13. E. D. Jarvis, C. Scharff, M. R. Grossman, J. A. Ramos, F. Nottebohm, *Neuron* **21**, 775 (1998).
14. S. S. Burmeister, E. D. Jarvis, R. D. Fernald, *PloS Biol.* **3**, e363 (2005).
15. L. Grosenick, T. S. Clement, R. D. Fernald, *Nature* **445**, 429 (2007).
16. K. J. O'Donovan, W. G. Tourtellotte, J. Milbrandt, J. M. Baraban, *Trends Neurosci.* **22**, 167 (1999).
17. C. W. Whitfield, A.-M. Cziko, G. E. Robinson, *Science* **302**, 296 (2003).
18. C. M. Grozinger, N. Sharabash, C. W. Whitfield, G. E. Robinson, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 14519 (2003).
19. S. A. Ament, M. Corona, H. S. Pollack, G. E. Robinson, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 4226 (2008).
20. M. E. Cummings *et al.*, *Proc. R. Soc. London Ser. B. Biol. Sci.* **275**, 393 (2008).
21. K. Replogle *et al.*, *BMC Genomics* **9**, 131 (2008).
22. H. Liu, M. M. Wu, H. H. Zakon, *Dev. Neurobiol.* **67**, 1289 (2007).
23. C. Cirelli, C. M. Gutierrez, G. Tononi, *Neuron* **41**, 35 (2004).
24. F. A. Champagne, D. D. Francis, A. Mar, M. J. Meaney, *Physiol. Behav.* **79**, 359 (2003).
25. I. C. Weaver *et al.*, *Nat. Neurosci.* **7**, 847 (2004).
26. D. L. Champagne *et al.*, *J. Neurosci.* **28**, 6037 (2008).
27. D. W. Pfaff, *Drive* (MIT Press, Cambridge, MA, 1999).
28. D. S. Falconer, T. F. C. Mackay, *Introduction to Quantitative Genetics* (Longmans Green, Harlow Essex, UK, ed. 4, 1996).
29. A. Caspi, T. E. Moffitt, *Nat. Rev. Neurosci.* **7**, 583 (2006).
30. D. K. Lahiri, B. Maloney, *Nat. Rev. Neurosci.* 10.1038/nrn2022-c1 (2006).
31. A. Abbott, *Nature* **454**, 154 (2008).
32. J. Wang, K. G. Ross, L. Keller, *PLoS Genet.* **4**, e1000127 (2008).
33. B. J. Dickson, *Science* **322**, 904 (2008).
34. D. A. Wheeler *et al.*, *Science* **251**, 1082 (1991).
35. S. Fink, L. Excoffier, G. Heckel, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 10956 (2006).
36. Y. Ben-Shahar, A. Robichon, M. B. Sokolowski, G. E. Robinson, *Science* **296**, 741 (2002).
37. A. L. Toth, G. E. Robinson, *Trends Genet.* **23**, 334 (2007).
38. W. Enard *et al.*, *Nature* **418**, 869 (2002).
39. W. Shu *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 9643 (2005).
40. S. Haesler *et al.*, *PLoS Biol.* **5**, e321 (2007).
41. M. Groszer *et al.*, *Curr. Biol.* **18**, 354 (2008).
42. J. Sebat *et al.*, *Science* **316**, 445 (2007), published online 14 March 2007; 10.1126/science.1138659.
43. J. D. Jensen, A. Wong, C. F. Aquadro, *Trends Genet.* **23**, 568 (2007).
44. J. C. Hall, *J. Neurogenet.* **17**, 1 (2003).
45. We thank J. Desjardins, A. Fernald, K. A. Hughes, D. B. Kelley, K. Maruska, C. Olin, M. B. Sokolowski, L. J. Stubbs, members of the Clayton and Robinson laboratories, and two anonymous reviewers for reviews of this manuscript and C. Harrell for graphical assistance. Research by the authors cited here was supported by the following grants: NIH R01 NS051820 and NS045264 (D.F.C.); NIH NS34950 Javits Award and United States–Israel Binational Science Foundation 200596 (R.D.F.); and NIH R01 GM073644, NSF Frontiers in Biological Research EF04-25852, U.S. Department of Agriculture AG2003-35302-13490, and a Burroughs Wellcome Fund Innovation Award (G.E.R.).

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REVIEW

# Oxytocin, Vasopressin, and the Neurogenetics of Sociality

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**There is growing evidence that the neuropeptides oxytocin and vasopressin modulate complex social behavior and social cognition. These ancient neuropeptides display a marked conservation in gene structure and expression, yet diversity in the genetic regulation of their receptors seems to underlie natural variation in social behavior, both between and within species. Human studies are beginning to explore the roles of these neuropeptides in social cognition and behavior and suggest that variation in the genes encoding their receptors may contribute to variation in human social behavior by altering brain function. Understanding the neurobiology and neurogenetics of social cognition and behavior has important implications, both clinically and for society.**

Social interactions affect every aspect of our lives, from wooing a mate and caring for our children to determining our success in the workplace. Abnormal manifestations of social behavior, such as the pathological trusting associated with Williams-Beuren Syndrome (*1*), social withdrawal in depression, and decreased social cognition in autism, profoundly affect the lives of those who suffer from these disorders. Neuroscientists once considered social behavior to be too hopelessly complex to understand at a mechanistic level, but advances in animal models of social cognition and bonding, as well as application of new technologies in human research have demonstrated that the molecular basis of social behavior is not beyond the realm of our understanding. There appears to be marked conservation in the molecular mechanisms regulating social behavior across diverse species, including our own.

Interacting with other neurotransmitter systems within specific neural circuits, neuropeptides have emerged as central players in the regulation of social cognition and behavior. Neuropeptides may act as neurotransmitters, if released within synapses, or as neurohormones, activating receptors distant from the site of release, which provides evolutionary flexibility to their actions (*2*). Within vertebrates, a majority of work relating neuropeptides to social behavior has focused on members of the oxytocin/vasopressin family. Homologs of oxytocin and vasopressin existed at least 700 million years ago and have been identified in such diverse organisms as hydra, worms, insects, and vertebrates. Among these distant taxa, oxytocin- and vasopressin-related peptides play a general role in the modulation of social and reproductive behaviors. In contrast to this apparent conservation in function, the specific behaviors affected by these neuropeptides are notably species-specific.

Only recently have scientists begun to dissect the roles of oxytocin, vasopressin, and their related receptors in human social behavior. Whereas human social behavior is more nuanced and complex than the behaviors typically assayed in other animals, this complexity has created unique opportunities to design finely honed tasks that have revealed a potential role for these peptides in personality, trust, altruism, social bonding, and our ability to infer the emotional state of others. Here, we review the evidence of evolutionary conservation within the vasopressin/oxytocin peptide family, briefly discuss the role of these peptides and their respective receptors in modulating social behavior and bonding, and provide a synthesis of recent advances implicating the oxytocin and vasopressin systems in human trust, cooperation, and social behavior.

## Conservation of Neuropeptide Systems Regulating Social Behavior

The mammalian oxytocin and vasopressin nonapeptides, so called for their nine–amino acid composition, differ from each other at only two amino acid positions (Fig. 1). Oxytocin, vasopressin, and their respective nonmammalian vertebrate lineages are thought to have arisen from a gene-duplication event before vertebrate divergence. Within these lineages, peptides vary by a single amino acid, and their genes are found near each other on the same chromosome. Invertebrates, with few exceptions, have only one oxytocin/vasopressin homolog, whereas vertebrates have two (*3*, *4*).

In mammals, oxytocin and vasopressin are produced primarily within hypothalamic brain regions and then shuttled to the pituitary for peripheral release or projected to various brain regions. Notably, just as oxytocin and vasopressin are expressed within the hypothalamus of mammals, their homologs are expressed within similar neurosecretory brain regions of organisms as diverse as worms and fish. A characterization of annepressin (the homolog of oxytocin/vasopressin in segmented worms) and vasotocin (vasopressin's counterpart in bony fish) revealed conserved neural expression of these genes

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within sensory-neurosecretory cells expressing common transcription factor combinations and tissue-restricted microRNAs (*5*). Furthering the idea that vasopressin/oxytocin homologs have ancient gene regulatory features that direct their expression in an evolutionarily conserved neural architecture, transgenic rats with a genomically integrated blowfish locus containing the isotocin gene, the teleost homolog of oxytocin, express isotocin within oxytocinergic neurons of the hypothalamus (*6*). These isotocin transgenic rats also show conserved physiological regulation of the transgene; osmotic challenge, a potent regulator of both oxytocin and vasopressin release, is sufficient to induce a sixfold increase in isotocin expression. This finding has been replicated in transgenic mice carrying the blowfish isotocin locus and the bovine oxytocin locus (*7*, *8*). These impressive results provide evidence that both the cis- and trans-acting elements controlling oxytocin/vasopressin neural expression, as well as its physiological regulation, are highly conserved across both vertebrates and invertebrates.

Oxytocin and vasopressin's roles in facilitating species-typical social and reproductive behaviors are as evolutionarily conserved as their structure and expression, although the specific behaviors that they regulate are quite diverse (*9*). For instance, conopressin, the snail homolog of oxytocin/vasopressin, modulates ejaculation in males and egg-laying in females. Within vertebrates, the distinct oxytocin and vasopressin peptide lineages often show sexually dimorphic expression and behavioral effects (*10*). The oxytocin lineage of peptides influences female sociosexual behaviors including sexual intercourse, parturition, lactation, maternal attachment, and pair bonding. Conversely, vasopressin typically influences male reproduction and behavior. Vasopressin is involved in erection and ejaculation in species including humans, rats, and rabbits (*11*, *12*), and it mediates a variety of male-typical social behaviors including aggression, territoriality, and pair bonding in various species. This sexual dichotomy in function is not universal, however, as it is becoming increasingly clear that both peptides have behavioral roles in males and females.

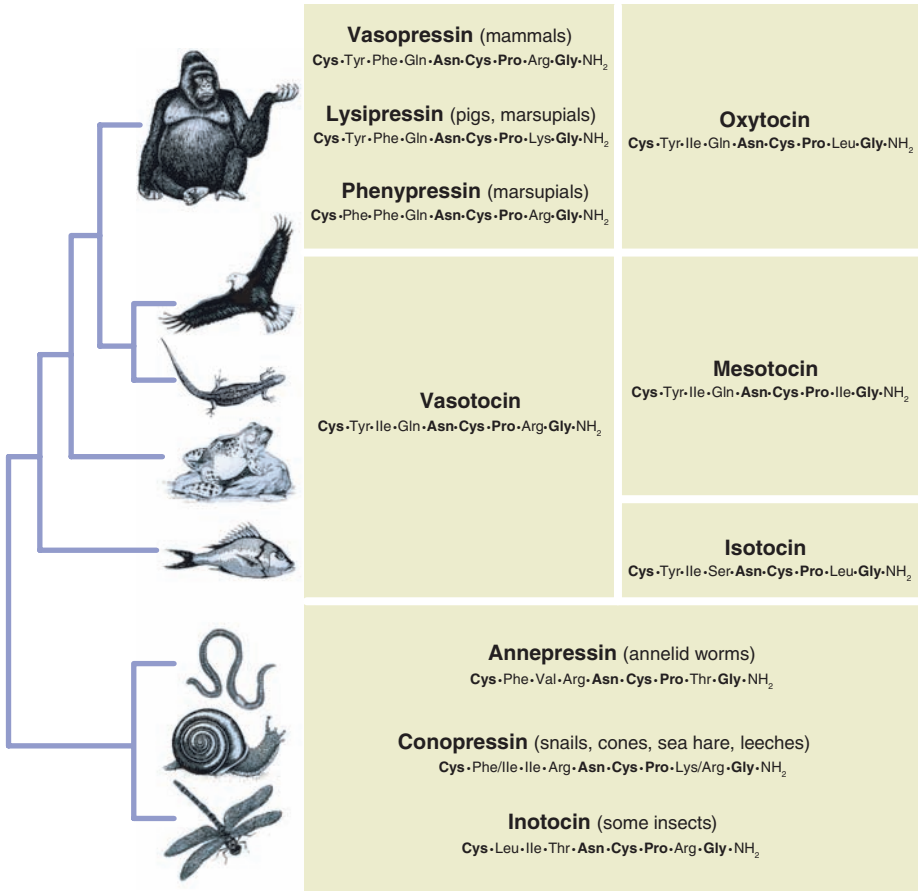


**Fig. 1.** Oxytocin and vasopressin homologs.

## Oxytocin, Nurturing, and Social Attachment

The reproductive actions of oxytocin have been documented for over a century, and even in humans, studies identified the peripheral release of oxytocin during parturition, lactation, and sexual function as early as the 1950s. However, it was not until the 1970s and 1980s that scientists discovered the extent of oxytocin's involvement in behavior. In rats, central infusion of oxytocin stimulates maternal behavior in virgin females who would ordinarily ignore or attack pups. Conversely, experimental manipulations that decrease oxytocin levels or block oxytocin receptor activation within the brain reduce maternal behaviors (*3*).

In contrast to the induction of a generalized maternal state in rodents, maternal bonding in other species, including sheep and humans, consists of both a nurturing component and development of a selective attachment between the mother and her offspring. In sheep, oxytocin release in response to vaginocervical stimulation during parturition independently induces nurturing behaviors and facilitates the mother-infant bond selectivity after birth. Although oxytocin-induced maternal nurturing is mediated by some of the same brain regions in rodents and sheep, oxytocin also modulates maternal-infant bond selectivity in sheep by altering neurotransmitter activity within the olfactory bulb, essentially "priming" the olfactory systems for selective learning of offspring scent (*13*).

Humans display a great diversity of social attachments, one of which is selective preference for a particular mate, known as a pair bond. Pair bonding is exclusive to the 3 to 5% of mammalian species that are socially monogamous, and traditional laboratory organisms, such as rats and mice, do not display mate-based pair bonds. Instead, studies of monogamous prairie voles have yielded extensive insight into the molecular basis of pair bonding (*14*). Similar to its role in maternal bonding, central oxytocin administration facilitates partner-preference formation, a laboratory proxy of pair bonding, whereas blockade of the oxytocin receptor inhibits partner-preference formation in female prairie voles. This suggests that over evolutionary time within this species, a system specialized for maternal bonding in females was co-opted to modulate mate-directed bonds as well (*15*).

Selective bonding, including pair bonding and some mother-infant bonding, is hypothesized to result from concurrent neuropeptide modulation of pathways regulating reward and reinforcement and those involved in processing social information (*16*). Despite normal olfactory abilities, oxytocin knockout mice are unable to recognize previously encountered conspecifics, suggesting a specific role for this neuropeptide in the processing of social cues. In female prairie voles, blockade of either oxytocinergic or dopaminergic signaling within the reward- and reinforcement-associated nucleus accumbens prevents the development of a partner preference. Investigation of human pair bonding is still in its infancy, and there is no clear evidence that oxytocin contributes to pair-bond formation in humans.

## Vasopressin and the Genetic Bases for Variation in Social Behavior

Even though both oxytocin and vasopressin show a conserved role in modulating social behavior in

general, the specific behaviors they influence show extensive variation among different species (*9*, *17*). For instance, vasopressin administration stimulates behaviors associated with monogamy, such as paternal care, mate guarding, and a selective preference for one's mate in male prairie voles; similar treatment does not induce these behaviors in nonmonogamous species. Likewise, in birds, the vasopressin homolog, vasotocin, increases vocalization and aggressive behavior in territorial male field sparrows but has only weak effects on aggression in colonial zebra finches. These species-specific behavioral effects are thought to be mediated, in part, by variation in brain receptor patterns rather than differences within the peptides (*18*).

Both oxytocin and vasopressin receptors display marked diversity in brain expression patterns. Oxytocin has a single identified receptor, whereas vasopressin acts in the brain on its two centrally expressed receptor subtypes, V1a and V1b. Of these two receptors, V1a plays a more prominent role in vasopressinergic modulation of social behavior and thus has been the focus of most research examining vasopressin's role in regulating social behavior (*15*, *19*). Male monogamous prairie voles, unlike polygamous meadow and montane voles, display selective mating-induced partner preferences, care for offspring, and selective aggression toward conspecifics. The development of these behaviors in male prairie voles is vasopressin-dependent. The brain distribution of vasopressin V1a receptor between these species is as divergent as their social behavior, and two experiments highlight the importance of these receptor patterns in mediating behavioral differences in these species (Fig. 2). First, simply increasing receptor expression within the reward and reinforcement circuitry in the meadow vole brain via viral vector-mediated gene expression enables individuals in this nonmonogamous species to form a selective preference for their mate, indicating that V1a receptor patterns influence a species' sociobehavioral repertoire (Fig. 2) (*20*). Along these same lines, transgenic insertion of the prairie vole V1a receptor gene and 2.7 kb of 5′ flanking sequence into the mouse genome leads to a prairie vole–like receptor pattern and altered social behavior (*21*). Together, this work highlights a potential evolutionary mechanism for creating behavioral diversity by altering receptor gene expression patterns. This idea is supported by investigation of individual differences in receptor patterns and behaviors within prairie voles. Individual voles, like humans, show differences in behaviors associated with monogamy, such as fidelity, space use, and paternal care. These behavioral differences are associated with pronounced variation in brain V1a receptor patterns, suggesting that receptor patterns modulate some aspects of both inter- and intraspecies behavioral diversity (*22*, *23*).

The genetic mechanisms underlying the phylogenetic and individual plasticity in V1a receptor expression in the brain and social behavior have begun to be explored. One potential candidate for generating diversity in V1a receptor gene (*avpr1a*) expression is a highly polymorphic, complex, repeat-containing DNA element known as a microsatellite, located in the 5′ flanking region of the *avpr1a* gene (*21*) (Fig. 3A). There are dramatic species differences and more subtle individual variation in this microsatellite element in voles, which are sufficient to drive in vitro expression differences in reporter gene assays (*24*). In vivo, when prairie voles with the longest and shortest microsatellite alleles are bred to homozygosity, the resulting progeny show brain V1a receptor expression and social behavior that differs according to *avpr1a* microsatellite length (Fig. 3A) (*22*). However, it remains unclear whether this region has effects on monogamous phenotypes in naturalistic settings (*25*). Although variation in *avpr1a* microsatellite length alone may not explain the evolution of the monogamous mating strategy in voles (*26*), these findings do suggest that polymorphisms in the *avpr1a* locus may contribute to both species differences and individual variation in V1a receptor distribution in the brain and consequently social behavior.

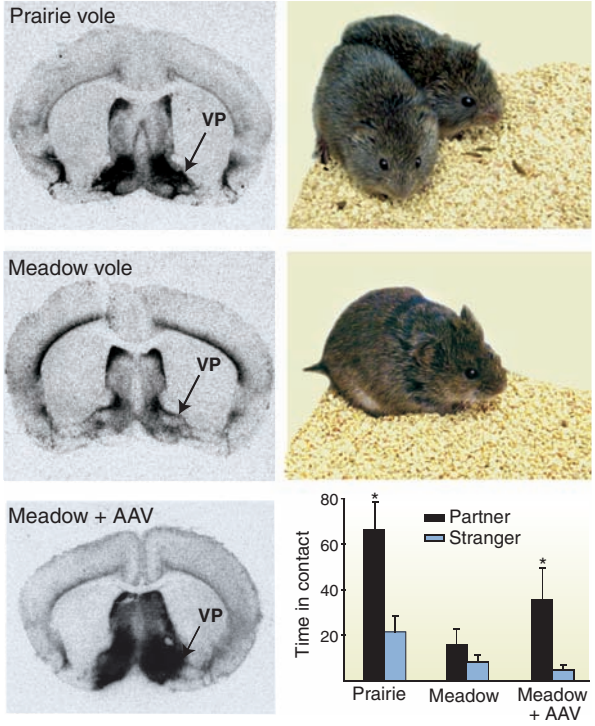


**Fig. 2.** Autoradiograms of vasopressin V1a receptor patterns in the ventral pallidum (VP) of socially monogamous prairie voles and polygamous meadow voles. When V1a receptor levels are artificially increased within the VP of meadow voles using adeno-associted viral vector (AAV) gene transfer (meadow + AAV), they display social behavior that is reminiscent of that of monogamous prairie voles, preferring social contact with their partner over a stranger (*20*). Error bars indicate SE; asterisks indicate $P < 0.05$. Time in contact is given in minutes.

### Neurogenetics of Variation in Human Social Behavior

A number of recent findings suggest that variation in the *AVPR1A* locus may also contribute to sociobehavioral diversity in humans. Four polymorphic microsatellites, three within the 5′ flanking region and one within the intron of the gene, have been characterized and used in gene association studies. Various *AVPR1A* alleles have been directly associated with differences in human social behavior, personality traits relevant to social interaction, and the onset of reproduction (*27*, *28*). One study of 203 individuals has even found an association between the length of the most extensively studied of these polymorphisms, RS3, and altruism, a trait arguably necessary for successful formation of societies (*27*). Using an established economic game, researchers found that participants with longer V1a microsatellite alleles allocated more funds to another individual, despite the participant receiving as real money any unallocated funds at the end of the game.

Most recently, investigators asked the relevant question of whether *AVPR1A* genetic variability contributes to differences in human pair bonding among a cohort of 552 Swedish twin pairs, all of whom were living with a partner (*29*). Eighteen questions were used to probe partner bonding, perceived marital problems, and marital status. In particular, one allelic variant of a microsatellite in the 5′ flanking region of *AVPR1A*, allele RS3 334, was associated with significantly lower scores on the partner bonding scale in males only. Males who are homozygous for this allele were twice as likely to have experienced marital problems or threat of divorce and half as likely to be married if involved in a committed relationship. The presence of this allele in the male partner also correlated with perceived relationship quality in their female partner, suggesting the intriguing possibility that male *AVPR1A* genotype influences both partners.

In another line of research, *AVPR1A* variation has been hypothesized to specifically influence the sociobehavioral deficits characteristic of autism spectrum disorders. Three independent studies have identified associations between variants of this gene and autism. The most recent of these

studies more specifically identified an association between *AVPR1A* polymorphisms and socialization skills in high-functioning autistic participants in which language abilities were normal (*27*). It should be noted that these studies do not suggest that *AVPR1A* polymorphisms are a cause of autism, but they are consistent with the hypothesis that variation in this locus may be one contributor, among many others, to the social behavioral deficits associated with this spectrum of disorders. These studies should be viewed with caution, however, because the modest associations identified were with different alleles and haplotypes.

However, one allele is of particular interest: allele RS3 334. This allele, one of 16 different length variants in this repetitive region, was nominally implicated in autism in one study (*30*) and correlates most strongly with lower-quality partner bonding in males (*29*). A separate study also reported that individuals who carry this allele, as compared with all other alleles, have the highest levels of amygdala activation when performing an emotional face-matching task (*31*). When a different analysis on the same data was used, it revealed that longer microsatellites at this locus were associated with higher levels of amygdala activation during the face-matching task (Fig. 3B). Likewise, the only reported study examining *AVPR1A* expression in the brain in relation to polymorphisms has found that homozygous long RS3 microsatellite carriers have higher levels of V1a receptor hippocampal mRNA postmortem (*27*) (Fig. 3B).

A degree of skepticism should be maintained when considering any individual association study, and these studies require additional functional experiments examining the link between *AVPR1A* polymorphisms, gene expression, neural activity, and behavior. However, the repeated association of the *AVPR1A* locus with sociobehavioral traits and, in particular, the identification of allele RS3 334 in two independent studies has heightened interest in the hypothesis that variation in *AVPR1A* may contribute to variation in human sociobehavioral traits.

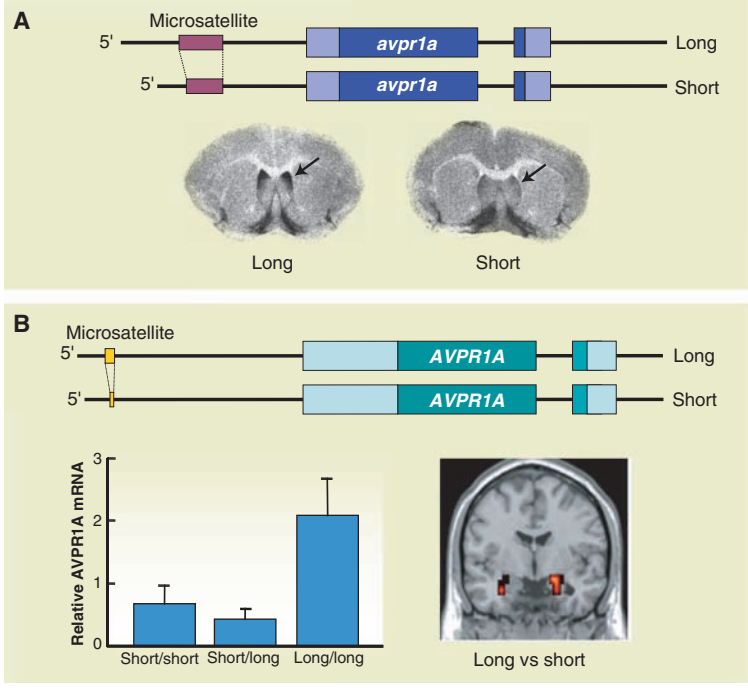


**Fig. 3.** Influence of genetic polymorphisms on gene expression levels, brain activation, and social behavior. **(A)** Within prairie voles, subtle microsatellite length variation upstream of the *avpr1a* transcription start site is associated with differences in V1a receptor expression patterns and behavior. **(B)** Allele length in an analogous microsatellite polymorphism upstream the human *AVPR1A* locus predicts V1a mRNA expression levels in the hippocampus (*27*), and longer alleles are also correlated with higher levels of amygdala activation during a face-viewing task (*31*). Error bars indicate SE.

## Neuropeptides, Human Social Cognition, and Trust

Recent human studies have directly manipulated oxytocin and vasopressin systems by using intranasal administration to investigate the potential role for these peptides in modulating human social interactions. None of these studies have measured cerebrospinal levels of these peptides after intranasal infusion, but the reported behavioral effects of intranasal administration have been consistent, suggesting that whether acting peripherally or centrally, intranasally administered peptides do affect the brain and cognition.

Although the majority of these experiments have focused on oxytocin, limited studies with intranasal vasopressin have investigated its effects on social cognition. Human social inferences are derived largely from viewing facial expression, especially in the eye region. In human males, vasopressin administration decreases the perceived friendliness of faces and increases agonistic facial motor patterns (*32*). In contrast, females rate faces as friendlier and show affiliative facial motor programs after vasopressin application. Intranasal oxytocin has also been investigated in a similar paradigm, albeit in males only. When asked to categorize faces based on their expression, participants given intranasal oxytocin were better at classifying the emotions displayed on these faces and presumably inferring the mental state of another individual (*33*). Intranasal oxytocin infusion increases gaze to the eye region of human faces, providing a relatively simple potential mechanism for increasing the accuracy of mental state inference through increased information availability (*34*).

Complementary studies also support a role for oxytocin in modulating trust, thereby influencing cooperative interactions. Intranasal oxytocin increases the amount of money that an "investor" is willing to offer to a "trustee" who, after the amount is amplified by the experimenter, can then choose to return a smaller or larger sum back to the initial investor (*35*). Oxytocin does not, however, increase monetary allocations when the return on an investment is determined by a random lottery. This important control indicates that the effects of administration of this peptide are specific to the social interaction between the investor and trustee and therefore represents a quantifiable indication of interpersonal trust.

Two independent studies have now demonstrated the potential for maladaptive affects of oxytocin during social situations. In an extension of trust studies, researchers manipulated an investment scenario to simulate a situation in which the investor is "betrayed" by a trustee who returns less money than the initial investment (*36*). After the discovery of a betrayal of trust, the initial investment amounts decrease for placebo controls but not for oxytocin-treated investors. Similarly, in a different paradigm, pairing a shock with a face presentation skews the viewer's emotional rating of the face toward a more negative assessment, unless they have been administered oxytocin. In that case, they are likely to rate the shock-paired faces as more forgiving and sympathetic (*37*).

Insights into the neural mechanisms by which oxyotcin modulates social cognition have come from imaging studies that have consistently found that oxytocin decreases amygdala activity, regardless of the experimental scenario (*36*–*38*). The amygdala has been implicated in social information processing in both humans and animals, and bilateral amygdala lesions in humans impair their ability to judge the trustworthiness of others (*39*). As amygdala activation is also indicative of threatening or fearful stimuli, oxytocin mediated attenuation of amygdala activation may facilitate social interactions by decreasing potentially negative, anxiety-provoking associations.

## Neuropeptides, Neurogenetics, and Society

Intranasal peptide administration and functional brain imaging studies are driving a revolution in our understanding of the roles of oxytocin and vasopressin in humans. However, our under-

standing is still extremely incomplete and hampered by both technical and design limitations. For instance, all oxytocin administration studies to date have been performed in males, and oxytocin's influence on bonding and social behavior in women has not been investigated. Furthermore, it is not known whether intranasal application of vasopressin or oxytocin mimics physiologically relevant events or represents pharmacological artifacts.

Among genetic studies, convergent evidence supports a role for the *AVPR1A* locus in modulating human social behavior, but the link between genes, the brain, and behavior remains weak. For instance, *AVPR1A* polymorphism is associated with differences in amygdala activation and autism, but its correlation with gene expression has only been investigated in the hippocampus. Finally, only one study has investigated the distribution of oxytocin and vasopressin receptors within the human postmortem brain (*40*), and techniques have improved since its publication. Development of selective positron emission tomography ligands for both oxytocin and vasopressin receptors will allow for in vivo studies of receptor expression and shed new light on correlations between genetic polymorphisms, brain receptor variability, and social cognition in humans. Although these limitations hinder our understanding of these neuropeptide systems, they are largely not insurmountable.

Many diseases, such as depression and social phobia, display symptomatic altered or deficient social behavior. In severe instances, such as autism and schizophrenia, abnormal social behavior is extremely debilitating. Identifying the molecular underpinnings of these social deficits may yield important clues into their treatment. For example, peripheral infusion of oxytocin increased retention of social cognition via enhanced emotional understanding of speech intonation and, unexpectedly, decreased repetitive behaviors (*41*). As peptides do not efficiently cross the blood/brain barrier, it is unclear how peripheral infusion of oxytocin mediates these effects, but these results are nevertheless intriguing. Even within healthy populations, social support enhances our ability to deal with stress and recover from disease. Oxytocin administration enhances the stress-alleviating effects of social support (*42*). The therapeutic potential of manipulating the oxytocin system remains to be explored in clinical trials, and the development of potent, selective agonists that penetrate the blood/brain barrier would be an important advancement toward this goal.

An understanding of the neurobiology of social behavior raises important questions for society. Should salesmen be allowed to use airborne oxytocin agonists to manipulate trust toward their own benefit? Should marital therapists include oxytocin infusions along with behavioral therapies to salvage relationships? Will genetic testing be used to screen potential partners or prospective sons-in-law? These and other questions may become the topics of discussion for bioethicists as we gain more insights into the neurobiology and neurogenetics of oxytocin, vasopressin, and sociality.

### References and Notes


1. M. A. Martens, S. J. Wilson, D. C. Reutens, *J. Child Psychol. Psychiatry* **49**, 576 (2008).
2. M. Ludwig, G. Leng, *Nat. Rev. Neurosci.* **7**, 126 (2006).
3. H. K. Caldwell, W. S. Young III, in *Handbook on Neurochemistry and Molecular Neurobiology*, R. Lim, Ed. (Springer, New York, ed. 3, 2006), pp. 573–607.
4. R. Acher, J. Chauvet, M. T. Chauvet, *Adv. Exp. Med. Biol.* **395**, 615 (1995).
5. K. Tessmar-Raible *et al.*, *Cell* **129**, 1389 (2007).
6. B. Venkatesh, S. L. Si-Hoe, D. Murphy, S. Brenner, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 12462 (1997).
7. P. Gilligan, S. Brenner, B. Venkatesh, *J. Neuroendocrinol.* **15**, 1027 (2003).
8. M. Y. Ho, D. A. Carter, H. L. Ang, D. Murphy, *J. Biol. Chem.* **270**, 27199 (1995).
9. T. R. Insel, L. J. Young, *Curr. Opin. Neurobiol.* **10**, 784 (2000).
10. G. J. De Vries, G. C. Panzica, *Neuroscience* **138**, 947 (2006).
11. J. Gupta, R. J. Russell, C. P. Wayman, D. Hurley, V. M. Jackson, *Br. J. Pharmacol.* **155**, 118 (2008).
12. G. Segarra *et al.*, *J. Pharmacol. Exp. Ther.* **286**, 1315 (1998).
13. K. D. Broad, J. P. Curley, E. B. Keverne, *Philos. Trans. R. Soc. London Ser. B Biol. Sci.* **361**, 2199 (2006).
14. C. S. Carter, A. C. DeVries, L. L. Getz, *Neurosci. Behav. Rev.* **19**, 303 (1995).
15. M. M. Lim, L. J. Young, *Horm. Behav.* **50**, 506 (2006).
16. L. J. Young, Z. Wang, *Nat. Neurosci.* **7**, 1048 (2004).
17. L. J. Young, *Horm. Behav.* **36**, 212 (1999).
18. J. L. Goodson, A. H. Bass, *Brain Res. Rev.* **35**, 246 (2001).
19. C. H. Hoyle, *Brain Res.* **848**, 1 (1999).
20. M. M. Lim *et al.*, *Nature* **429**, 754 (2004).
21. L. J. Young, R. Nilsen, K. G. Waymire, G. R. MacGregor, T. R. Insel, *Nature* **400**, 766 (1999).
22. E. A. D. Hammock, L. J. Young, *Science* **308**, 1630 (2005).
23. A. G. Ophir, J. O. Wolff, S. M. Phelps, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 1249 (2008).
24. E. A. D. Hammock, L. J. Young, *Mol. Biol. Evol.* **21**, 1057 (2004).
25. A. G. Ophir, P. Campbell, K. Hanna, S. M. Phelps, *Horm. Behav.* 10.1016/j.yhbeh.2008.07.009 (2008).
26. S. Fink, L. Excoffier, G. Heckel, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 10956 (2006).
27. S. Israel *et al.*, *Prog. Brain Res.* **170**, 435 (2008).
28. Z. M. Prichard, A. J. Mackinnon, A. F. Jorm, S. Easteal, *Hum. Mutat.* **28**, 1150 (2007).
29. H. Walum *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 14153 (2008).
30. S. J. Kim *et al.*, *Mol. Psychiatry* **7**, 503 (2002).
31. A. Meyer-Lindenberg *et al.*, *Mol. Psychiatry* 10.1038/mp.2008.54 (2008).
32. R. R. Thompson, K. George, J. C. Walton, S. P. Orr, J. Benson, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 7889 (2006).
33. G. Domes, M. Heinrichs, A. Michel, C. Berger, S. C. Herpertz, *Biol. Psychiatry* **61**, 731 (2007).
34. A. J. Guastella, P. B. Mitchell, M. R. Dadds, *Biol. Psychiatry* **63**, 3 (2008).
35. M. Kosfeld, M. Heinrichs, P. J. Zak, U. Fischbacher, E. Fehr, *Nature* **435**, 673 (2005).
36. T. Baumgartner, M. Heinrichs, A. Vonlanthen, U. Fischbacher, E. Fehr, *Neuron* **58**, 639 (2008).
37. P. Petrovic, R. Kalisch, T. Singer, R. J. Dolan, *J. Neurosci.* **28**, 6607 (2008).
38. P. Kirsch *et al.*, *J. Neurosci.* **25**, 11489 (2005).
39. R. Adolphs, *Nat. Rev. Neurosci.* **4**, 165 (2003).
40. F. Loup, E. Tribollet, M. Dubois-Dauphin, J. J. Dreifuss, *Brain Res.* **555**, 220 (1991).
41. J. A. Bartz, E. Hollander, *Prog. Brain Res.* **170**, 451 (2008).
42. M. Heinrichs, T. Baumgartner, C. Kirschbaum, U. Ehlert, *Biol. Psychiatry* **54**, 1389 (2003).


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REVIEW

# Wired for Sex: The Neurobiology of *Drosophila* Mating Decisions

**Barry J. Dickson**

**Decisions about whom to mate with can sometimes be difficult, but making the right choice is critical for an animal's reproductive success. The ubiquitous fruit fly, *Drosophila*, is clearly very good at making these decisions. Upon encountering another fly, a male may or may not choose to court. He estimates his chances of success primarily on the basis of pheromone signals and previous courtship experience. The female decides whether to accept or reject the male, depending on her perception of his pheromone and acoustic signals, as well as her own readiness to mate. This simple and genetically tractable system provides an excellent model to explore the neurobiology of decision making.**

Behavior unfolds as animals select specific actions on the basis of sensory input, internal physiological states, and individual experience. A major goal for neuroscience is to understand how information processing and storage in neural circuits guides such action selection, and thus behavior. Genetic approaches in model organisms greatly facilitate the identification, characterization, and manipulation of individual circuit elements and can thereby establish causal relationships linking cellular biochemistry, circuit function, and animal behavior.

The sex life of the fruit fly *Drosophila melanogaster* is an ideal subject for such a study. Males decide whom to court, and females decide with whom to mate. The world-wide distribution and abundance of *Drosophila*, and its success as a

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