those of the montane vole. These differences in OT and AVP receptor distributions appear to be specific because the distribution of other behaviorally relevant receptors, such as the benzodiazapine and μ opiate receptors, is virtually identical between these vole species[28].

The location of the peptide receptors in the prairie vole brain might provide clues to the cognitive mechanisms involved in pair bonding. For example, in the prairie vole brain there are high densities of OT receptors in the prelimbic cortex and nucleus accumbens, regions that are involved in the mesolimbic dopamine reward pathway (Fig. 3). Montane voles have few receptors in these regions. Therefore, it could be hypothesized that in the female prairie vole OT released upon mating activates this reward pathway, thus conditioning the female to the odor of her mate. Indeed, a dopamine $D_2$ receptor antagonist prevents

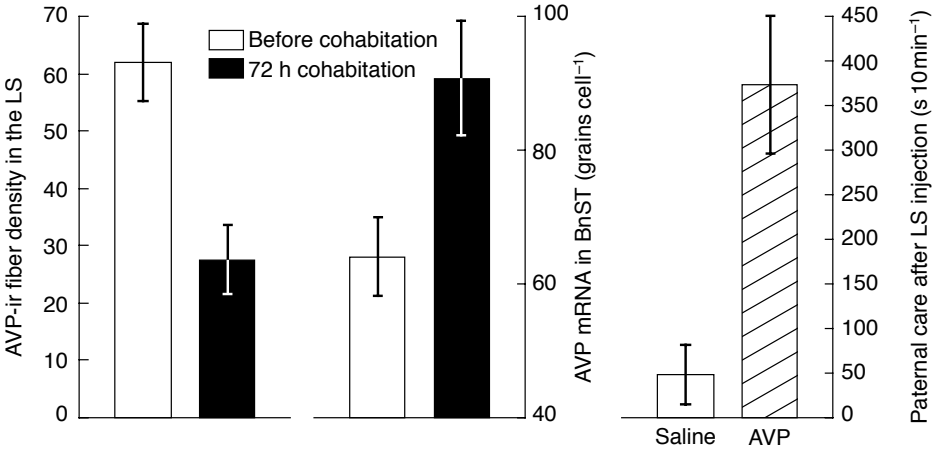


**Fig. 2.** ***Effect of 72 hours of cohabitation (and mating) with a female on AVP-immunoreactive (AVP-ir) fiber density in the lateral septum (LS) of the male prairie vole[25].*** *The apparent decrease in lateral septum (LS)-fiber AVP content in the male prairie vole is associated with an increase in AVP mRNA synthesis in the cells of the bed nucleus of the stria terminalis (BnST), which project to the LS (left, Ref. 27). These observations are consistent with a release of AVP into the LS as a consequence of cohabitation with a female. Direct injections of AVP into the LS (right) potently induce paternal care in sexually naive male prairie voles[20].*

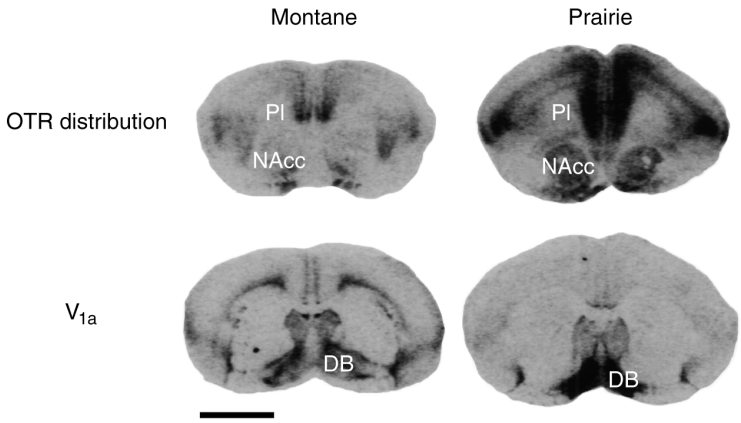


**Fig. 3.** ***Autoradiographical localization of oxytocin receptor (OTR) and vasopressin-receptor subtype $V_{1a}$ binding in montane and prairie vole brains.*** *Oxytocin (OT) and vasopressin (AVP) receptor autoradiographical studies (top and bottom rows, respectively) were perfomed on anatomically similar coronal sections from montane and pairie vole brains. The OT receptor autoradiograms are from sections slightly rostral to the $V_{1a}$ receptor sections. Compared with OTR binding in montane vole brains, binding in prairie vole brains is high in the prelimbic cortex (PI) and the nucleus accumbens (NAcc), whereas $V_{1a}$ receptor binding is intense in the diagonal band (DB). Similar species differences are found throughout the brain. Scale bar, 2.5 mm.*

the formation of a partner preference whereas a $D_2$ receptor agonist induces partner preference in female prairie voles (G. Yu, Z. Wang and T.R. Insel, unpublished). This process, in conjunction with the AVP- or OT-associated consolidation of social memory, might result in the formation of the pair bond with that specific male. In the montane vole, OT would not have these reinforcing properties but presumably activates other targets (for example, the lateral septum) that are important for nonsocial behaviors.

## Molecular mechanisms underlying monogamy

This association between neuropeptide receptor distribution and social behavior suggests a potential mechanism by which social organization might evolve. By altering the neuroanatomical distribution of behaviorally relevant receptors, new brain regions and thus new neural circuits might become responsive to the neuropeptide. This notion is supported by the marked species diversity among mammals in the pattern of OT and $V_{1a}$ receptor distribution and their regulation by gonadal steroids[35]. This phylogenetic plasticity in the regulation of receptor gene-expression might have played a significant role in the evolution of many types of species-specific social behaviors.

How could such differences in receptor distribution develop? Recent research has focused on examining the molecular mechanisms that determine the distribution of OT and AVP binding sites in the brain. Developmental differences in presynaptic innervation are unlikely to contribute to the adult receptor-binding pattern because OT knockout mice have normal OT receptor distribution and concentration[37]. Sequence analysis of the coding regions of the genes that encode OT and $V_{1a}$ receptors reveal similar receptor protein-structures between monogamous and promiscuous vole species[33,37]. Furthermore, analysis of receptor synthesis by *in situ* hybridization suggests that the species differences in the pattern of receptor binding are due entirely to differences in regional gene expression and not to differential transport from other regions[33,37]. That is, the distribution of receptor mRNA is nearly identical to the distribution of receptor binding sites in both species.

Region-specific gene expression in the brain is determined by the interaction of *cis* regulatory sequences, usually located in the 5′ flanking region of genes[38–42], and the action of regulatory proteins or transcription factors. Therefore, analysis of these sequences in the genes encoding OT and $V_{1a}$ receptors might identify potential genetic elements that are important in the control of species-specific, regional gene expression. Comparison of the first 1500 base pairs (bp) of the prairie vole and montane vole OT receptor promoter has revealed variations in potential regulatory elements that might contribute to the species differences in expression of the OT receptor gene[37]. In addition, comparison of the vasopressin receptor gene between these species has revealed more striking differences in the promoter structure: the 5′ flanking region of the prairie vole gene that encodes the vasopressin receptor contains a 450 bp sequence that is absent from this gene in the montane vole, even though the coding sequence for the receptor is 99% homologous between species. An interesting structural feature that is common to the promoters of OT and $V_{1a}$ receptor genes is the presence of long stretches of simple dinucleotide or trinucleotide repeat sequences[37,43–46]. Although present in the 5′ flanking regions of the receptor genes of several species, the length, position and composition of the sequences differ markedly between species. Indeed, it has been suggested that such 'microsatellite' sequences are associated with hypermutability of surrounding sequences and might also influence the regulation of gene expression[47]. It is conceivable that diversity in these sequences between species could contribute to the diversity in the regulation of gene expression. Indeed, the unique sequence found in the prairie vole but not in the montane vole, the $V_{1a}$ receptor 5′ promoter contains multiple repetitive sequences. In addition to this diversity in gene sequence, it is possible that species differences in the tissue-specific availability of transcription factors could account for the species-specific expression pattern.

The association between brain OT and $V_{1a}$ receptor binding patterns and monogamy in voles suggests a functional relationship: prairie voles are monogamous because of their regional sensitivity to endogenous OT and AVP. This hypothesis could be tested by altering the pattern of neuropeptide-receptor expression in a species that does not normally express these behaviors. The development of transgenic and viral vector technologies[48] provides exciting opportunities for manipulating receptor gene expression in a targeted manner. Transgenic mice have been created recently using a transgene construct containing the 5′ flanking region of the prairie vole OT-receptor gene spliced upstream of the bacterial reporter gene encoding β-galactosidase[49]. The prairie vole promoter was found to direct the expression of β-galactosidase in several brain regions of the mice that were known to express OT receptor, including the cortex, septum, amygdala and hypothalamus[50]. This study demonstrates that heterologous promoters can be used to drive region-specific gene expression in a targeted manner. Similar experiments are under way with the vasopressin-receptor gene. With the appropriate regulatory

sequences identified, it might be possible, using either conventional pronuclear injection techniques or viral vector technology, to create transgenic montane voles that carry a functional OT or $V_{1a}$ receptor transgene with expression driven by prairie vole promoters. This might result in montane voles in which the pattern of neuropeptide-receptor gene expression and potentially, social behavior have been altered. If successful, and provided that the appropriate transcription factors and second-messenger pathways are in place, these experiments should demonstrate the behavioral consequences of altered receptor expression and potentially establish a link between specific genes and monogamy in rodents.

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**Acknowledgements**
*The research for the preparation of this manuscript was supported by the grants MH56897 for LY, MH54554 for ZW, and MH56539 and the Whitehall Foundation for TRI.*

# Matrix metalloproteinases and diseases of the CNS

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**Matrix metalloproteinases (MMPs) are increasingly being implicated in the pathogenesis of several CNS diseases. In multiple sclerosis, MMPs could be responsible for the influx of inflammatory mononuclear cells into the CNS, contribute to myelin destruction and disrupt the integrity of the blood–brain barrier; in Alzheimer's disease, MMPs might mediate the deposition of amyloid β-proteins; and MMPs are known to contribute to the invasiveness of malignant glioma cells and might regulate their angiogenic capacity. Nonetheless, MMPs could also have beneficial roles in recovery from CNS injury. Therefore, both the identity of the MMP and its cellular origin could determine whether disease pathogenesis or regeneration occurs, and thus synthetic MMP inhibitors might be valuable for treating some CNS diseases.**

*Trends Neurosci.* (1998) 21, 75–80

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MATRIX METALLOPROTEINASES (MMPS) are proteolytic enzymes that are involved in the remodelling of the extracellular matrix (ECM) in a variety of physiological and pathological processes. The MMP family consists of at least 18 members (Table 1) that have common propeptide and N-terminus catalytic domains (Fig. 1). Additional, fibronectin-like repeats, transmembrane domains and C-terminus hemopexin-like domains allow categorization of MMPs into the collagenase, gelatinase, stromelysin and membrane-type

 0166 - 2236/98/$19.00 PII: S0166-2236(97)01169-7