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Cellular Mechanisms of Social Attachment

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Pharmacological studies in prairie voles have suggested that the neuropeptides oxytocin and vasopressin play important roles in behaviors associated with monogamy, including affiliation, paternal care, and pair bonding. Our laboratory has investigated the cellular and neuroendocrine mechanisms by which these peptides influence affiliative behavior and social attachment in prairie voles. Monogamous prairie voles have a higher density of oxytocin receptors in the nucleus accumbens than do nonmonogamous vole species; blockade of these receptors by site-specific injection of antagonist in the female prairie vole prevents partner preference formation. Prairie voles also have a higher density of vasopressin receptors in the ventral pallidal area, which is the major output of the nucleus accumbens, than montane voles. Both the nucleus accumbens and ventral pallidum are key relay nuclei in the brain circuits implicated in reward, such as the mesolimbic dopamine and opioid systems. Therefore, we hypothesize that oxytocin and vasopressin may be facilitating affiliation and social attachment in monogamous species by modulating these reward pathways.

Key Words: **oxytocin; vasopressin; V1a receptor; prairie voles; affiliation; nucleus accumbens; ventral pallidum.**

Microtine rodents, or voles, provide a useful model species for investigating the neuroendocrine events associated with monogamy, such as affiliation, pair bond formation, and paternal care (Winslow, Hastings, Carter, Harbaugh, and Insel, 1993; Carter, DeVries, and Getz, 1995; Young, Wang, and Insel, 1998; Carter, 1998; Insel and Young, 2001). Vole species display a large variation in social behavior, ranging from being highly social (monogamous and biparental) to being solitary (promiscuous and uniparental). Both field and laboratory studies have demonstrated that prairie voles (*Microtus ochrogaster*) are a highly social species that forms enduring, selective pair bonds between mates after mating. In contrast to prairie voles, montane voles (*M. montanus*) display much less affiliative behavior and do not form pair bonds. Thus, prairie and montane voles provide an excellent opportunity for comparative studies of the neural mechanisms influencing these behaviors.

Over the past decade, several laboratories have demonstrated that the neuropeptides oxytocin (OT) and vasopressin (AVP) are involved in the behavioral changes that occur during the transition from the virgin to the pair-bonded state. Specifically, in the female prairie vole, an intracerebroventricular (icv) infusion of OT facilitates the formation of a partner preference and increases social contact after cohabitation even in the absence of mating (Williams, Insel, Harbaugh, and Carter, 1994; Cho, DeVries, Williams, and Carter, 1999). Furthermore, an icv infusion of a selective OT receptor antagonist (OTA) into female prairie voles blocks the formation of the pair bond despite extended mating bouts (Insel and Hulihan, 1995). In the male prairie voles, AVP plays an analogous role to OT in females: Infusion of the neuropeptide facilitates partner preference, increases affiliative behavior, and increases selective aggression toward intruders (Winslow *et al.*, 1993; Young, Nilsen, Waymire, MacGregor, and Insel, 1999; Cho *et al.*, 1999). In this paper, we discuss recent experiments that further elucidate the neural mechanisms by which oxytocin and vasopressin influence monogamous behavior.

OXYTOCIN AND PAIR BONDING: COGNITIVE MECHANISMS

Oxytocin is involved in a number of sociosexual behaviors in mammals, including affiliation (Witt, Winslow, and Insel, 1992), sexual behavior (Witt and Insel, 1991), the onset of maternal care (Pedersen, Caldwell, Walker, Ayers, and Mason, 1994), and the

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formation of the mother-infant bond (Kendrick, Da Costa, Broad, Ohkura, Guevara, Levy, and Keverne, 1997). Thus, it is not surprising that oxytocin is involved in the formation of the pair bond in monogamous species. But what are the cognitive mechanisms that facilitate pair bond formation after mating? Our research on oxytocin has generated two hypotheses. First, oxytocin is required for the expression of social recognition. Genetically engineered mice that lack a functional oxytocin gene fail to recognize individuals to whom they have been repeatedly exposed. A single icv injection of oxytocin prior to the initial encounter restores social recognition (Ferguson, Young, Hearn, Insel, and Winslow, 2000b). The failure to recognize individuals as familiar does not appear to be due to general problems in olfactory processing or learning and memory, since the OT knockout mice habituate to nonsocial odors and perform as well as wildtypes in the Morris water maze. Furthermore, Fos-immunoreactivity (Fos-ir) studies have demonstrated that after a 90-sec social encounter, wildtype and OT knockout mice have similar levels of Fos induction in several regions involved in processing olfactory stimuli, including the main olfactory bulb, the piriform cortex, and the cortical amygdala. However, the OT knockout mice fail to show an induction of Fos-ir in the medial amygdala, a main projection of the olfactory bulb and a region rich in OT receptors (Ferguson, Winslow, Aldag, Insel, and Young, 2000a). Thus, one hypothesis to explain the pharmacological effects on partner preference formation is that oxytocin facilitates social recognition in prairie voles, while the OT antagonist interferes with pair bond formation by inducing social amnesia for the mate. This hypothesis, while consistent with the knockout mouse results, still does not explain why prairie voles form pair bonds after mating while montane voles do not.

The second hypothesis is based on the neuroanatomical distribution of OT receptors (OTR) in the prairie vole. Prairie voles have high densities of oxytocin receptors in the nucleus accumbens (NAcc) and prelimbic cortex (PLC) (Fig. 1) (Insel and Shapiro, 1992). The PLC and the NAcc are key components of the mesolimbic dopamine pathway and are thought to be involved in the reinforcing or rewarding effects of natural stimuli and drugs of abuse (McBride, Murphy, and Ikemoto, 1999). They are also known to play an important role in conditioned learning. Given this neuroanatomical evidence, we hypothesize that oxytocin transmission in these areas may facilitate pair bonding in females by reinforcing the association between the rewarding effects of NAcc activation and the male she just mated with. Thus, the cellular mechanisms of social attachment may well utilize the neural circuitry common to reward and reinforcement. Also, the fact that the nonmonogamous montane voles have virtually no oxytocin receptors in the NAcc (Fig. 1) is consistent with their failure to form this association or partner preference. To test the hypothesis that OTR activation in the NAcc is involved in partner preference formation, we have experimentally addressed two questions in female prairie voles: (1) Do icv infusions of oxytocin, which are known to facilitate partner preference formation, also modulate NAcc activity? (2) Is OT neurotransmission in the NAcc or PLC necessary for pair bonding?

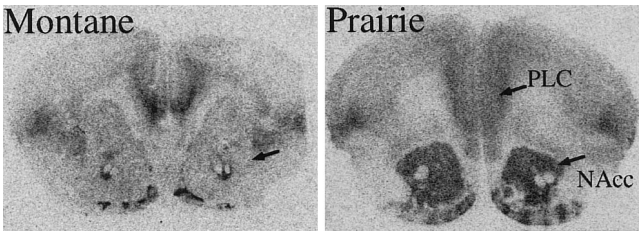

FIG. 1. Autoradiograms illustrating the distribution of oxytocin receptor binding in the nucleus accumbens (NAcc) and prelimbic cortex (PLC) of the monogamous prairie vole and the promiscuous montane vole. Note the lack of receptors in the NAcc of the montane vole.

OXYTOCIN AND NAcc ACTIVATION

In order to understand how OT may be affecting the NAcc, it is necessary to determine whether the OTRs in this region are located on cell bodies localized in the region or on terminals from other projection sites. There are two sets of data to suggest that the OTRs are located in cell bodies within the NAcc. First, OTR mRNA is detected in the NAcc using *in situ* hybridization (unpublished data). Second, we performed unilateral 6-hydroxydopamine lesions in the NAcc to destroy dopaminergic projections from the ventral tegmental area. Female prairie voles (n = 5) were unilaterally injected with 4 μg of 6-hydoxydopamine into the NAcc and allowed to recover for 7 days. The brains were then examined for OTR binding and dopamine transporter binding using ^{125}I-OTA and ^{125}I-RTI-55. There was a significant reduction in dopamine transporter binding at the injection site, but OTR binding was identical in both hemispheres. This suggests that the OTRs are most likely located on NAcc cell

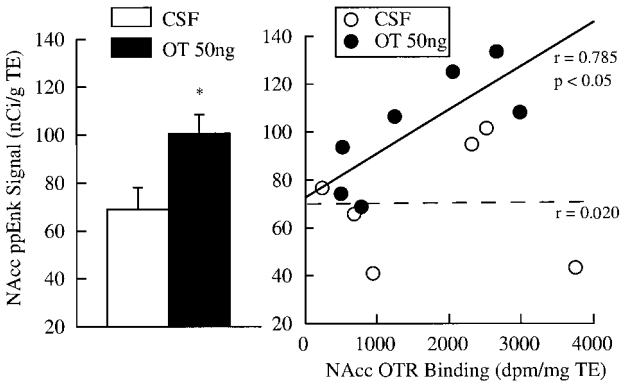

FIG. 2. Oxytocin (OT) injected intracerebroventricularly increases preproenkephalin (ppEnk) mRNA in the NAcc of female prairie voles (*$P < 0.05$, two-tailed t test). There is a significant correlation in the oxytocin-injected group between the amount of ppEnk mRNA signal and the density of oxytocin receptor (OTR) binding in the NAcc (solid line, $r = 0.785$). There was no correlation between ppENK signal and OTR binding in the animals receiving CSF injections (dashed line). ppENK mRNA signal is expressed in nanoCuries per gram of tissue equivalents (nCi/g TE) and OTR binding signal is expressed in decompositions per minute per milligram of tissue equivalents (dpm/mg TE).

bodies, rather than on dopaminergic nerve terminals originating in other regions.

To determine if OT administered icv influenced cells in the NAcc, we measured the effect of an icv oxytocin infusion on preproenkephalin (ppEnk) gene expression in the NAcc. ppEnk mRNA was simply used as a natural marker of OTR activation because it had been previously shown that OTR activation upregulates ppEnk gene expression (Bale and Dorsa, 1997). Using a 48-bp ^{35}S-labeled oligonucleotide probe specific for the rat ppEnk gene, we performed *in situ* hybridization to quantify ppEnk mRNA in the NAcc 4 h after an icv infusion of either CSF ($n = 6$) or oxytocin ($n = 7$, 50 ng in 2 μl of artificial CSF). As a control, preprodynorphin (ppDyn) mRNA was quantified in adjacent sections since it is also expressed in the NAcc but has not been shown to be regulated by oxytocin. Hybridized sections were opposed to film for 1 week and the mRNA signals were quantified using the NIH Image analysis system and converted to nCi/g tissue equivalents using ^{14}C autoradiographic standards. Subjects were sexually naïve adult female prairie voles. Oxytocin infusion resulted in a significant increase in ppEnk mRNA in the NAcc compared to CSF infusion ($P < 0.05$, two-tailed t test), but had no effect on ppDyn expression (Fig. 2). Since there is significant variability in OTR density in the NAcc across individual prairie voles (Young, 1999), we then correlated OTR density in the NAcc and the level of ppEnk mRNA after OT infusion (Fig. 2). OTR binding was performed as previously described and binding intensity was converted to DPM/mg tissue equivalents using ^{125}I autoradiographic standards (Young, Huot, Nilsen, Wang, and Insel, 1996). There was a significant correlation between OTR density in the NAcc and ppENK mRNA ($r = 0.785$, $P < 0.05$), with animals having the lowest levels of OTR binding having ppENK mRNA levels similar to that of CSF-injected animals. There was no correlation between OTR density and ppDyn mRNA in either CSF- or OT-injected animals. These results demonstrate that icv oxytocin administration, which we have previously shown to facilitate pair bond formation, does indeed modulate gene expression in the NAcc.

The induction of ppENK mRNA in the NAcc by oxytocin is interesting given the evidence of opiate involvement in social attachment (Panksepp, Nelson, and Bekkedal, 1997) and may represent a mechanism by which oxytocin modulates the reward pathway and behavior. We have yet to explore the possible role of opiates and the interaction of enkephalin and oxytocin in the regulation of social attachment in voles.

OXYTOCIN IN THE NAcc AND PLC AND PARTNER PREFERENCE

Next, we determined whether blocking oxytocin receptor activation in the NAcc during cohabitation would prevent the formation of a partner preference, the initial step in the development of a pair bond. Female prairie voles were injected bilaterally into the NAcc, PLC, or caudate-putamen (CP) with either CSF or the selective oxytocin antagonist d(CH_2)$_5$[Tyr(Me)^2,Thr^4,Orn^8,Tyr^9-NH_2]-vasotocin (1 ng/side in 200 nl of CSF). The CP, which is not a component of the dopamine reward pathway, served as a control injection site because of its close proximity to the NAcc and PLC. Each animal received two injections, the first immediately before and the second delivered 12 h into a 24-h period of cohabitation with mating. A 3-h partner preference test was performed as previously described immediately after the cohabitation (Williams, Catania, and Carter, 1992). Females receiving CSF in all brain regions, or OT antagonist into the CP, exhibited a strong partner preference ($P < 0.05$, Wilcoxon signed rank sum test). However, OT antagonist injected into the NAcc and the PLC prevented the formation of a partner preference (Fig. 3).

Dopamine neurotransmission in the NAcc is also

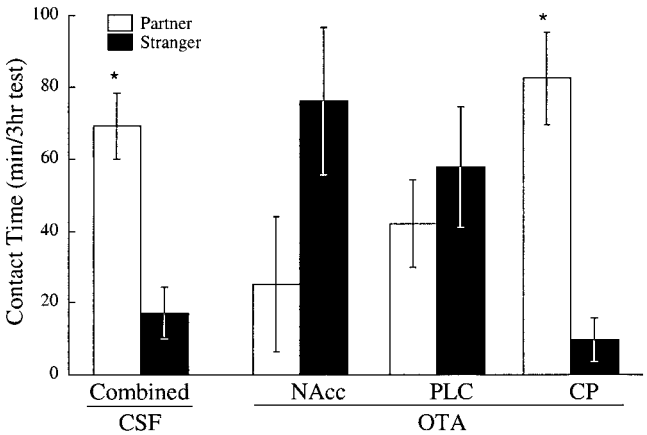

FIG. 3. The effects of CSF and a selective oxytocin antagonist (OTA) injected into the NAcc, PLC, or the caudate-putamen (CP) on partner preference in female prairie voles after 24 h of mating. Females injected with CSF into each region (combined) or with OTA into the CP spent more time in contact with their partner than with a stranger (*$P < 0.05$; Wilcoxon signed rank sum test). OTA injected into the NAcc and the PLC prevented the formation of a partner preference.

involved in partner preference formation. Mating in the female prairie vole is associated with an increase in extracellular dopamine in the NAcc as measured by microdialysis, and bilateral infusion of a dopamine D2 receptor antagonist into the NAcc blocks mating-induced partner preferences (Gingrich, Liu, Cascio, Wang, and Insel, 2000). These studies support the hypothesis that mating facilitates the formation of a partner preference in the female prairie vole through activation of the mesolimbic dopamine reward pathway in the NAcc and PLC and that the activation of both the OTR and dopamine D2 receptor in these regions is necessary for partner preference formation. It is not yet clear how OTR and D2 receptor activation may interact to modulate social attachment.

VASOPRESSIN RECEPTORS IN THE VENTRAL PALLIDUM

Given the apparent role of OTR in the reward circuitry for pair bonding in female prairie voles, is a similar process involved in pair bonding in the male prairie vole? Males appear less sensitive to OT but all of the major features of monogamy are facilitated by AVP and inhibited by a V1a vasopressin receptor (V1aR) antagonist (Winslow *et al.*, 1993). Comparison of the distribution of V1aR in the prairie and montane vole brains reveals that prairie voles have a high density of V1aR in a region of the ventral forebrain located ventromedially to the NAcc, while montane voles express few receptors in this region (Fig. 4).

In previous reports, this region was identified as the diagonal band. More careful neuroanatomical analyses of V1aR binding, however, have shown that the site of high V1aR density is lateral to the diagonal band. We used neurochemical markers to delineate the boundaries of the various nuclei located in the ventral forebrain. Preproenkephalin and substance P mRNA, which are restricted to the NAcc, were used to identify the dorsal boundary of the ventral pallidum (VP). In addition, an acetylcholinesterase stain was used to define the boundaries of the diagonal band (Fig. 4). We then compared these sections to adjacent brain sections of V1aR autoradiography. The results demonstrate that the V1aR are located lateral to the diagonal band in a region corresponding to the VP, but may also include the ventralmost extent of the lateral septum and the substantia innominata. Cellular analysis of V1aR protein using immunocytochemistry is needed to accurately determine the exact boundaries of the receptor field in this region.

There is some evidence that the species differences in V1aR distribution in prairie voles contributes to the species differences in male social behavior. First, an icv infusion of AVP increases affiliative behavior in prairie voles, but not in montane voles, demonstrating that prairie and montane voles have different behavioral responses to AVP (Young *et al.*, 1999). In addition, we have developed an adenoassociated viral vector containing the prairie vole V1aR inserted downstream of a neuron-specific enolase promoter. When injected into adult prairie vole brains, this vector expresses the V1aR gene stably for at least 4 months (Pitkow, Sharer, Ren, Insel, Terwilliger, Young, 2001). We used this technique to examine the effect of increasing V1aR expression in the VP area and a control region, the caudate-putamen. Male prairie voles with artificially elevated V1aR expression in the VP, but not the caudate-putamen, displayed increased levels of affiliative behavior as measured by olfactory investigation and time huddling with a juvenile stimulus animal (Pitkow, Sharer, Ren, Insel, Terwilliger, Young, 2001). Furthermore, comparative analysis of the V1aR binding patterns in other species suggests an association between V1aR density in the VP area and monogamy. For example, the monogamous California mouse, *Peromyscus californicus*, also has a high density of V1aR in the VP region, while the nonmonogamous white-footed mouse, *P. leucopus*, does not (Bester-Meredith, Young, and Marler, 1999).

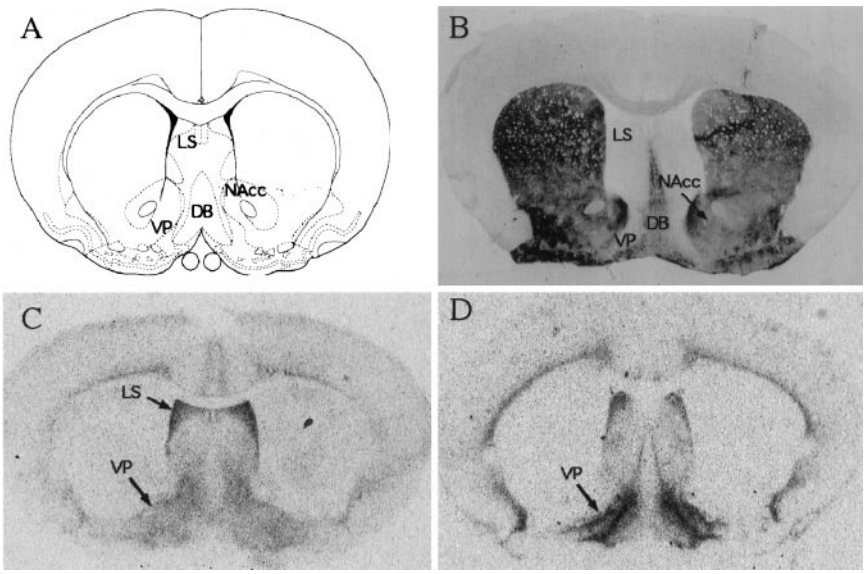

FIG. 4. Vasopressin V1a receptor binding in the ventral pallidum of montane and prairie voles. (A) Rat brain atlas illustrating the neuroanatomical boundaries of the NAcc, diagonal band (DB), ventral pallidum (VP), and lateral septum (LS) (Paxinos and Watson, 1998). (B) Acetylcholinesterase stain of a corresponding prairie vole section. The acetylcholinersterase stain is concentrated in the diagonal band and the nucleus accumbens. (C) V1a receptor binding in the nonmonogamous montane vole. Note the high density of receptors in the LS, but relative absence of V1aR in the VP. (D) V1a receptor binding in the monogamous prairie vole. Note the high density of receptors in the region corresponding to the VP.

Moreover, the monogamous common marmoset has a higher density of V1aR binding in the VP than rhesus monkeys (Young, 1999).

The VP is a major output of the shell of the NAcc and, like the NAcc, receives dopaminergic input from the ventral tegmental area (Klitenick, Deutch, Churchill, and Kalivas, 1992). Like the NAcc, the VP is an important neurobiological substrate for the rewarding and reinforcing properties of natural stimuli and psychostimulants (McBride, Murphy, and Ikemoto, 1999). Experiments have shown that cocaine self-administration leads to an increase in extracellular dopamine concentration in the VP; also, infusion of psychostimulants directly into the VP leads to the development of a conditioned place preference for the environment in which the injections were experienced (Gong, Neill, and Justice, 1996). In addition, depletion of dopamine specifically in the VP prevents this cocaine-induced place preference (Gong, Neill, and Justice, 1997). It is possible that, in the prairie vole, AVP released during mating activates V1aR in the VP. This, in turn, might lead to a conditioned *partner* preference in the monogamous prairie vole and thereby provide the necessary substrate for the formation of a pair bond. Likewise, the lack of V1aR in the VP of nonmonogamous species may explain their inability to form partner preferences after mating. The VP is an interesting candidate site of action in the modulation of social behaviors associated with monogamy; however, site-specific injections of V1aR antagonists into the VP are needed to confirm its role in social attachment in prairie voles.

CONCLUSIONS

It has been postulated that there are parallels between social attachment and narcotic addiction and that similar neural circuitry and neurochemistry may underlie both phenomena (Panksepp, Nelson, and Bekkedal, 1997). In fact, there is significant evidence for a role of endogenous opioids in modulating affiliative behaviors. For example, β-endorphin is released in monkeys during social grooming, while blockade of opioid receptors results in increased motivation to be groomed (Keverne, Martensz, and Tuite, 1989). Opiates also modulate infant–mother attachments and separation distress calls in rat pups (Nelson and Panksepp, 1998). Our research on the neurobiological mechanisms regulating affiliation and pair bonding in voles supports the idea that brain reward circuitry plays a key role in regulating social attachments. There appear to be sex-specific mechanisms regulating

pair bonding in voles, with oxytocin acting in the NAcc to facilitate social attachment in females and vasopressin, perhaps acting in the VP, facilitating social attachment and affiliation in males. In females, dopaminergic systems are also involved. These two different neuropeptides may be promoting attachment by linking social stimuli to a common cognitive mechanism, using the NAcc and VP as relays in a shared reward circuitry.

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