

Monogamy: dopamine ties the knot

Scott Edwards & David W Self

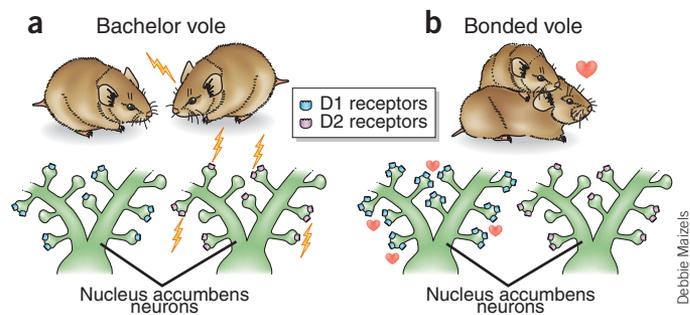
Prairie voles form lasting pair bonds with their mating partners after a single experience of sexual activity, and this reward-related learning depends on dopamine. A new paper reports that two dopamine receptor subtypes contribute differently to the initial formation of pair bonds and to their maintenance by the promotion of selective aggression toward alternative mates.

Monogamy is rare among mammalian species, with only 3–5% forming lifelong pair bonds¹. The prairie vole *Microtus ochrogaster* forms such enduring bonds after a single initial mating encounter, but why are these prairie-dwelling critters ‘addicted to love’ when their mountain- and meadow-dwelling cousins indulge in lifelong promiscuity? The answer may lie in the same neurobiological culprit already implicated in drug addiction, the neurotransmitter dopamine. In this issue, Aragona and colleagues² report a role for particular dopamine receptor subtypes both in establishing pair bonds in sexually naive male prairie voles and also in maintaining the integrity of the bond after it has formed.

Other neurotransmitters are known to support social affiliation, including the neuropeptides oxytocin and vasopressin³, and monogamous prairie voles have a higher density of oxytocin receptors in the nucleus accumbens compared to more promiscuous vole species. The nucleus accumbens is also a major recipient of dopaminergic innervation involved in both natural and drug rewards. This anatomical overlap has led investigators to hypothesize that pair bonding reflects a form of reward-related learning in male voles, where dopamine release during mating reinforces positive associations with a partner’s specific olfactory signature⁴. Indeed, dopamine release in the nucleus accumbens is implicated in sexual behavior in rats^{5,6} and in the mating-induced establishment of pair bonds in prairie voles⁷. Aragona and colleagues now show that dopamine has two very different and opposing influences on pair-bond forma-

Figure 1 Dopamine signaling in the formation and maintenance of pair bonds in male prairie voles. **(a)** In naive bachelor voles, partner preference establishment after an initial mating encounter with a female requires dopamine signaling via D2-like dopamine

receptors (purple) in the rostral shell of the nucleus accumbens. **(b)** D1-like dopamine receptors (blue) are upregulated in the shell and core of the nucleus accumbens once a pair bond has formed. An established pair bond is maintained by selective aggression toward unfamiliar females, and D1 receptor antagonists block this behavior.



Debbie Marzels

tion, depending on which dopamine receptor subtype is activated. The D2 receptor subtype facilitates initial pair-bond formation, whereas the D1 receptor subtype blocks it. Furthermore, after a nuptial encounter, D1 receptor signaling prevents bonded males from straying with other available females.

After a 24-hour period of *ad libitum* mating, male prairie voles prefer to spend more time in close side-by-side contact with their mating partner than with female strangers, and this ‘partner preference’ provides a measure of whether a pair bond has been established. When males are paired with females for only 6 hours and are not allowed to copulate, a pair bond normally does not form and males spend equal time with paired females and strangers. Aragona and colleagues first found that infusion of a D2 receptor agonist into the nucleus accumbens of male prairie voles before a brief encounter with a female induced the formation of partner preference, even in the absence of mating (Fig. 1a). Only D2 receptors in the rostral shell of the nucleus accumbens were effective, as agonist infusions into caudal or core subregions had no effect, which is consistent with a

specific role for the rostral shell in appetitive conditioning⁸. On the other hand, coinfusion of a D1 receptor agonist with the D2 agonist prevented pair-bond formation. Similarly, D1 agonist infusion prevented the pair-bond formation that normally occurs after 24 hours of mating in untreated voles, even though it did not alter their sexual behavior. Dopamine and other nonselective agonists activate both D1 and D2 receptors, but with somewhat higher affinity for D2 receptors, which could explain why moderate doses of these agonists induce partner preference whereas higher doses do not⁷. Therefore, D2 receptor activation alone is sufficient to establish pair bonds, but simultaneous activation of D1 receptors during mating opposes their formation.

Once mating-induced pair bonds were established, the authors found an increase in cell-surface D1 receptors in the nucleus accumbens of bonded male voles (Fig. 1b). Because D1 receptor activation prevented initial pair-bond formation, they asked whether this reorganization of D1 and D2 receptor-mediated input to nucleus accumbens neurons maintains the original pair bond by preventing the formation of new bonds

The authors are in the Department of Psychiatry, the Seay Center for Basic and Applied Research in Psychiatric Illness, University of Texas Southwestern Medical Center, Dallas, Texas 75390-9070, USA.
e-mail: david.self@utsouthwestern.edu

with female strangers. To assess pair-bond stability following D1 receptor upregulation, the authors used a resident-intruder behavioral test. If a pair-bonded female partner was the intruder in the test, then the resident males engaged in close affiliative behavior, but if the intruder was a female stranger, males instead became extremely aggressive and attacked the female intruder. When the investigators infused a D1 receptor antagonist into the nucleus accumbens to block the upregulated D1 receptors, this selective aggression was abolished: bonded male voles eagerly engaged in close contact with female strangers as if they had returned to their nonbonded bachelor status. This suggests that the increase in D1 receptor expression in the nucleus accumbens maintains monogamy by transforming the response to new females from affiliative interest to aggression.

Aragona and colleagues also show that non-monogamous meadow voles have naturally high levels of D1 receptor expression in the nucleus accumbens, even before mating. Blocking D1 receptors in these voles increased their affiliative behavior toward both female partners and strangers but did not induce partner preference. The authors hypothesize that higher D1 receptor levels contribute to the generally asocial demeanor of meadow voles, but that other factors may also contribute to their lack of pair bonds. One caveat is that D1 receptors were blocked during a 6-hour cohabitation period that is not normally sufficient to induce partner preference in prairie voles; and the D1 receptors were not blocked during the test for expression of the partner preference. It also remains unclear whether a similar D1 versus D2 dichotomy regulates pair-bond formation in female prairie voles.

From an anatomical perspective, D1 and D2 receptors exist (at least partially) in distinct striatal projection neurons⁹ that could underlie their differential effects in inducing and maintaining

pair bonds. D2 receptors are expressed in neurons that project to the ventral pallidum, where vasopressin receptors could interact downstream in complex neural networks that help form partner preferences¹⁰. Differences in the signaling pathways activated by these receptors might also explain their opposing influences. D1 and D2 receptors couple to stimulatory and inhibitory G proteins, respectively, with opposite effects on intracellular cyclic AMP (cAMP) production, and preliminary studies by the authors suggests a role for cAMP signaling in the nucleus accumbens in pair-bond formation¹¹.

D1 and D2 receptors are also thought to make differential contributions to other forms of reward-related learning. Whereas D1 receptors are important for learning new associations, D2 receptors enhance the influence of previously learned associations on appetitive behavior^{12–14}. In this sense, these receptors seem to function somewhat differently in pair-bond formation in the prairie vole, because D2 rather than D1 receptor activation facilitates initial bonding during mating.

However, the prairie vole's fierce loyalty to a single partner is paralleled by the strong cravings of drug addicts and their avoidance of alternative rewards (including potential mates) to the point of personal devastation. In this regard, it is interesting that the study by Aragona and colleagues reveals a striking similarity between the roles of D1 and D2 receptors in pair-bond formation in voles and in cocaine-seeking behavior in rats¹⁵. In rats reinforced by cocaine self-administration, D2 receptor stimulation triggers relapse to cocaine seeking, reminiscent of the ties that bind prairie voles to their life-long partners. Conversely, D1 receptor stimulation inhibits cocaine-seeking behavior, perhaps because animals are satisfied and have no desire for more cocaine, or potential suitors for that matter. The development of cocaine addiction may also be related to different changes in D1

and D2 responses, as rats become more sensitive to stimulation of D2 receptors and less so to that of D1 receptors (S.E. & D.W.S., *Soc. Neurosci. Abstr.* **28**, 2002). Heightened D2 receptor activity could foster a 'pair bond' between user and drug, but without an upregulation in D1 receptor expression, drug users lack a physiological brake on reward-seeking behavior like that in their pair-bonded prairie vole counterparts. Thus, where dopamine receptor signaling is concerned, drug addiction could reflect a sort of pathological inverse of pair-bond formation in prairie voles.

Ultimately, our knowledge of naturally occurring pair bonds may shed light on the psychopathology of abnormal attachment and asocial behavior related to addiction or other mental illnesses. Our ability to unravel the neurobiological knot that ties together monogamous prairie voles, for better or for worse, could eventually help us to develop new treatments for some psychiatric disorders.

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Internalizing channels: a mechanism to control pain?

Diane Lipscombe & Jessica Raingo

The opioid receptor-like receptor inhibits the Ca_v2.2 calcium channel even without the receptor ligand, nociceptin. A new study finds that long-term exposure to nociceptin causes internalization of the receptor-channel complex.

The accurate perception of painful stimuli is essential for survival, but constant pain can render life unbearable. All nociceptive stimuli,

useful and unwanted, use similar signaling pathways, which complicates efforts to design drugs that prevent continuous pain without affecting normal sensory processing. The human body produces its own analgesic endorphins that act on pathways involved in mediating chronic but not acute pain. By studying the molecules and pathways targeted by endog-

enous analgesics, Altier *et al.* in this issue have uncovered unexpected mechanisms that might help curtail persistent, unwanted pain¹.

The opioid receptor-like receptor (ORL1), also known as the orphanin FQ receptor, is G protein coupled and expressed at high levels in the dorsal horn of the spinal cord as well as in the brain². Its endogenous ligand, nociceptin,

The authors are in the Department of Neuroscience, Brown University, Providence, Rhode Island 02912, USA.
e-mail: diane_lipscombe@brown.edu