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Blueprints for Bonding? New Genetic Tools to Parse the Neural Basis of Pair Bonding in Prairie Voles

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When Laura Ingalls Wilder penned her children's book, "Little House on the Prairie", she probably had no idea how close she came to describing the social lives of prairie voles, small monogamous rodents that live in the middle of North America. Unlike laboratory mice and rats, who mate-and-leave, prairie voles form long term pair bonds, share a burrow, and exhibit robust biparental care. It is because of prairie voles that scientists now know that oxytocin, an ancient hormone implicated in reproduction, is also vital for diverse social behaviors and pair bond formation, a discovery that subsequently inspired studies examining the role of oxytocin in complex human social behaviors and as a therapeutic target for numerous neuropsychiatric disorders characterized by deficits in social behavior.

However, one of the challenges that has consistently plagued research on oxytocin systems in prairie voles (and many other species) has been a lack of the genetic tools necessary to label and manipulate specific, oxytocin-sensitive cell populations within the brain. The development of CRISPR-Cas9 and other genome editing approaches is reshaping the landscape of neuroscience research, and knock-in prairie voles become the latest to be added to the list of species who have gained genetic tractability through these approaches. Yet despite the promise and utility of these systems, their implementation in certain species remains challenging.

Here, a report in this issue of *Neuroscience* details generation of the first knock-in prairie vole that directly addresses this deficit. Specifically, Horie and colleagues inserted a transgene encoding Cre-recombinase, a molecular tool that can be used to induce or knock out gene expression, downstream of the prairie vole oxytocin receptor gene. Even for prairie voles, it remains unclear how well these techniques will scale. The authors report a single transgene-positive animal out of two live births from 55 injected embryos. Optimistically, this may reflect an extremely promising rate of 50% correct targeting; alternatively, an immensely lucky outcome. Either way, it's an important step in the right direction and a hugely important advance for prairie vole research. Moreover, such an advance sets the stage for new levels of comparative approaches in other species with intriguing patterns of development, physiology, or behavior, previously not amenable to the molecular genetic analyses standard only in common model organisms.

Beginning in the nucleus accumbens, one of the major sites of species-specific expression of this receptor that correlates with social attachment behaviors, Horie and colleagues show that expression of Cre-recombinase in these animals is limited to cells that express oxytocin receptor. However, transgene insertion comes at a price; when two copies of the transgene are present, the resulting prairie voles have almost no oxytocin receptor expression.

Horie and colleagues then demonstrate the utility of their transgenic voles by delineating the oxytocin-sensitive neuronal populations that innervate the prairie vole nucleus accumbens. Using a series of molecular tricks, they express green fluorescent protein selectively in oxytocin-receptor-expressing neurons that innervate the nucleus accumbens. While this approach has some limitations – there is no labeling reported for neurons in the PVN or VTA, consistent with previous reports that the tools implemented are not taken up or transported in neuropeptidergic neurons (Tervo et al., 2016) – it provides a powerful entrypoint for future efforts to manipulate prairie vole neural circuits with an unprecedented level of precision.

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