Genes and Social Behavior
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REVIEW

Genes and Social Behavior

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What genes and regulatory sequences contribute to the organization and functioning of neural circuits and molecular pathways in the brain that support social behavior? How does social experience interact with information in the genome to modulate brain activity? Here, we address these questions by highlighting progress that has been made in identifying and understanding two key "vectors of influence" that link genes, the brain, and social behavior: (i) Social information alters gene expression in the brain to influence behavior, and (ii) genetic variation influences brain function and social behavior. We also discuss how evolutionary changes in genomic elements influence social behavior and outline prospects for a systems biology of social behavior.

Genes and social behavior have long had a tempestuous relationship in both science and society, and the "nature-versus-nurture" debate still has its adherents. This controversy persists because the relations among genes, the brain, and social behavior have complex entanglements across several different time scales (*1*), ranging from organismal development and physiology all the way to evolutionary time (Fig. 1). Genes do not specify behavior directly but rather encode molecular products that build and govern the functioning of the brain through which behavior is expressed. Brain development, brain activity, and behavior all depend on both inherited and environmental influences, and there is increasing appreciation that social information can alter brain gene expression and behavior. Furthermore, variation in behavior shapes the evolution of genomic elements that influence social behavior through the feedback of natural selection.

What is social behavior? Animals perform many activities during the course of their lives with the goal of surviving and reproducing: they find food and mates, defend themselves, and in many cases care for their offspring or other relatives. These activities become social when they involve interactions among members of the same species in a way that influences immediate or future behavior. One of the fundamentals of social behavior is communication (*2*). Diverse social behaviors involve the production, reception, and interpretation of signals that influence individual behavior in a manner that depends on social context.

Given the diversity and complexity of social behavior, is it realistic to anticipate that conserved mechanisms and general principles operate to control social behavior at the genomic level? We believe so. Although specific behavioral outcomes vary widely from species to species, the biological needs that drive these behaviors are deeply shared. Social behavior has clearly evolved multiple times, but probably within a framework of conserved neural mechanisms. All systems of social behavior share the following features: (i) They are acutely sensitive and responsive to social and environmental information. (ii) This information is transduced within individual organisms by one or more primary sensory pathways. (iii) The transduced neural signals are processed and integrated in specific circuits of the brain via conserved signal transduction and neuromodulatory systems. (iv) The resulting internal state of the animal ultimately controls its behavior.

Understanding the relations between genes and social behavior is especially challenging, because methods of experimental genetics have not been developed for animal species with the most compelling social repertoires—such as songbirds, cichlid fish, social insects (featured in this Review), and voles [discussed in Donaldson and Young's Review in this issue (*3*)]. Fortunately, through progress in whole-genome sequencing and comparative genomics, "model social" species are taking their place alongside the classic model genetic species in molecular analyses of behavior (*4*). It is now possible to compare model social species that vary in behavior and brain activity with one or more large-scale technologies (transcriptomics, epigenomics, proteomics, metabolomics, etc.). Results can be readily translated to model genetic species such as the mouse (*Mus musculus*) or the fruit fly (*Drosophila melanogaster*) for sophisticated genetic manipulations (*5*, *6*). Biologists no longer have to choose to study either a model genetic or a model social species; instead, they can choose both. This underscores the importance of actively pursuing research on diverse organisms that can capture the full richness and range of social behaviors.

In this article, we review selected findings that illustrate the relations between genes, the brain, and social behavior. As an organizational heuristic, we highlight two "vectors of influence" (Figs. 2 and 3): Vector 1 (Fig. 2) describes how social information leads to changes in brain gene expression, brain function, and social behavior, and Vector 2 (Fig. 3) describes how genetic variation between individuals leads to variation in social behavior.

Social Influences on Brain Gene Expression (Vector 1)

The genome was once thought to be a relatively passive blueprint guiding organismal development. Recent results show that genomes in fact remain highly responsive throughout life to a variety of stimuli associated with social behavior. Social information can lead to changes in the brain and behavior through effects on the genome (Fig. 2).

The first demonstrations of gene responses to social stimuli focused on a handful of immediate early genes (*7*), and one of these has proven especially useful. Referred to now as *egr1* (*8*), this transcription factor–encoding gene was discovered and named independently (*ngfi-a*, *zif-268*, *krox-24*, *tis8*, *zenk*) in different species. A specific link to social behavior was first suggested by studies in songbirds (*9*). Songbirds engage in rich social interactions that are mediated by their songs, which are learned vocal signals. The structure of songbird society varies by species, ranging from territorial to colonial, but in all cases, songbirds recognize and discriminate individual conspecifics according to their vocalizations. In the male zebra finch (*Taeniopygia guttata*), the singing of another male bird induces *egr1* expression in a specific subregion of the auditory forebrain devoted to hearing (*9*). Not simply an auditory response, *egr1* expression in this region is specifically linked to the social importance of the signal. Pure tones or white noise are ineffective stimuli. Moreover, the *egr1* response varies with recent familiarity to the particular song; previously unheard songs elicit strong responses, whereas familiar songs elicit little or no response (*10*). This has given rise to the speculation that the function of the genomic response is to help the brain update its natural representations in a changing social environment (*7*). A familiar song probably represents a familiar individual, whereas an unfamiliar song may represent a potentially threatening intruder.

The *egr1* response is also enhanced when the bird is listening in the presence of conspecifics, compared with when he is alone. This provides a neuromolecular analog of the "audience effect," a phenomenon in which an individual's performance depends on whether it is alone or with others (*11*). Other social interactions trigger *egr1* responses in other regions of the songbird brain, and the magnitude of the response can vary according to the intrinsic sociality of the species (*12*) and the immediate context of the experience (*13*).

egr1 was also the focus of another marked demonstration of gene responses in the brain resulting

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from recognition of social opportunity in a highly social cichlid fish (*Astatotilapia burtoni*) (*14*). In many animal societies, dominance hierarchies structure all social interactions; position in the hierarchy governs access to resources that determine who reproduces and how often. *A. burtoni* has an elaborate dominance hierarchy, reinforced both by aggressive fighting and the ability of dominant males to ascertain relative rank by observation alone, using transitive inference to determine which male in a group is most dominant (*15*). Subordinate males have reduced fertility. When the alpha male is removed from a group, a subordinate male quickly starts to exhibit dominant behavior. In this social ascent, he displays dramatic changes in body coloration and behavior. Within minutes, but after the onset of behavioral change, *egr1* is induced specifically in the hypothalamic anterior preoptic area in neurons containing gonadotropin-releasing hormone (GnRH), a peptide critical for reproduction. These neurons increase in size and degree of dendritic arborization, and they also increase expression of GnRH mRNA and protein. These cellular and molecular responses depend on the recognition of a social opportunity and ascension to dominance; they are not elicited in individuals who are already dominant. Because *egr1* is a transcription factor, it is likely that these effects on the GnRH neurons are direct, but this has not yet been demonstrated. These results show that social information also can lead to changes in behavior that transiently alter patterns of brain gene expression (a variant of Vector 1).

Although *egr1* is only one of many socially responsive genes (see below), its molecular and cellular character provides insights of general importance. First, *egr1* can be induced by brief experiences, its expression reaching a peak 20 to 60 min later, in a "genomic action potential" (*7*). Second, *egr1* can immediately suppress or enhance the transcription of other genes, depending on which proteins it interacts with in different cell types (*16*). Third, results with *egr1* suggest how social experience might trigger changes in larger gene networks in the brain. By means of the application of high-throughput technologies for measuring the expression of many genes simultaneously, it is now clear that responses to social stimuli can be massive, involving hundreds or thousands of genes and perhaps many different brain regions at once.

In one of the first such studies, microarrays were used to measure brain gene expression patterns in the honey bee (*Apis mellifera*) at distinct life stages, finding expression differences in thousands of genes (*17*). Worker honey bees change jobs as they age. They spend the first 2 to 3 weeks of their adult life working in the hive caring for the brood, maintaining the nest and other activities, and then shift to collecting nectar and pollen outside the hive on behalf of their colony for the remainder of their 4- to

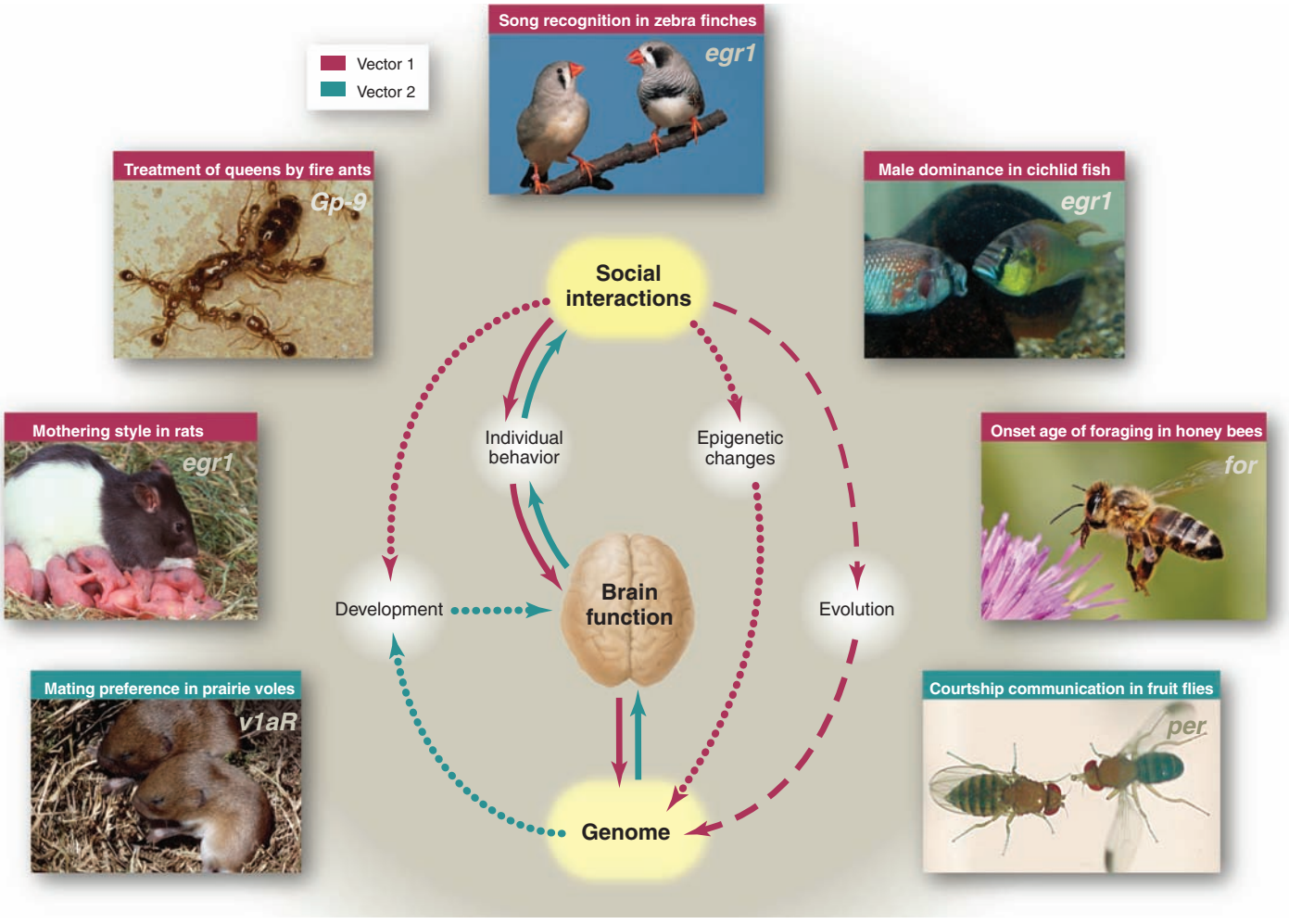

Fig. 1. Complex relationships connect genes, the brain, and social behavior. These relationships operate over three time scales: (i) physiological time via effects on brain activity (solid lines), (ii) developmental time via slower effects on brain development and genome modification (dotted lines), and (iii) evolutionary time via the processes of natural selection (dashed line). Arrow colors refer to Figs. 2 and 3 (pink, Fig. 2; blue, Fig. 3), which provide details about the nature of these interactions. Images depict some of the animals and genes featured in this review, clockwise from top: zebra finch (*T. guttata*), cichlid fish (*A. burtoni*), honey bee (*A. mellifera*), fruit fly (*D. melanogaster*), prairie vole (*M. ochrogaster*), rat (*R. norvegicus*), and fire ant (*S. invicta*). The genes listed (in italics on the photographs) are responsive to social interactions as described in the text.

6-week life. Despite this fixed pattern of behavioral maturation, the precise age when a bee redirects its energies from work in the hive to foraging depends on its perceptions of the colony's needs, which are communicated in part by pheromones. For example, if a bee colony loses a large fraction of its foraging force, some of the younger bees can speed up their rate of maturation and become "precocious" foragers. This occurs because inhibitory pheromones produced by older, foraging-age bees become less available. Although it looks like a bee foraging on a flower is a solitary affair, the onset age of foraging is subject to strong social influence. Perception of bee pheromones alters the expression of hundreds of genes in the bee brain over a period of days to weeks (*18*). Particularly affected are genes encoding transcription factors (*18*) and metabolic proteins (*19*).

Shifts in the expression of large populations of genes during social experience are also being observed in microarray-based experiments in fish and songbirds, and in these cases the alterations are both large and rapid. In the swordtail fish, *Xiphophorus nigrensis*, different social experiences quickly induce distinct patterns of gene response expression when measured at the level of the whole brain (*20*). For example, some genes are turned on in females as they interact with attractive males but are off when they interact with other females, and vice versa. In zebra finch song-recognition experiments, thousands of other RNAs (in addition to *egr1*) increase or decrease in the auditory forebrain within 30 min of the onset of an unfamiliar song stimulus (*21*). A day after the song has been entrained by repetition, however, the same now-familiar song no longer induces the behavioral response or the "unfamiliar" molecular response. But an altogether previously unknown and different gene expression profile has now emerged, which may represent the new baseline state.

These observations suggest that social information can have large global effects on gene expression in the brain, perhaps best described as shifts in neurogenomic states rather than as activation of particular genes in local neural circuits. A future challenge will be to confront the anatomical complexity of the brain, to describe and understand these genomic states at both finer and coarser scales of anatomy and time. For example, a single neuron may exist in different functional states as a result of modulation of synaptic proteins, which can alter the efficiency by which transient synaptic signals are consolidated into stable, lasting cellular changes (*7*). In neuronal circuits and ensembles, changes in the expression of ion channel proteins could affect how quickly the cell can respond and lead to changes in network function (*22*). At the whole-brain level, changes in the global neurogenomic state in the brain (such as the familiar daily sleep-waking cycle) involve massive changes in gene expression throughout the brain as a function of behavioral state (*23*).

Social Influences on Brain Gene Expression: Long-Term Epigenetic Effects

Social signals can also trigger long-lasting epigenetic modifications of the genome. These are heritable changes in expression of specific genes that are not attributable to changes in DNA sequence (Fig. 2). This phenomenon was first discovered in the transgenerational transmission of mothering style in rats (*Rattus norvegicus*) (*24*). Female rats that lick, groom, and nurse their pups extensively have offspring that are less responsive to stress and more responsive to their own pups. In contrast, pups that received less attention from their mothers are more easily stressed and show reduced responsiveness to their offspring.

Fig. 2. Vector 1: From social information to changes in brain function and behavior. Social information is perceived by sensory systems and transduced into responses in the brain. Social information leads to developmental influences often mediated by parental care, as well as acute changes in gene expression that cause diverse effects (e.g., changes in metabolic states, synaptic connections, and transcriptional networks). Social information also can cause epigenetic modifications in the genome. Variation in both environment (V_E) and genotype (V_G) influences how social information is received and transduced and how these factors themselves interact ($V_E \times V_G$).

Because these differences in responsiveness to stress can be passed from generation to generation, they had previously been assumed to be inherited via traditional genetics. Instead, they stem from the fact that frequent mother/pup contact triggers at least two epigenetic changes in DNA methylation and very likely many more such molecular events. Methylation of the promoter region of the glucocorticoid receptor gene (which binds glucocorticoid stress hormones) allows the protein product of the *egr1* gene discussed above to up-regulate glucocorticoid receptor expression, especially in the hippocampus (*25*). In addition, methylation of the α1b promoter region of the estrogen receptor gene results in the up-regulation of estrogen receptors in the hypothalamus (*26*). Together with the results presented above for zebra finches, cichlid fish, and honey bees, these findings demonstrate that social experience can induce a range of changes in brain gene expression, from brief to enduring.

To date, epigenetic effects associated with social behavior have been studied at only a few genetic loci, but it is likely that many genes are similarly affected, especially in gene regulatory networks in the hypothalamic-pituitary-gonadal axis, known to be important for the regulation of a variety of vertebrate social behaviors (*12*, *27*). Genome-wide assays of epigenetic changes, assessing different regions and cell types in the brain, are necessary to fully understand how specific epigenetic modifications can both influence and be caused by social behavior.

Genotype-Environment Interactions and Social Behavior

The effects of social information on brain function and social behavior differ among individuals as a result of genetic variation between individuals (Fig. 2) (*28*). Such interactions between genotype and environment must always be accounted for in molecular analyses of social behavior. This has become an important focus in medicine, as psychiatric geneticists have been searching for genotype-environment interactions that might help to shed light on a wide range of psychiatric disorders. Some disorders, such as autism and depression, reflect social behavior gone awry. Evidence for genotype-environment interactions in psychiatric disorders has been reported, but these kinds of studies are still in their infancy (*29*–*31*).

Evidence of genotype-environment interactions influencing both social behavior and gene expression has been found in the fire ant *Solenopsis invicta* (*32*). Fire ants, like honey bees, live in colonies with thousands of workers, but while honey bee colonies have just a single queen, fire ant colonies can have one or more. The tendency to have either one or more queens has a genetic basis in fire ants. A genetic locus has been identified, *General Protein 9* (*Gp-9*), that is involved in regulating a key aspect of fire ant social organization—namely, the treatment of queens by the workers. Homozygous *BB* queens are larger and more fecund than *Bb* queens, and *BB* workers will only accept a single *BB* queen, resulting in one-queen colonies. *Bb* workers will accept multiple *Bb* queens, resulting in larger multiqueen colonies that are ecologically more invasive. *BB* workers become tolerant of multiple *Bb* queens when they are in colonies containing mostly *Bb* workers. In contrast, *Bb* workers do not change queen tolerance when they are in colonies containing mostly *BB* workers. *BB* workers in a *Bb* colony take on a *Bb* gene expression profile; comparable studies for *Bb* workers in *BB* colonies have not been done. For *BB* workers in *Bb* colonies, gene expression profiles are more strongly affected by colony genotype than their own genotype.

From Genes to Social Behavior (Vector 2)

Genetic or behavioral variants, either within populations of the same species or between species, offer an opportunity to understand how genetic

information influences the development and function of neural circuits and molecular pathways that mediate social behavior (Fig. 3). With the explosion in genome sequencing, the detection and analysis of genomic variation is becoming more routine, even in species without extensive histories of genetic analysis. However, such a comparative approach is particularly effective when direct experimental manipulation of genes or molecular pathways can be incorporated in the analysis to study behavioral consequences. A now-classic precedent is seen in the study of courtship communication in fruit flies [other aspects of fly courtship neurogenetics are reviewed in this issue by Dickson (*33*)]. Courtship involves some of the fundamentals of social behavior, even if it occurs fleetingly and in species with otherwise relatively solitary lifestyles, such as fruit flies. Like other more complex forms of social behavior, courtship involves communication between conspecifics to collect and process critical information—in this case about species, gender, receptivity, and quality of a potential mate.

Drosophila has a courtship song produced by the wings that is characterized by species-specific temporal coding. A comparison of two *Drosophila* species led to the identification of a specific difference in the *period* gene that was correlated with temporal differences in song structure. Transferring a small piece of the *period* gene from *D. melanogaster* to *D. simulans* caused the *melanogaster* males to produce the *simulans* call, rather than the *melanogaster* call (*34*). Thus, manipulation of even a single gene can have profound effects on behaviors associated with reproductive success.

Species differences were also exploited to study the molecular basis of mating preferences in the monogamous prairie vole, (*Microtus ochrogaster*) in comparison with the polygamous montane vole (*M. montanus*). As discussed elsewhere in this issue (*3*), sequence variation in the 5′ region of the vasopressin receptor gene *v1aR* causes differences, both in where this gene is expressed in the brain and in mating preferences. Recent findings showing no such relation between genetic variation and monogamy in other vole species (*35*) provide an excellent opportunity to explore how changes in different components of signaling pathways might result in similar changes in social behavior.

Behavioral variants within populations of *D. melanogaster* led to the discovery of another gene involved in social behavior in honey bees. Regulatory polymorphisms in *foraging* (*for*) are implicated in inter-individual genetic differences in foraging behavior, because flies with higher levels of *for* expression forage more actively than flies with lower levels of *for* expression (*6*). Foraging in *Drosophila* is not a social behavior, but these findings led to analysis of *for* orthologs in social insects. In social insects, differences in *for* expression are related to social activity, rather than genetic differences between individuals. In honey bees, brain *for* expression is higher in foragers than in hive bees, and socially induced precocious foragers show a precocious increase in *for* brain expression. Pharmacological treatment that activates the *for* pathway causes precocious foraging (*36*). Socially induced changes in *for* expression may be widespread in social insects (*37*).

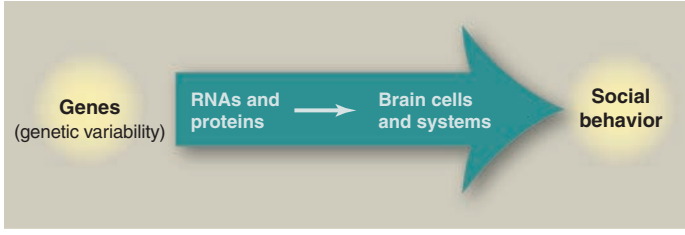

Fig. 3. Vector 2: From genes to social behavior. Genes influence the social behavior of an individual through their effects on brain development and physiology. This linkage is sensitive to both genetic (V_G) and environmental (V_E) variation and to their interactions ($V_G \times V_E$).

Much like *for* but in vertebrates, variation in the forkhead box P2 gene (*foxp2*) influences behaviors that have important social roles in multiple species, including human speech (*38*) and other forms of animal communication (*39*–*41*). *for* encodes guanosine 3′,5′-monophosphate–dependent protein kinase, and *foxp2* encodes a developmentally important transcription factor. Genes like *for* and *foxp2* may function as elements in a developmental or neural toolkit for building the circuits and systems underlying diverse socially embedded behaviors (*37*), even though they do not directly encode social behavior in any mechanistic sense.

For genes like *for* and *foxp2*, the link between gene and social behavior may be best appreciated by considering the evolutionary time scale (Fig. 1, pink dashed line). Through selection, genes may evolve according to their effects on a social behavior, even if their mechanistic roles in the neural expression of that behavior are subtle and indirect. Effects of selection may be detected in several aspects of comparative genome sequence data, including differences in amino acid codon frequencies, regulatory sequences, and gene copy number (*42*). Molecular evolution algorithms can be used to determine whether genes such as *for* and *foxp2* have been subjected to positive selection in particular lineages (*43*). Such analyses provide important tools for understanding the evolution of genes and other genomic elements that influence social behavior.

Prospects

Some progress has been made in understanding the specific relationships between genes and social behavior in a few species, but this enterprise is still in the formative stages. Understanding the molecular basis of social behavior presents a formidable intellectual challenge for several reasons. First, because behavior is diverse, assorted species must be used to extract the general principles that govern the molecular bases of social behavior. Dissecting a complex behavior into its components can help to identify root similarities across distantly related species (*4*). But even if deep molecular conservation is found among diverse species, one important issue remains. How can molecular pathways involved in behavior be conserved even when species show major differences in brain structure and the overall organization of the nervous system?

The second challenge is that the molecular path linking genes and behavior is invariably complicated (*44*). There are many levels of neural and neuroendocrine regulation that lie between the genome and a social behavior, including transcription, translation, posttranslational modifications, epigenetic changes, brain metabolism, neural (electrochemical) activity, and neuromodulation. Moreover, this regulation occurs in complex and dispersed temporal and spatial patterns within the brain, over physiological time, developmental time, and throughout an individual's life. The study of social behavior adds an additional tier of complexity because it depends on interactions and communication among individuals. In most cases, social behavior must be studied in a natural context in which the full repertoire of environmental influences and behaviors are expressed.

Despite the challenges, genetic and genomic approaches hold great promise for elucidating the molecular basis of social behavior. We have reasonably detailed knowledge of the two physical substrates responsible for behavior: the brain and the genome. We have a strong and growing arsenal of large-scale technologies and increasingly sophisticated methods of systems biology to profile changes in the brain during social behaviors. The time is ripe to combine this knowledge and these tools to aim for a comprehensive understanding of social behavior in molecular terms.

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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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