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Commentary

Opioid Receptors: Binding that Ties

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Prairie voles form stable, monogamous mating pairs, and are a valuable model for understanding the neurobiology of enduring partner relationships. The report by Burkett *et al* (2011) investigates the role of μ-opioid receptors (MOR) in partner preference formation in prairie voles. The authors found that systemic naltrexone treatment of female prairie voles during initial exposure to a male reduced subsequent mating bouts and nonsexual socialization with this familiar partner, when a choice test including a novel male was performed afterwards. The authors then targeted two regions in the basal ganglia, the shell of the nucleus accumbens, and the caudate putamen, with direct infusions of a selective MOR antagonist to determine if MOR in either region was necessary for partner preference. They found that MOR in the dorsal striatum, but not the shell of the nucleus accumbens, modulated partner preference formation, suggesting a role for dorsal striatal MOR in this complex social behavior. Radioligand binding and *in situ* hybridization data supported these results, as MOR expression was higher in the dorsal striatum than in nucleus accumbens.

This work extends knowledge about social learning by introducing two new concepts. This is the first study to implicate endogenous opioid peptides in pair bonding. Although many studies have shown the importance of oxytocin and arginine vasopressin in affilial behavior, this study demonstrates that the endogenous ligand for MOR, presumably enkephalin, is also important in the formation of stable social relationships. Second, it was surprising to find that the dorsal striatum had the key role in MOR-mediated preference formation, as previous studies have focused on nucleus accumbens. However, the anatomical data presented in the manuscript agree with the distribution and gradient of expression found in previous anatomical studies of this receptor in rats, where MOR are expressed strongly in the 'patch' component of the striatum, with a differential pattern along a ventrolateral gradient. Additionally, MOR are enriched in several rat brain regions that have been associated with emotional processing, such as the locus coeruleus, hippocampus, cerebral cortex, and striatum. MOR are more widely distributed in humans than rats, but these receptors are certainly strongly expressed in the striatum, where there is also a gradient of expression from highest in the dorsal to lowest in the ventral portions of the striatum, with the lowest expression occurring in the ventral-most third of the caudate putamen and nucleus accumbens (Voorn *et al*, 1996).

This study and others using similar animal models may provide insights into the role of endogenous opioid peptide signaling in complex social behaviors involved in the formation of stable, emotionally committed relationships. In 1978, Herman and Panksepp (1978) showed that social attachment in guinea pig was mediated by the opioid system, when they systemically administered morphine or naloxone, an opioid agonist and antagonist, respectively, to adult and juvenile guinea pigs, and measured distress vocalizations (adults) and proximity maintenance behavior (juveniles). Morphine reduced adult isolation-elicited distress vocalizations, whereas naloxone increased them; the agonist also decreased the juvenile's preference to be near its mother. These results were later corroborated in other species such as dogs, chicks, and rats, confirming the evolutionary conservation of these important survival-linked behaviors.

Prairie voles are being used to model social relatedness and its discontents, including behaviors as diverse as isolation-related depression and social drinking. For example, a study investigating amphetamine-associated deficits in social bonding implicated dopamine-D_1-like receptors in the nucleus accumbens (Liu *et al*, 2010). Importantly, this work may extend beyond partner relationships, and generalize to social relationships. For instance, prairie voles have been used to investigate prosocial pharmacotherapeutics for autism, a disorder that involves extreme social deficits, and was first suggested by Sahley and Panksepp (1987) to be related to the opioid system. Some of the neurochemical and anatomical substrates revealed in studies of voles and other rodents have now been confirmed in humans; for example, variation in the vasopressin receptor 1a gene was associated with increased amygdala activation and decreased marriage quality (Walum *et al*, 2008).

As opioid agonists and antagonists are widely used in medical contexts, there may also be some clinical implications to be drawn from this study. For example, naltrexone, an opioid antagonist, is used to reduce relapses to drug and alcohol seeking. One important factor in drug recovery involves extending one's social network to develop healthy

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relationships with drug-free individuals. This study suggests that blocking MOR may interfere with the social learning involved in forming relationships, so although naltrexone therapy reduces the risk of relapse in a physiological sense, if it interferes with social bonding behavior, it may have adverse impacts in other ways. Perhaps this can be mitigated by psychosocial interventions, such as social skills training, as this skill set may be underdeveloped in this population.

Finally, these results have intriguing implications, as dorsal striatum is involved in the learning of goal-directed behaviors and habit formation, which puts the present results in an interesting light. Although their social structures differ in many ways, monogamy appears to be typical for both prairie voles and humans, even if it is not universally the case. However, the value of stable relationships, and the involvement of both males and females in nest building and parenting, is evident in both voles and humans. This leads us to consider whether monogamy is actually mediated by the same circuitry as habit formation. Although the word 'habit' is usually associated with behaviors with adverse consequences such as drug use or gambling, stable patterns of behavior can also be advantageous, efficient, and reliable. In this sense, the involvement of brain circuits associated with habit may be a crucial and positive mediator in establishing stable pair bonds. However, in abusive relationships, it can be difficult for the abused to escape the abusive partner despite aversive consequences—so perhaps this same brain region can interfere with the ability to make adaptive changes just as it can contribute to stable social behavior.

DISCLOSURE

The authors declare no conflict of interest.

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