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Social Circuits: Peptidergic Regulation of Mammalian Social Behavior

Minireview

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Mammals have developed patterns of social relationships that enhance the survival of individuals and maximize the reproductive success of species. Although social stimuli and social responses are highly complex, recent studies are providing substantial insights into their neural substrates. Neural pathways employing the nonapeptides vasopressin and oxytocin play a particularly prominent role both in social recognition and the expression of appropriate social responses. New insights into social neuroscience are discussed, along with the relevance of this rapidly developing field to human relationships and disease processes.

Mammalian Social Behavior

Mammalian species often display elaborate social structures that facilitate their ability to overcome a wide range of obstacles that would otherwise limit their success. For example, parental care is provided to support the young, mate selection is regulated to favor the propagation of adaptive traits, and cooperative strategies are employed for food acquisition and defense. The range of social behaviors displayed by particular mammalian species varies tremendously, in accord with the diverse challenges posed by their distinct ecological niches.

A critical requirement for social behavior is the ability of animals to identify conspecifics (Insel and Fernald, 2004). Sensory modalities employed for social recognition vary among mammalian species. Whereas humans and nonhuman primates make extensive use of visual and auditory cues, rodents utilize two distinct olfactory systems: the main olfactory system to detect a wide array of volatile odorants, and an accessory olfactory system to detect pheromones, compounds used specifically for intraspecies communication. Social stimuli provide information regarding a variety of attributes that subsequently influence behavioral interactions. These include gender, age, group membership, reproductive status, dominance status, and health. In rodent mate choice, a female must determine whether to accept or reject a suitor based on information regarding genetic similarity (regulated by major histocompatibility complex genes), dominance status, and health (e.g., presence of parasitic infection). In some species, the act of copulation may trigger modification of neural pathways leading to stable pair bond formation. Conversely, encounters between males may lead to outcomes that are far from collaborative, stimulating aggressive displays reflecting the predisposition of males to compete for resources such as territory or mating opportunities.

In light of the complex sets of environmental and internal stimuli that must be integrated, the challenge of elucidating the neural substrates of social behavior may seem quite daunting. Prospects for discerning neural principles that may generalize across mammalian species would seem to be further complicated by the substantial variability of social structures seen among even closely related species. Despite such apparent obstacles, remarkable breakthroughs in social neuroscience have been made over the last decade, indicating that the neurobiology of social behavior in diverse mammalian species is experimentally tractable and relevant to human behavior and health.

Vasopressin and Oxytocin Enhance Social Recognition

A major focus of the neurobiology of social behavior is on the critical roles of the neuropeptides vasopressin (AVP) and oxytocin (OT). These two related nonapeptides (identical at 7 of 9 amino acid positions) are encoded by genes believed to have arisen from duplication of a common ancestral gene (Gimpl and Fahrenholz, 2001). AVP and OT are predominantly expressed in neurons of the hypothalamic paraventricular and supraoptic nuclei that project to diverse central sites and to the posterior pituitary gland (De Vries and Buijs, 1983). The release of these neurohypophyseal hormones from the posterior pituitary produces well-known peripheral effects (AVP: vasoconstriction, renal water resorption; OT: uterine contractions and milk ejection). In addition, AVP is expressed in projections from the extended amygdala to the lateral septum, nucleus accumbens, and amygdala (De Vries and Buijs, 1983). Following their central release, both AVP and OT act as neuromodulators via diverse modes of interneuronal signaling (Landgraf and Neumann, 2004). Two central receptors for AVP, V1aR and V1bR, have been identified and are widely expressed throughout the brain. There is a single known central OT receptor, which is widely distributed throughout the CNS (Gimpl and Fahrenholz, 2001).

A role for AVP in promoting social recognition was initially indicated by social habituation studies in the rat. Such procedures make use of the predisposition of rodents to investigate novel conspecifics more intensively than familiar animals. Typically, a novel juvenile male or ovariectomized female (used to minimize the induction of aggressive or mating behavior) "visitor" is placed in the home cage of the male subject. The visitor then becomes the subject of anogenital sniffing, a form of social investigation involving the sampling of olfactory stimuli. Repeated exposures to the visitor elicit progressive decreases in investigation time; such habituation indicates the development of social recognition. The social discrimination assay provides a variation on this theme (Engelmann et al., 1995). Here, a

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subject is simultaneously presented with a novel visitor to which it was previously exposed. Social recognition is indicated by reduced investigation of the visitor with which the subject had a prior encounter (relative to the novel visitor).

Using such behavioral assays, central AVP administration was found to facilitate social recognition, and nonselective antagonists (as well as anti-AVP antiserum) to impair it (reviewed in Ferguson et al., 2002). Genetic evidence also highlights the role of endogenous AVP in regulating social recognition. The Brattleboro rat, a strain bearing a spontaneous null mutation in the AVP gene, displays impaired social recognition (Engelmann and Landgraf, 1994).

Studies of AVP-mediated social recognition reveal that the V1aR plays a prominent role in multiple mammalian species, including mice, rats, and voles. Whereas overexpression of this receptor via viral infection improves social recognition, injection with a selective V1aR antagonist impairs it (reviewed in Bielsky and Young, 2004; Ferguson et al., 2002). Moreover, mice engineered to lack functional V1aRs exhibit markedly impaired social recognition (Bielsky and Young, 2004).

Significant progress has been made in identifying brain regions through which AVP influences social recognition. Intracerebral injections of agonists and antagonists revealed effects in the olfactory bulb, hippocampus, and septum (Bielsky and Young, 2004; Ferguson et al., 2002). In contrast, injection of AVP into the medial preoptic area did not appear to affect social recognition. Several lines of evidence suggests the involvement of the septum in AVP-mediated social recognition. Whereas administration of AVP and overexpression of V1aRs in the septum promote social recognition, septal administration of V1aR antagonists impair social recognition (Engelmann and Landgraf, 1994). Moreover, injection of AVP into the septum of Brattleboro rats rescues their social recognition impairment (Engelmann and Landgraf, 1994).

A dramatic demonstration of region specificity in social recognition is reported in an elegant study by Bielsky et al. (2005) in the current issue of *Neuron*. Using a combination of mouse gene-targeting technology, site-specific gene replacement, and pharmacological inhibitors, Isadora Bielsky and colleagues demonstrated that lateral septal V1aRs are critical for social recognition. Whereas V1aR antagonist injections into the septum of wild-type mice impaired social recognition, injections into the amygdala were without effect. Moreover, replacing V1aR expression in the lateral septum of V1aR null mutant mice by infection with a virus bearing the prairie vole gene was sufficient to reverse the mutants' social recognition deficits. These results demonstrate the power of combining mouse gene-targeting technology and gene replacement to identify the underlying neural circuitry mediating social recognition.

Like AVP, OT has been implicated in the regulation of social recognition. Although pharmacological effects can be inconsistent, gene targeting indicates an important role for this peptide. OT mutant mice fail to recognize previously encountered conspecifics, and this deficit can be rescued with central administration of OT. Furthermore, central administration of an OT antagonist in wild-type animals impaired social recognition, indicating that the OT mutant social recognition phenotype was not the consequence of a developmental defect (Ferguson et al., 2000).

OT also acts in a region-specific manner to modulate social recognition (Bielsky and Young, 2004; Ferguson et al., 2002). Both peptides influence this behavior when administered to the olfactory bulb and the hippocampus. However, unlike AVP, OT does not appear to act in the septum. Instead, OT influences social recognition in the medial preoptic area and amygdala, sites that are insensitive to AVP administration (Ferguson et al., 2002; Bielsky et al., 2005). In fact, injection of OT into the amygdala of OT mutant mice reverses their social recognition impairment (Ferguson et al., 2001).

Such differences in the regions at which AVP and OT exert similar effects raise questions about how they interact to modulate social recognition. It is possible that they act independently, in neural circuits that control distinct aspects of social recognition. If this is the case, then one might anticipate differences in the manner in which AVP and OT mutations impact social recognition. However, published reports indicate that the social recognition phenotypes of the two mutants are quite similar. It is unclear, however, whether the assays employed were sufficiently sensitive to detect phenotypic differences in all aspects of social recognition. Alternatively, these peptides may not act in independent circuits, but at different sites along a common pathway. For example OT may act at a stage of the social recognition process that precedes stages that require AVP. Consistent with this, OT has been found to act prior to exposure to the conspecific (Ferguson et al., 2001), while AVP can augment social recognition during and after conspecific exposure.

Divergent Effects of Vasopressin and Oxytocin on Social Behaviors

The regulation of social behavior not only requires the recognition of familiar conspecifics, but also modification of behaviors that may impact the likelihood and consequences of a social encounter. For example, anxiety and novelty avoidance might be expected to reduce the likelihood of approaching a conspecific. Learning and memory mechanisms may also affect social behavior by modifying the impact of prior social encounters on an individual's behavioral responses. It is therefore interesting that, although AVP and OT are both required for social recognition, they differentially regulate anxiety-like behavior and avoidance learning. For example, AVP and V1aR activation have been shown to increase anxiety-like behaviors in males, while OT has been shown to decrease them (Bielsky and Young, 2004; Windle et al., 1997). Opposing effects of the peptides on avoidance learning have also been identified (reviewed in Engelmann et al., 1996). In active avoidance paradigms, AVP improves acquisition and impairs extinction. In contrast, OT impairs acquisition and improves extinction of active avoidance learning. Opposing effects of the two peptides have also been observed in passive avoidance learning (reviewed in Engelmann et al., 1996).

Recently, Daniel Huber and colleagues identified the amygdala as a candidate site at which AVP and OT may exert their opposing affects on anxiety-like behavior

and avoidance learning (Huber et al., 2005). This region had previously been identified as an important site for anxiety-like behavior, fear conditioning, and extinction. The authors found that V1aRs and OT receptors are expressed within distinct subregions of the central nucleus of the amygdala. In addition, they identified two classes of neuronal responses to AVP and OT. One class of neurons was excited by OT but not AVP. These neurons were located in the lateral and capsular subregions, were GABAergic, and projected to the medial subregion of the nucleus. The second class of neurons was inhibited by OT and excited by AVP. These neurons were located in the medial subregion of the central nucleus, were inhibited by OT through a GABA-dependent mechanism, and projected outside the nucleus. These results provide compelling evidence that the AVP and OT peptide systems interact within the amygdala in a manner that could produce opposing effects on neuronal activity.

The fact that AVP and OT facilitate social recognition, but produce distinct and sometimes opposite effects on other behaviors, raises questions about why these two separate peptide systems evolved. One reason may be the need to regulate gender differences in social behaviors that share a social recognition component but require differential modulation of anxiety-like behavior, avoidance learning, or aggression. It is possible that prosocial behaviors require an inhibition of novelty avoidance, suppression of prior social avoidance learning, and decreased aggression. OT has been implicated in each of these processes, as well as social behaviors that require such behavior modifications. For example, OT regulates sexual behavior and social interactions in both males and females, as well as maternal behavior in females (Gimpl and Fahrenholz, 2001). In contrast, AVP increases anxiety-like behavior, inhibits extinction of avoidance learning, and promotes aggression, all behavior modifications that would influence the formation of territories and dominance hierarchies. These are characteristic components of male social behavior, and accordingly, the AVP system is much more prominent in males than females. Interestingly, the regulation of social recognition by AVP is dependent on androgens and is sexually dimorphic. AVP does not promote social recognition in castrated males or in females (reviewed in Ferguson et al., 2002). This contrasts with the social recognition deficits observed in OT mutant mice, which occur to a similar extent in males and females (Ferguson et al., 2000).

Just as gender differences in the function of AVP and OT systems provide insights into their functional significance, so can species differences in the action of these neuropeptides. An illustrative example is provided by voles, which display both gender-specific and species-specific social behaviors. Whereas prairie voles are social, form monogamous bonds, and engage in biparental care of offspring, montane (and meadow) voles are solitary and nonmonogamous, with females bearing the burdens of parental care. In male prairie voles, mating stimulates the formation of a monogamous pair bond and increases aggression in a manner that is dependent upon AVP. Central administration of AVP, but not OT, increased partner preferences and aggression. Conversely, V1aR antagonists block the formation of partner preference (Winslow et al., 1993). In addition, the nonmonogamous meadow vole can be induced to form a partner preference when V1aRs are expressed via viral infection into the ventral forebrain, a region that typically expresses low levels of V1aR in nonmonogamous vole species (Lim et al., 2004; Young et al., 1997). Interestingly, polymorphisms in both the AVP gene (Murgatroyd et al., 2004) and in the V1aR gene (Hammock et al., 2005) generate interindividual differences in anxiety and sociobehavioral traits.

In contrast to male prairie voles, females do not require mating to form a pair bond and do not exhibit enhanced aggression and mate-guarding behavior. Furthermore, OT but not AVP is important in regulating partner preference in females (Insel and Hulihan, 1995; Williams et al., 1994). Thus, AVP and OT may have evolved to regulate sexually dimorphic social behaviors associated with distinct influences on anxiety-like behavior, avoidance learning, and aggression.

Although AVP and OT clearly influence social recognition in multiple species, much less is known about how their effects on stress responses, anxiety-like behavior, avoidance learning, and aggression influence social behavior. Why, for example, does AVP both increase anxiety and pair bonding? One hypothesis suggests that social contact is sought to relieve anxiety (Kendrick, 2004). Alternatively, anxiety may be important for the mate-guarding behavior that accompanies the formation of a pair bond. Future studies employing site-specific gene manipulation and batteries of ethologically relevant behavioral assays would be useful for exploring how AVP- and OT-regulated behaviors are integrated. Furthermore, it will be of interest to determine the extent of cross-talk between these peptide systems in the regulation of behavior. Some data indicate little interaction. For example, AVP did not rescue the OT mutant social recognition phenotype (Ferguson et al., 2000), OT expression was not altered in V1aR mutant mice (Bielsky and Young, 2004), and AVP, but not OT, was increased in the hypothalamus of rats bred for increased anxiety-like behavior (Wigger et al., 2004). However, decreased AVP expression was observed in OT mutant mice (Young et al., 1996), and an OT receptor antagonist blocked AVP-induced partner preference in male prairie voles (Cho et al., 1999). This suggests at least some cross-talk between these systems, a possibility that is emphasized by the recent insights into their physiological effects in the amygdala (Huber et al., 2005).

Relevance to Human Social Behavior

Considering the complexity of human societies, it is prudent to wonder whether the neural pathways and neuromodulators that regulate rodent social interactions perform similar roles in humans. An obvious challenge stems from the difficulty with which diverse social phenomena such as arrogance, embarrassment, charisma, and rumor-mongering may be quantified in rodents. Moreover, the sensory systems registering social context are primarily olfactory in rodents, whereas they are predominantly visual and auditory in humans. Nevertheless, it is very likely that substantial resources are devoted to the processing of social information in the primate brain, as indicated by the observation of specialized cortical and limbic regions that appear to be

involved in the recognition of faces and the emotions they convey.

Evidence pertinent to the roles of AVP and OT systems in the regulation of human social behaviors has until recently been indirect. With regard to the AVP system, an allelic variant of the human *V1aR* gene has been associated with childhood autism by two independent groups (Kim et al., 2002; Wassink et al., 2004). As in rodents, OT is released during human female sexual arousal, and several correlational studies detected associations between OT levels during breast feeding and ratings of mother-infant bonding.

Recently, an intriguing study that more directly implicates OT in human social behavior has been reported by Kosfeld et al. (2005). OT was delivered via nasal spray (a route enabling the peptide to circumvent the blood-brain barrier) to participants in a "trust game." Subjects assumed the role of either an investor or a trustee for a transaction, and the investor was provided an option of transferring money to the trustee. Transfer resulted in the addition of money to the sum, sufficient for both parties to benefit from the transaction. However, because the trustee received the entire sum and payback to the investor was optional, the investor assumed a risk by engaging in the transaction. Interestingly, OT treatment substantially increased the number of subjects making maximal investments, indicating increased trust placed by investors in trustees. It is noteworthy that OT treatment did not influence the amount of money that trustees transferred back to investors. Thus, OT treatment appeared to have a selective impact on social behavior in a manner that promoted trust rather than altruism.

The observation that OT promotes social interaction in rodents and man emphasizes the relevance of animal models of social behavior to humans. However, significant limitations exist in the extent to which insights into the social neurobiology of rodents may generalize to our species. These arise from divergent social structures and from marked species variations in factors such as sensory cues for social recognition, social responses to OT and AVP, and the expression patterns of receptors for these neuropeptides. Further insights into such features of human social neurobiology will facilitate the understanding and treatment of disorders characterized by marked dysregulation of social behavior, such as autism, schizophrenia, and social phobia. However, the implications of this work extend further, promising fundamental insights into neuropsychological mechanisms through which our social perceptions and actions are influenced. In this context, it will be intriguing to consider the extent to which the effectiveness of methods designed to engage allegiance to organizations such as religious, cult, military, and political groups may relate to their capacity to engage our social circuitry.

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