9. Green, J., and Akam, M. (2013). Evolution of the pair rule gene network: Insights from a centipede. Dev. Biol. *382*, 235–245.

10. Janssen, R., Budd, G.E., Prpic, N.-M., and Damen, W.G. (2011). Expression of myriapod pair rule gene orthologs. EvoDevo *2*, 5.

11. Minelli, A., Chagas-Júnior, A., and Edgecombe, G.D. (2009). Saltational evolution of trunk segment number in centipedes. Evol. Dev. *11*, 318–322.

12. Shear, W.A., Ferreira, R.L., Iniesta, L.F.M., and Marek, P. (2016). A millipede missing link: Dobrodesmidae, a remarkable new polydesmidan millipede family from Brazil with supernumerary rings (Diplopoda, Polydesmida), and the establishment of a new suborder Dobrodesmidea. Zootaxa *4178*, 371–390.

13. Maruzzo, D., Minelli, A., Ronco, M., and Fusco, G. (2007). Growth and regeneration of the second antennae of *Asellus aquaticus* (Isopoda) in the context of arthropod antennal segmentation. J. Crust. Biol. *27*, 184–196.

14. Drago, L., Fusco, G., and Minelli, A. (2008). Non-systemic metamorphosis in male millipede appendages: long delayed, reversible effect of an early localized positional marker? Front. Zool. *5*, 5.

15. Akkari, N., Enghoff, H., and Minelli, A. (2014). Segmentation of the millipede trunk as suggested by a homeotic mutant with six extra pairs of gonopods. Front. Zool. *11*, 6.

Social neuroscience: Staying bonded over oxytocin and endocannabinoids

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Oxytocin is known to be critical for the formation of social relationships in prairie voles. A new study further explores the role of oxytocin in maintaining an established social relationship, and in recruiting the endocannabinoid system to do so.

Social relationships encompass a wide variety of interactions, ranging from simple communication between two individuals to the more complex interactions involved in forming affiliative bonds like those between romantic or sexual partners, or parent and child. In humans, the presence of these social bonds can have tremendous impact on life expectancy and quality[1]. Thus, it is unsurprising that a lot of research has focused on understanding social relationships, and the neuromodulators and neural circuitry underlying their formation, expression, and maintenance[2,3]. A significant body of this research into social relationships is focused on the role of the oxytocinergic system. Work in animal models, notably in rodent species, has demonstrated that the oxytocinergic system is crucial for social relationships[4]. In a new study published in this issue of *Current Biology*, Borie and colleagues[5] have further elaborated on the role of the oxytocinergic system in social relationships, particularly in the maintenance of 'pair bonds'. In their work, the authors have illuminated a novel role for the endocannabinoid system in this oxytocin-dependent maintenance of pair bonds.

Pair bonding is a social relationship wherein a pair of non-kin conspecifics form a relationship, often long-lasting, in order to procreate. This is usually seen in monogamous species, and a pair bond will often demonstrate sexual preference or exclusivity to each other along with biparental care of offspring. Our understanding of the role of oxytocin in pair bonding is in large part due to the study of the sister vole species, the monogamous prairie vole (*Microtus ochrogaster*) and the non-monogamous montane vole (*Microtus montanus*). While oxytocin expression in the brain is similar across both species, the distribution of oxytocin receptors is highly characteristic to each. Prairie voles show higher densities of oxytocin receptors in several brain regions, notably the prelimbic cortex and the nucleus accumbens[6]. Blocking oxytocin receptors in the nucleus accumbens or the medial prefrontal cortex of prairie voles (using a selective oxytocin antagonist) prevents the formation of partner preference following mating. Further, partner preference in prairie voles can be bidirectionally modulated by enhancing[7] or reducing[8] expression of oxytocin receptors in the nucleus accumbens with the use of a viral-vector mediated gene transfer or knockdown strategy. Thus, it seems that the oxytocinergic system plays an integral role in the formation of pair bonds, with the nucleus accumbens being a key node in this circuit. However, questions remain about whether it also plays a role in the subsequent maintenance of pair bonds.

In a pair bond, the relationship between two animals evolves from a first meeting, to mating and forming a preference for their mated partner over a stranger, and to maintaining this preference over a long period of time. Indeed, prairie voles mate for life. We know that the oxytocinergic system is essential for the initial expression of partner preference. However, does it also contribute to the subsequent maintenance of a pair bond?

This is the question the authors have tried to elucidate. Pair bonds can be formed in the laboratory by introducing virgin female prairie voles to male partners (paired) or to a same-sex littermate (virgin, non-paired control). The authors show that once a pair bond has been established, differences arise in the oxytocin-mediated synaptic transmission between paired and control females. There appears to be an enhancement of glutamatergic transmission in the nucleus accumbens in paired voles following administration of an oxytocin agonist (TGOT). This is seen with a decrease in spontaneous excitatory postsynaptic currents (sEPSC) in virgin females (Figure 1A), and an increase in evoked excitatory postsynaptic currents (eEPSC) in paired females (Figure 1B). While virgin females show no partner preference (Figure 1C), the oxytocin-mediated potentiation in glutamatergic transmission appears to correlate with partner preference in paired females (Figure 1D). Furthermore, paired pulse responses (PPR) in paired animals indicate that the action of the oxytocinergic system is presynaptic. Surprisingly, however, it is a knockdown of the oxytocin receptors on the postsynaptic nucleus accumbens cells that results in a loss of the potentiation seen in paired animals. Thus, there exists a retrograde signal that links the postsynaptic oxytocin receptors to a presynaptic facilitation of glutamate release. What would that be?

The authors focus on endocannabinoids, known to function as retrograde signaling molecules[9], as a potential bridge between the oxytocin receptors on postsynaptic nucleus accumbens cells and presynaptic glutamatergic release. In paired females, blocking the endocannabinoid system using an antagonist (AM4113) prevents the oxytocin-induced potentiation seen in the nucleus accumbens (Figure 2A,B). Furthermore, the use of this endocannabinoid antagonist also increases the occurrence of 'rejection-like' behaviors in paired females towards their mated partners (Figure 2C,D). Thus, blocking the endocannabinoid system abrogates the oxytocin-mediated potentiation of the nucleus accumbens and increases partner rejection in paired females. Taken together, the

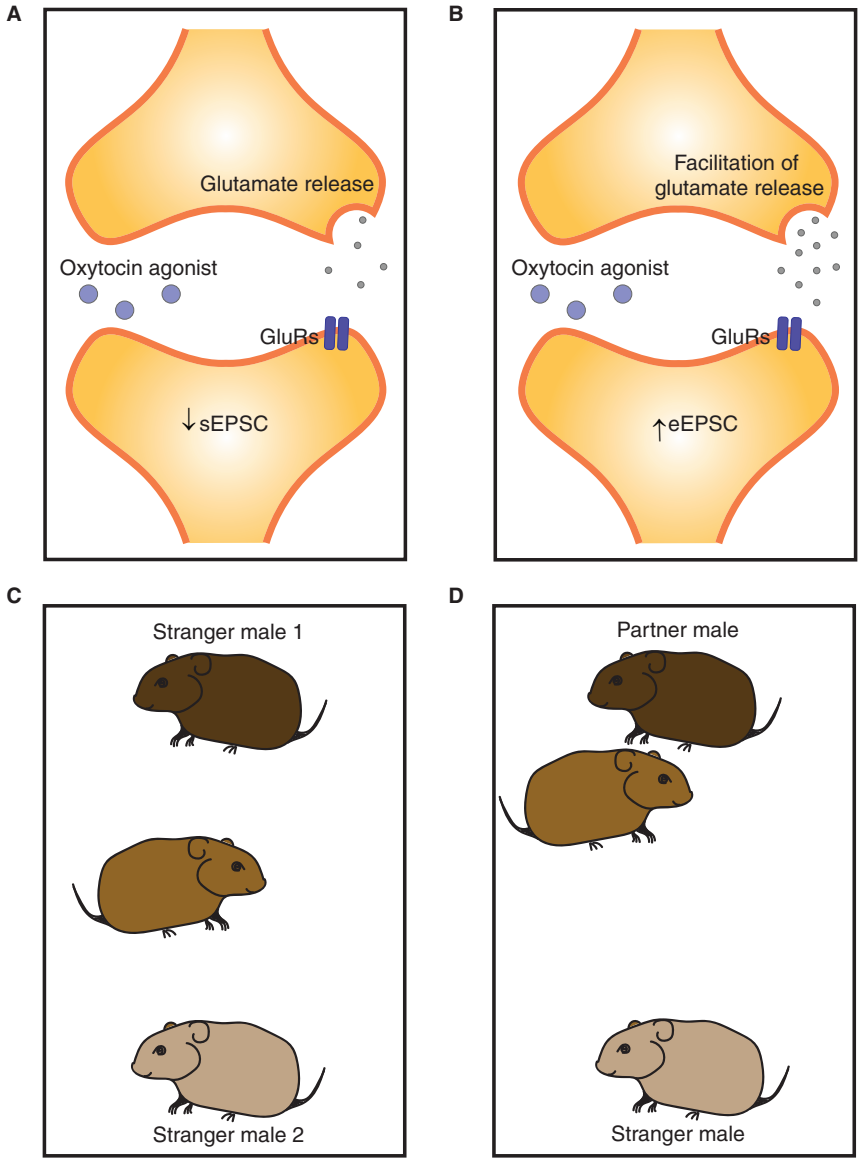

Figure 1. Oxytocin-mediated potentiation in the nucleus accumbens and partner preference.
Compared with virgin females (A), paired females (B) exhibited altered spontaneous (sEPSC) and evoked excitatory postsynaptic currents (eEPSC) in response to application of an oxytocin agonist. Virgin females show no preference for males (C) while paired females show a preference for partner males (D), and this preference is correlated to oxytocin-mediated potentiation (not shown). GluR, glutamatergic receptors (AMPA and NMDA).

oxytocinergic system, and its recruitment of the endocannabinoid system, is responsible for maintenance of pair bonds by affecting activity within the nucleus accumbens and by reducing partner rejection behaviors in female animals.

Overall, this paper provides novel information on the role of the oxytocinergic system in social relationships. First, the effect of oxytocin on an individual depends on their social experience, and the role of oxytocin evolves as a relationship changes. This adds another layer to the complexity of action of oxytocin and perhaps accounts for the inter-individual variability often observed in oxytocin studies. Additionally, the effect of oxytocin on the activity within the nucleus accumbens may be time-dependent. Indeed, the

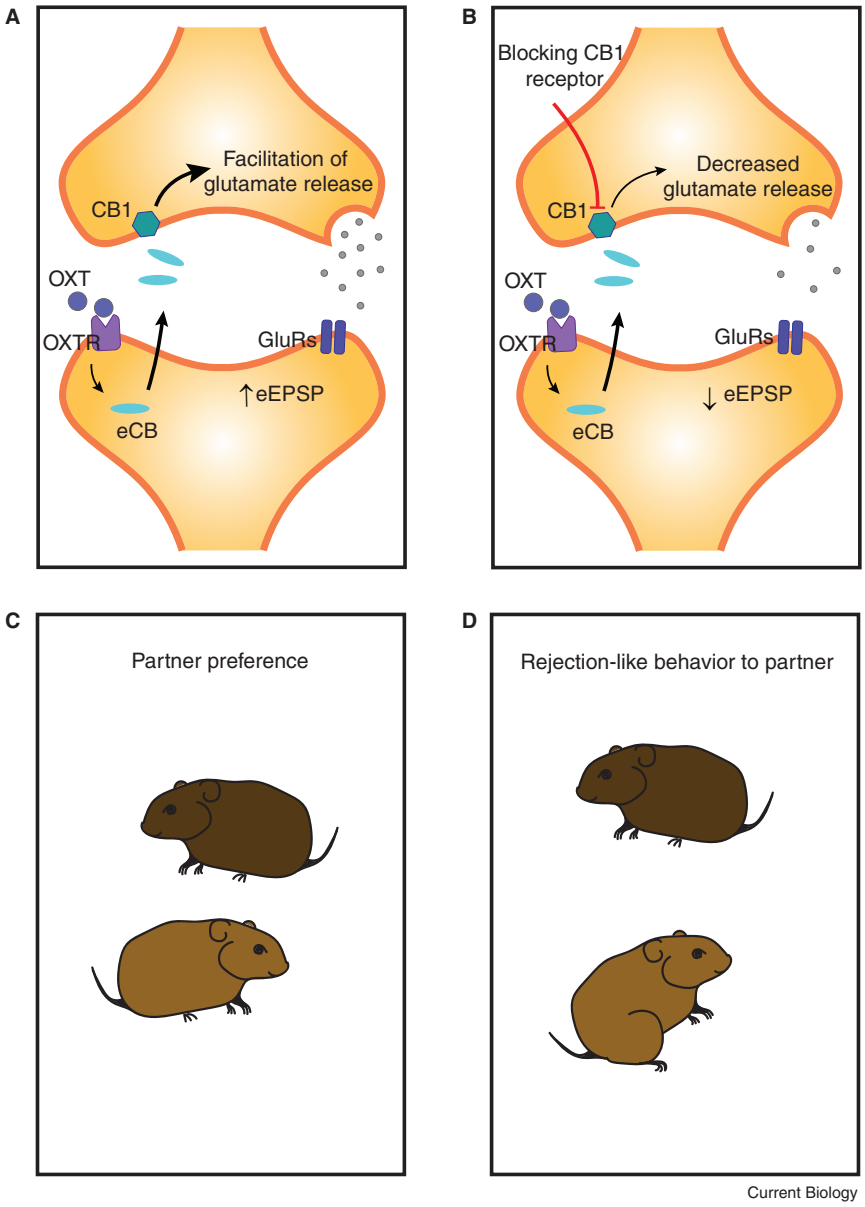

Figure 2. Role of the endocannabinoid system in oxytocin-mediated potentiation on the nucleus accumbens and on maintenance of pair bond.
(A) Postsynaptic oxytocin receptors use a retrograde endocannabinoid signaling pathway to alter potentiation (excitatory postsynaptic potential, eEPSP) within the nucleus accumbens. (B) Use of an endocannabinoid receptor antagonist blocks the oxytocin-mediated potentiation. (C,D) Blocking the endocannabinoid receptor also increases rejection-like behavior towards partner animals. CB1, cannabinoid 1 receptor; eCB, endocannabinoids; GluR, glutamatergic receptors (AMPA and NMDA); OXT, oxytocin; OXTR, oxytocin receptor.

current work suggests that the effect of the oxytocin agonist on glutamatergic transmission is dependent on both social experience and on time. Next, the endocannabinoid system likely helps mediate the effects of oxytocin by serving as a bridge between the postsynaptic oxytocin receptors in the nucleus accumbens and presynaptic glutamatergic release. Furthermore, blocking the endocannabinoid system affects the maintenance of the social relationship. Of course, this new avenue of oxytocin action requires further study and characterization.

Oxytocin and its homologs are present in numerous taxa, where they appear to be involved in the formation of social and reproductive relationships. For instance, in the nematode worm (*Caenorhabditis elegans*), it appears that an oxytocin homolog is responsible for promoting mating behavior[10]. Similarly, it is known to promote affiliative behaviors in rodents[4], non-human primates[11,12], and humans[13]. The endocannabinoid system is also know to influence social behavior across several species, though its recruitment appears to be highly context-dependent[14]. Indeed, the current work supports the context-dependent nature of this neuromodulatory pathway[5]. Given the prevalence of the oxytocinergic and endocannabinoid systems, it would be interesting to explore whether the mechanistic coupling between the two neuromodulator systems illuminated in the current study is valid across these disparate species. This would be particularly interesting considering the distribution of oxytocin receptors across various mammalian species. Humans share a high expression of oxytocin receptor in the nucleus accumbens with the monogamous prairie vole, while mice and rhesus macaques do not show this pattern of distribution[15]. How would this affect the recruitment of the endocannabinoid system in these species? This is an important question to answer, especially given the use of rodents and rhesus macaques as model species to study social behavior.

There is also evidence that the oxytocinergic system acts in concert with numerous other neuromodulatory systems. In voles, it is known that the dopaminergic system interacts with the oxytocinergic system to facilitate pair bond formation[16]. We also know that the oxytocinergic system is known to act in concert with the opioid system. For instance, when rhesus macaques are co-administered oxytocin and a mu-opioid receptor antagonist (naloxone), they show a sustained increase in attention towards the face and eyes of their social partners resembling a combinatorial boost in social attention[17]. It is likely that this interaction between the oxytocinergic and the opioid systems is a synergistic one with naloxone enhancing the release of oxytocin by blocking the mu-opioid receptors[18]. Further, there is evidence to support an interaction between the oxytocinergic and serotonergic systems[18] in modulating social behavior.

It would be fascinating to explore how these different neuromodulatory systems interact with the oxytocinergic system to help form and maintain social bonds and guide social interactions.

Oxytocin has long been considered as being of tremendous translational value in treating or managing human neuropsychiatric disorders. However, clinical trials in humans have yielded mixed results[19]. The results presented by Borie and colleagues further highlight the need for careful characterization of the oxytocinergic system with respect to other neuromodulatory systems. The effects of oxytocin are dependent on past social experience and all the neurobiological changes that come with it. This itself may in part explain the variable results observed with oxytocin administration in humans. Furthermore, past social experience also influences the secondary neuromodulatory pathways that oxytocin may recruit. Thus, it may be beneficial for researchers to target supplementary neuromodulatory systems, along with the oxytocinergic system, in trying to modulate social behaviors downstream of oxytocin.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Holt-Lunstad, J., Smith, T.B., and Layton, J.B. (2010). Social relationships and mortality risk: A meta-analytic review. PLoS Med. *7*, e1000316.
2. Chen, P., and Hong, W. (2018). Neural circuit mechanisms of social behavior. Neuron *98*, 16–30.
3. Gangopadhyay, P., Chawla, M., Dal Monte, O., and Chang, S.W.C. (2021). Prefrontal-amygdala circuits in social decision-making. Nat. Neurosci. *24*, 5–18.
4. Froemke, R.C., and Young, L.J. (2021). Oxytocin, neural plasticity, and social behavior. Annu. Rev. Neurosci. *44*, 359–381.
5. Borie, A.M., Agezo, S., Lunsford, P., Boender, A.J., Guo, J.-D., Zhu, H., Berman, G.J., Young, L.J., and Liu, R.C. (2022). Social experience alters oxytocinergic modulation in the nucleus accumbens of female prairie voles. Curr. Biol. *32*, 1026–1037.
6. Insel, T.R., and Shapiro, L.E. (1992). Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc. Natl. Acad. Sci. USA *89*, 5981–5985.
7. Keebaugh, A.C., and Young, L.J. (2011). Increasing oxytocin receptor expression in the nucleus accumbens of pre-pubertal female prairie voles enhances alloparental responsiveness and partner preference formation as adults. Horm. Behav. *60*, 498–504.
8. Keebaugh, A.C., Barrett, C.E., LaPrairie, J.L., Jenkins, J.J., and Young, L.J. (2015). RNAi knockdown of oxytocin receptor in the nucleus accumbens inhibits social attachment and parental care in monogamous female prairie voles. Soc. Neurosci. *10*, 561–570.
9. Castillo, P.E., Younts, T.J., Chávez, A.E., and Hashimotodani, Y. (2012). Endocannabinoid signaling and synaptic function. Neuron *76*, 70–81.
10. Garrison, J.L., Macosko, E.Z., Bernstein, S., Pokala, N., Albrecht, D.R., and Bargmann, C.I. (2012). Oxytocin/vasopressin-related peptides have an ancient role in reproductive behavior. Science *338*, 540–543.
11. Crockford, C., Wittig, R.M., Langergraber, K., Ziegler, T.E., Zuberbühler, K., and Deschner, T. (2013). Urinary oxytocin and social bonding in related and unrelated wild chimpanzees. Proc. R. Soc. B *280*, 20122765.
12. Chang, S.W.C., and Platt, M.L. (2014). Oxytocin and social cognition in rhesus macaques: implications for understanding and treating human psychopathology. Brain Res. *1580*, 57–68.
13. Feldman, R. (2012). Oxytocin and social affiliation in humans. Horm. Behav. *61*, 380–391.
14. Wei, D., Allsop, S., Tye, K., and Piomelli, D. (2017). Endocannabinoid signaling in the control of social behavior. Trends Neurosci. *40*, 385–396.
15. Freeman, S.M., and Young, L.J. (2016). Comparative perspectives on oxytocin and vasopressin receptor research in rodents and primates: Translational implications. J. Neuroendocrinol. *28*, https://doi.org/10.1111/jne.12382.
16. Walum, H., and Young, L.J. (2018). The neural mechanisms and circuitry of the pair bond. Nat. Rev. Neurosci. *19*, 643–654.
17. Dal Monte, O., Piva, M., Anderson, K.M., Tringides, M., Holmes, A.J., and Chang, S.W.C. (2017). Oxytocin under opioid antagonism leads to supralinear enhancement of social attention. Proc. Natl. Acad. Sci. USA *114*, 5247–5252.
18. Fan, S., Weinberg-Wolf, H., Piva, M., Dal Monte, O., and Chang, S.W.C. (2020). Combinatorial oxytocin neuropharmacology in social cognition. Trends Cogn. Sci. *24*, 8–12.
19. Bakermans-Kranenburg, M.J., and van IJzendoorn, M.H. (2013). Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. Transl. Psychiatry *3*, e258.

Mitosis: Kinetochores determined against random search-and-capture

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The mechanism of chromosome biorientation during mitotic spindle assembly remains a century-old mystery. In contrast to the stochastic models that have dominated the field for decades, a new study now proposes that chromosome biorientation is instead deterministic and driven by microtubule self-organization at kinetochores.

The famous quote by George Box that "*all models are wrong, but some are useful*" never made more sense than it does today in the context of mitosis research. Since the discovery of microtubule dynamic instability, the paradigm for mitotic spindle assembly has been drawn from the elegant 'search-and-capture' hypothesis[1],