

Neuropeptides and the evolution of social behavior

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Comparative studies over the past year have revealed two new insights into the role of neuropeptides in the evolution of social behaviors. First, across vertebrate taxa, certain neuropeptide effects appear to be gender-specific. Second, species variations in receptor gene structure can alter neuropeptide receptor distribution and thereby contribute to species differences in social behavior.

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Abbreviations

AVP	vasopressin
AVT	vasotocin
IT	isotocin
MT	mesotocin
OT	oxytocin

Introduction

Social behavior includes affiliation, reproduction, communication, and aggression. Relative to motor reflexes and autonomic responses, social behavior seems a hopelessly complex subject for neurobiological study. However, the various social behaviors, such as reproductive and aggressive behaviors, are exquisitely selected by evolution, the result of precise adaptations in brain morphology, connectivity, and chemistry. The comparative neurobiological study of social behavior, particularly neurobiological comparisons of closely related species, may therefore reveal important insights into brain–behavior relationships. Several recent studies in a wide range of taxa have demonstrated that social behavior, notwithstanding its complexity, can be studied at the molecular, cellular, and systems levels.

Many of these comparative studies have focused on neuropeptides. There are three characteristics of neuropeptide systems that make them particularly well suited for the regulation of behavior. First, most neuropeptides and their receptors are localized in discrete neural pathways, in contrast to monoamine or amino acid neurotransmitters which are expressed diffusely throughout the forebrain. Second, neuropeptides generally function as neuromodulators, with relatively slow, enduring effects on neural function. And third, some neuropeptide systems demonstrate remarkable plasticity, not only during development, but also in response to physiological fluctuations in steroid hormone concentrations. This review will focus on recent studies illustrating the role of neuropeptides in the control of gender-specific and species-specific social behaviors.

Neuropeptides and social behavior

In an elegant study of one of the most elemental forms of affiliation, de Bono and Bargmann studied the natural variation in feeding behavior in isolated populations of *C. elegans* [1]. A single nucleotide difference in the *npr-1* gene accounted for the differences in behavior in social-versus solitary-feeding strains of nematodes. Two alleles of *npr-1* are found in the wild — both coding for a G-protein-coupled receptor that is structurally related to the mammalian neuropeptide Y (NPY) receptor. Social feeders have a phenylalanine residue at position 215 of the receptor protein (NPR-215F), whereas solitary feeders have a valine residue in that position (NPR-215V). Social feeders transgenic for NPR-215V became solitary, proving that a single base change in the coding region of this neuropeptide receptor gene could dramatically alter the social behavior of *C. elegans*.

In vertebrates, most of the findings relating neuropeptides to social behavior have focused on the family of nine-amino-acid peptides (nonapeptides), which includes oxytocin (OT) and vasopressin (AVP). The nonapeptide hormones and their receptors provide an intriguing example of biochemical evolution. Although once considered to be strictly vertebrate hormones, several studies have demonstrated that structurally similar ancestral peptides share evolutionarily conserved functions in invertebrates, with a role in reproduction. A recent study in snails has demonstrated that a member of the OT/AVP family, conopressin, is expressed in neurons projecting to the penis and vas deferens where it modulates ejaculation, and is found in other neurons that regulate egg laying and female reproductive behaviors [2]. A related peptide in earthworms, annetocin, was found to be expressed in the subesophageal ganglia, which are involved in the regulation of egg laying and reproductive movement [3*].

Invertebrates have a single OT/AVP-related peptide, but an apparent gene duplication early in vertebrate evolution has given rise to two peptide lineages. One of these lines consists of vasotocin (AVT) in non-mammals and vasopressin (AVP) in mammals. The other includes isotocin (IT) in fish, mesotocin (MT) in non-mammalian tetrapods, and oxytocin (OT) in mammals (Table 1). Hoyle has provided a recent review of the molecular and biochemical evolution of these peptides and their receptors [4*]. Moore and Lowry have reviewed the neuroanatomical evolution of AVT and AVP [5]. The neuroanatomical expression pattern and the physiological regulation of the OT/AVP genes are remarkably similar among vertebrates. These peptides are expressed in specific neurons within the hypothalamus and regulated by osmotic stimuli. One recent study has illustrated the remarkable conservation in the molecular mechanisms regulating OT/AVP gene expression [6]. The

Table 1

Biochemical evolution of nine-amino-acid neuropeptides.

Isotocin	CYISNCPIGA	Fish	CYIQNCPRGA	Vasotocin
Mesotocin	CYIQNCPIGA	Amphibia	CYIQNCPRGA	Vasotocin
		Reptiles		
		Birds		
Oxytocin	CYIQNCPLGA	Mammals	CYFQNCPRGA	Vasopressin

AVP and OT genes are linked in a tail-to-tail orientation in mammals. In fish, the corresponding genes for IT and AVT are linked head-to-tail and are separated by five intervening genes. When a cosmid containing the fish IT gene was transfected into the rat genome, IT was expressed selectively in rat hypothalamic oxytocin neurons and both OT and IT were upregulated by an osmotic challenge. These results suggest that the *cis*- and *trans*-activating elements mediating the regional expression of these neuropeptides are conserved across phylogeny.

Although studies in a wide range of vertebrates indicate that the general roles of the OT/AVP peptides in regulating sociosexual behaviors are conserved, the specific behavioral effects of these peptides vary with the social organization of the species. For instance, Goodson has demonstrated that AVT increases vocalization (dawn calls) and aggression in male field sparrows, which are territorial, but fails to increase calling and has only weak effects on aggression in zebra finches, which are colonial [7,8**]. Similarly, AVP increases aggression and affiliation in monogamous prairie voles, which guard their mates and territories against intruders, but has no effect on aggression in promiscuous montane voles, which do not normally exhibit mate guarding [9,10**].

Gender differences in peptide functions

The AVT–AVP system has been a prototype for neuroanatomic sexual dimorphisms since the original description by De Vries nearly 20 years ago [11]. Recent studies across a broad range of species, including fish [12], amphibia [13,14**], birds [15–17], and mammals [18], demonstrate that AVT or AVP is more abundant in males than females, especially in hypothalamic regions linked to reproductive behavior. This sexual dimorphism is limited to a subset of AVT/AVP neurons that are responsive to testosterone [13,19], and some gender differences are seasonally dependent [13]. In perhaps the most dramatic example of this dimorphism, AVT cells enlarge when sex-changing fish shift from a female to a male morph [20]. Fish which exhibit multiple morphs, such as the midshipman, exhibit a correlation between the size of AVT cells and male-like behavioral characteristics [12].

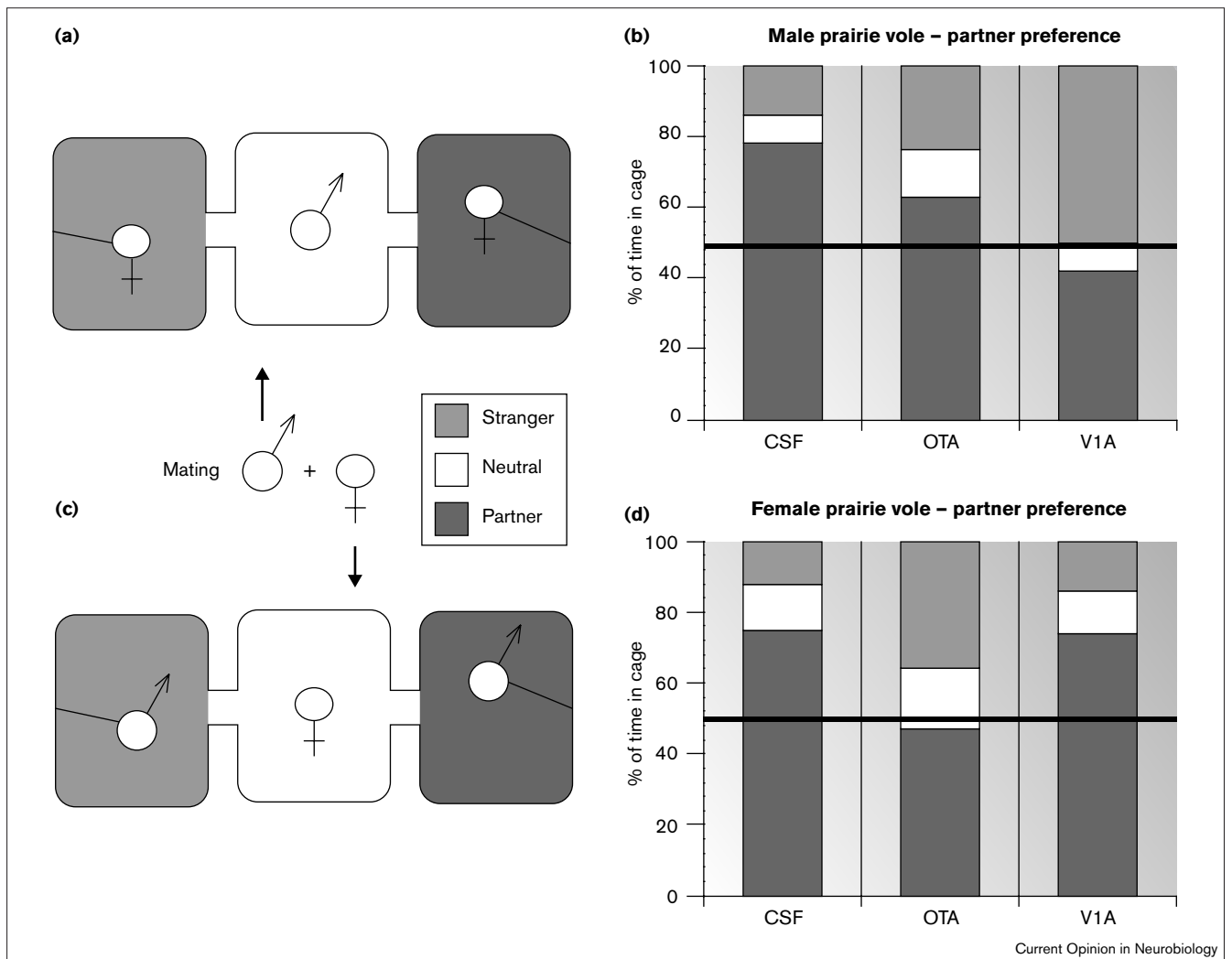
Recent studies have also demonstrated that the behavioral effects of AVT–AVP are more prominent in males whereas the IT–MT–OT line may be more important for females. Goodson and Bass [21**] have demonstrated this in the

plainfin midshipman fish, *Porichthys notatus*, which has two male morphs and a female morph, all with unique vocal characteristics. Using a laboratory preparation of forebrain-evoked, rhythmic vocal-motor activity, Goodson and Bass showed that peptides delivered to the preoptic area–anterior hypothalamus had different effects in the three morphs. Specifically, AVT, but not IT, decreased vocalization and decreased the duration of vocal bouts in Type I males, which acoustically court females. An AVP antagonist increased vocalization in these males. Conversely, IT (but not AVT) decreased vocalization in females. An OT antagonist which also blocks IT binding had the opposite effect. Type II males, which are similar to females in body size and shape and do not engage in courtship or parental care, respond to IT but not AVT, as do females.

Other studies have found a similar gender difference in the development of mating-induced partner preferences in monogamous prairie voles [22]. Prairie voles form selective, enduring pair bonds after mating. The development of a pair bond can be studied by measuring a partner preference — that is, the preference for the mate over a novel conspecific in a simple choice test. Both female and male prairie voles choose to huddle with the partner more than a stranger after mating, but not after being together for an equal period of time in the absence of mating [23,24]. As mating stimulates the release of AVP and OT in most mammals [25], these neuropeptides may contribute to the formation of a partner preference in prairie voles. Indeed, males given AVP will form a partner preference in the absence of mating and a selective AVP antagonist will block the development of a partner preference in males with normal mating behavior [26]. Curiously, identical AVP treatments in females are without effect, but OT facilitates, and a selective OT antagonist inhibits, the development of a partner preference in females [27] (but see also [28,29]; Figure 1).

The midshipman and vole findings are remarkably similar in that males respond to AVT–AVP and females respond to IT–OT. Although these results from markedly different taxa suggest that AVT–AVP facilitates male socio-sexual behaviors whereas IT–MT–OT modulates female socio-sexual behaviors, there are clear exceptions to this generalization. The direction of the behavioral effects may vary. For instance, Castagna and co-workers [30] have described a decrease rather than an increase in copulatory behavior following AVT administration to male Japanese

Figure 1



Partner preference formation in a monogamous rodent. Prairie voles are monogamous rodents that form long-term pair bonds after mating. An early step in pair bonding is the formation of a partner preference. **(a,c)** Voles that have mated were tested for a partner preference in a three-chamber apparatus in which the experimental male (a) or female (c) chooses between their tethered partner, a tethered stranger, or the neutral central cage. **(b)** As expected, control males with lateral ventricular injections of cerebrospinal fluid (CSF) before mating show a preference for the partner. In males receiving an oxytocin antagonist (OTA) injection, a partner preference

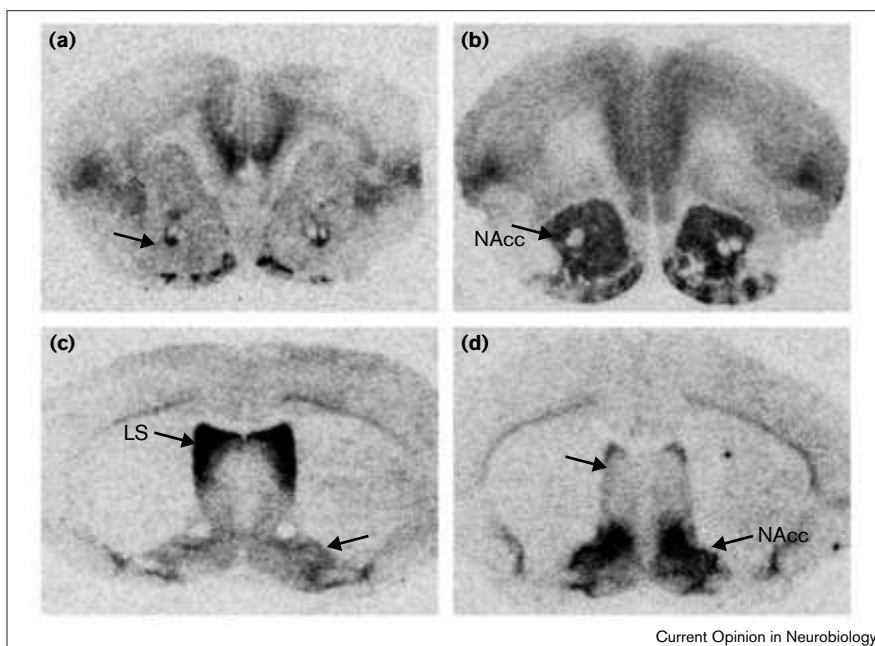
is still evident. However, when males are injected with a vasopressin antagonist (V1A) before mating, they fail to form a partner preference. **(d)** In contrast to males, females injected with either CSF or a vasopressin antagonist show a partner preference, whereas females injected with an oxytocin antagonist mate normally but fail to form a preference for the mate. Male and female voles received the same doses of each antagonist peptide (0.5 ng administered intracerebroventricularly) [26,27]. These results suggest that vasopressin is necessary for males and oxytocin is necessary for females to develop a partner preference during mating.

quail. And, given the potential for these peptides to bind to either OT or AVP receptors, high doses may influence both genders. For instance, AVP can facilitate the onset of rat maternal behavior [31], AVT alters egg-laying behavior of the female newt [13], and both peptides have been reported to influence partner preference formation in voles [29]. Moreover, in OT-knockout mice, female socio-sexual behavior appears to be preserved whereas males have a deficit in social recognition [32••]. In fact, female OT-knockout mice may also have a deficit in social recognition. However, the test used in this study was based on changes

in investigation of an intruder. As wild-type female mice investigate much less than male mice, a deficit in OT-knockout females could not be reliably detected. These exceptions notwithstanding, there is a pattern from fish to mammals that suggests that when these nine-amino-acid peptides split from their invertebrate precursors, the AVT–AVP and the IT–MT–OT lines evolved to modulate gender-specific social behaviors. The gender-specific roles of these peptides are restricted to brain functions, as both peptides also have peripheral functions, such as regulating blood pressure and kidney function, which are common to

Figure 2

Species differences in oxytocin and vasopressin receptors. Coronal forebrain sections from montane and prairie voles were labeled with (a,b) an iodinated analogue of oxytocin and (c,d) an iodinated analogue of vasopressin. In the nucleus accumbens (NAcc), oxytocin receptors (a) were not detectable in montane voles but (b) were prominent in prairie voles. In a more posterior section, vasopressin receptors (c) were prominent in the lateral septum (LS) of the montane vole, but (d) found mainly in the shell of the accumbens (NAcc) of the prairie vole.



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both sexes. In spite of gender differences in the central effects of the nonapeptide hormones, there is little evidence for a gender difference in brain receptors for either AVP or OT.

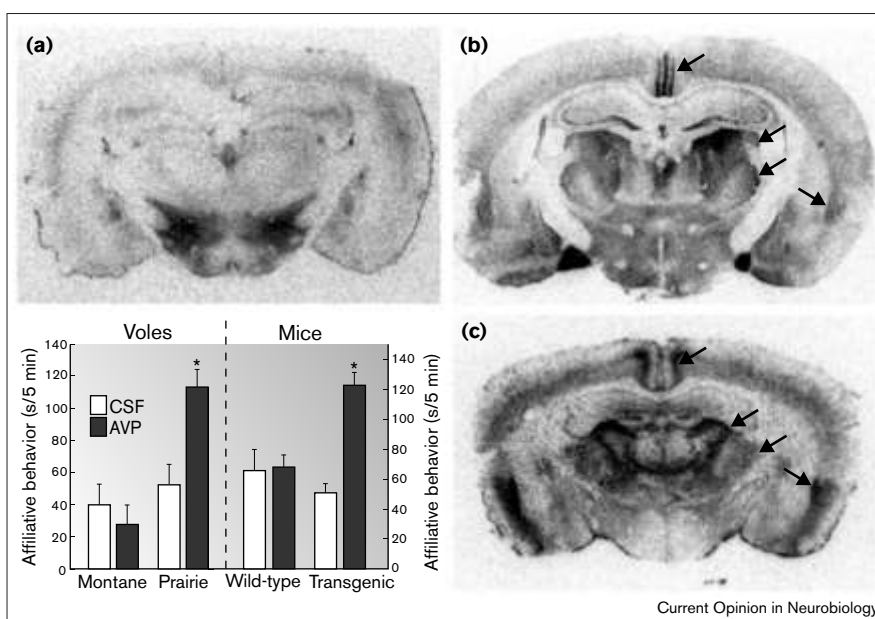
Species differences in peptide functions

Although there are surprisingly few, if any, gender differences in AVP and OT receptor distribution, there are extraordinary species differences in receptor distribution,

even among closely related species [33*]. In fact, nearly every species studied to date has a unique pattern of expression and regulation of OT/AVP receptors. As noted above, related species with different forms of social organization show marked differences in the behavioral response to AVT–AVP or OT. These species differences in behavioral response are associated with differences in the pattern of receptor expression. For instance, in monogamous prairie voles, in which OT induces a partner preference,

Figure 3

A vole gene in the mouse brain. Prairie voles and montane voles not only have differences in vasopressin receptor distribution (see Figure 2) but also differ in the 5' flanking region of the V1a vasopressin receptor gene. A transgene of the 5' flanking region as well as the coding region of the prairie vole V1a receptor gene was inserted into the mouse genome. The native pattern of brain V1a receptors in (a) wildtype mice and (b) prairie voles are markedly different. The transgenic mouse (c) resembled the prairie vole in terms of receptor binding (arrows point to homologous regions) and, like the prairie vole, responded to vasopressin with an increase in affiliation, measured as time huddling with a conspecific.



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OT receptors are found in the nucleus accumbens and pre-limbic cortex [34] (see Figure 2). In the non-monogamous montane vole, OT receptors are virtually absent in these regions but are highly expressed in the lateral septum [34]. As a selective OT antagonist administered into either the nucleus accumbens or the pre-limbic cortex can prevent formation of a partner preference in prairie voles, it seems likely that receptors in these regions are important for this behavior [35].

In a recent series of experiments, Young and co-workers have begun to investigate the molecular mechanisms for these species differences. In a result reminiscent of the de Bono and Bargmann findings with social and solitary *C. elegans* [1], the vasopressin receptor gene has been found to be different in social and asocial voles. In the vole case, however, the sequence differences are in the 5' flanking regions of the AVP receptor [10**] rather than the coding region as described in the *C. elegans* study. Both prairie and pine voles, which are highly affiliative and monogamous, have a 420-base microsatellite expansion just over 700 base pairs upstream of the transcription start site of the V1a receptor gene, the AVP receptor thought to regulate behavior. This expansion is absent in the V1a receptor gene of montane and meadow voles, which are asocial and non-monogamous [10**]. A transgenic mouse was created by inserting the prairie vole V1a receptor gene, including the promoter, into the mouse genome. This mouse expressed the receptor in a prairie vole-like pattern and, in contrast to non-transgenic mice, responded to AVP with an increase in affiliative behavior [10**] (see Figure 3).

Conclusions and implications

These studies, from nematodes to mammals, suggest the importance of neuropeptides for social behavior. Recent results lend support to the hypothesis of gender differences in the behavioral response to nonapeptide hormones, with AVT–AVP effects evident in males and IT–MT–OT effects most pronounced in females. At least in the AVT–AVP case, gender differences are also apparent in the number of peptide-synthesizing cells and the projections of these cells. Species differences in the behavioral response to these neuropeptides appear to be associated with species differences in the neuroanatomic distribution of receptors. Vole studies have implicated the promoter region of the receptor gene as a site for species variation. Mutations in the regulatory regions of OT/AVP receptors resulting in alterations in expression patterns may be important for the development of variations in social behavior and, under ecologically appropriate conditions, speciation. A major implication of this work is that variation in promoter sequences of the OT and V1a receptor genes may also contribute to within-species variation, resulting in individual differences in social behavior.

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