NEUROSCIENCE

Chemogenetic manipulation of neurons

The family of designer receptors now includes an orthogonally activated member for multiplexed chemogenetic control of neural activity.

Chemogenetics is an alternative to light-based (optogenetic) manipulation of neural activity, especially for applications that require long-term and minimally invasive control. For example, designer receptors exclusively activated by designer drugs (DREADDs) are available to modulate a variety of G-protein pathways in response to small-molecule ligands. They are useful chemogenetic tools but are typically activated only by clozapine-*N*-oxide (CNO). Michael Krashes, Bryan Roth and their teams at the US National Institutes of Health and the University of North Carolina have developed an orthogonal DREADD that is activated by the alternative ligand salvinorin B (SALB), allowing multiplexed control of neurons or other cells.

The researchers used the κ-opioid receptor (KOR) as a starting point for their rational design approach. For the designer drug they chose SALB (a metabolite of the KOR-specific agonist salvinorin A) that does not activate wild-type KOR *in vivo*. The researchers modified KOR with rationally chosen mutations in such a way that it did not respond to any peptides tested, with the exception of SALB. When they expressed the new receptor, named KORD, in a variety of neurons, the researchers consistently observed robust hyperpolarization in the presence of SALB, as expected for a receptor linked to an inhibitory G-protein pathway.

In addition to hyperpolarizing neurons in slice preparations, KORD also inactivates neurons *in vivo* upon SALB application. For example, mice subject to KORD-mediated silencing of GABAergic neurons in the ventral tegmental area (VTA) ran more than control mice did, and KORD activation in a class of neurons in the paraventricular hypothalamus induced mice to eat more. Importantly, because KORD is orthogonally activated, it can be combined with CNO-activated DREADDs to manipulate neurons bidirectionally. The researchers demonstrated this by expressing both KORD and the CNO-sensitive DREADD hM3Dq in the same neurons in the VTA. Depending on which designer drug was applied, the mice ran more or less than control animals.

The addition of KORD to the chemogenetic toolkit provides greater versatility for interrogating neural circuits. Moreover, it may be possible to combine chemogenetic and optogenetic approaches for more flexibility in the spatiotemporal control of neuronal activity.

Nina Vogt

RESEARCH PAPERS

Vardy, E. *et al.* A new DREADD facilitates the multiplexed chemogenetic interrogation of behavior. *Neuron* **86**, 936–946 (2015).