Using new 'chemogenetic' technique, scientists turn neurons 'on' and 'off'

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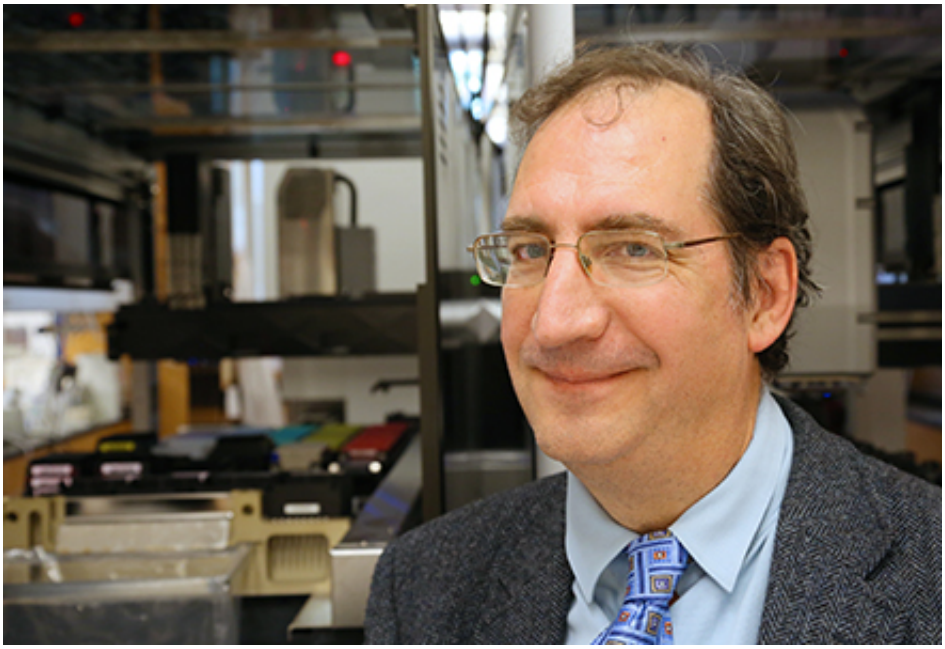

Bryan L. Roth, M.D., Ph.D., University of North Carolina Health Care. Credit: Max Englund, UNC School of Medicine

Researchers at the University of North Carolina School of Medicine and the National Institutes of Health (NIH) have perfected a noninvasive "chemogenetic" technique that allows them to switch off a specific behavior in mice - such as voracious eating - and then switch it back on. The method works by targeting two different cell surface receptors of neurons that are responsible for triggering the specific chemical signals that control brain function and complex behaviors.

When this complex signaling system goes awry, the results can lead to a plethora of diseases, including schizophrenia, depression, Alzheimer's Disease, Parkinson's Disease, eating disorders, and epilepsy. Cell surface receptors also play roles in cancers, diabetes, digestive conditions, and other diseases. This new technique could be modified to study them, as well.

This is the first technology to stem from the initial set of NIH BRAIN Initiative grants to create new cutting-edge research tools to improve our understanding of the brain.

"This new chemogenetic tool will show us how brain circuits can be more effectively targeted to treat human disease, " said Bryan L. Roth, MD, PhD, the Michael Hooker Distinguished Professor of Protein Therapeutics and Translational Proteomics at the UNC School of Medicine. "The problem facing medical science is that although most approved drugs target these brain receptors, it remains unclear how to selectively modulate specific kinds of receptors to effectively treat disease."

Roth addressed this problem by inventing a technology he dubbed "DREADDs" - Designer Receptor Exclusively Activated by a Designer Drug.

The first-generation DREADD technology was developed in 2007.

Essentially, in lab experiments, Roth's team altered the chemical structure of G protein-coupled receptors so that the receptors expressed synthetic proteins when reintroduced into a mouse. This way, the mutated receptor could only be activated or inhibited by a specific synthesized drug-like compound. The receptor became like a lock; the synthetic drug became the only key that fit the lock. Depending on what Roth's team wanted to study, they could lock or unlock the specific brain

circuits and behaviors associated with that one receptor.

This DREADD technology - also known as chemogenetics - is now used by hundreds of labs worldwide. It helped revolutionize our understanding of how brain circuits control normal and abnormal behavior, emotions, perception, pain sensation, memory, and many other processes. DREADDs have been used to improve the function of insulin-producing cells in mice as a way of treating diabetes. DREADD technology has also helped scientists treat epileptic seizures in mice.

But scientists could use this first DREADD to only manipulate a single receptor in one direction - excite the receptor or inhibit it.

Last year, Roth and UNC colleagues Thomas Kash, PhD, and Jian Jin, PhD, received a $2.84-million NIH BRAIN Initiative grant to develop the next generation of DREADDs.

Today in the journal *Neuron*, UNC and NIH researchers revealed the first fruit of that grant - a new chemogenetic technology they have named KORD (k-opioid receptor DREADD). This new tool, co-invented by Roth and Eyal Vardy, PhD, a former UNC postdoctoral fellow, can target two different kinds of receptors on the same neuron sequentially. This allowed them to study the function of two kinds of receptors as they relate to each other.

In the *Neuron* paper, Roth's team explain how they modified the receptors in the lab, packaged the receptors in an viral vector, and injected them into mice so that the synthetic receptors were expressed only in certain kinds of neurons in specific parts of the brain.

Then they administered the synthetic drug-like compound to demonstrate how neuronal signaling could be manipulated to turn the same neurons 'on' and 'off' and thereby turning 'on' and 'off' specific

behaviors in mice.

In one type of experiment, the NIH lab of Michael Krashes, PhD, was able to turn 'on' and 'off' voracious feeding behavior in mice. In another type of experiment, UNC researchers were able to turn 'on' and 'off' behaviors similar to those induced by drugs such as cocaine and amphetamines.

Elliot Robinson, an MD/PhD student at UNC and co-first author of the *Neuron* paper, said, "These experiments have validated KORD as a new tool for researchers interested in controlling the function of specific populations of cells while also highlighting their therapeutic potential."

Reid Olsen, UNC graduate student and paper co-author, said, "Using genetically modified mice, we can now tease apart the interactions between seemingly disparate neuronal systems in a logical fashion."

Roth added, "We are now sharing KORD and other DREADD technology freely with other scientists, and it is likely that new uses for these technologies will appear in the near future."

More information: Vardy E, Robinson JE, Li C, Olsen RHJ, DiBerto JF, Giguere PM, Sassano FM, Huang X-P, Zhu H, Urban DJ, White KL, Rittiner JE, Crowley NA, Pleil KE, Mazzone CM Mosier PD, Song J, Kash TL, Malanga CJ, Krashes MJ, Roth BL. A new DREADD facilitates the multiplexed chemogenetic interrogation of behavior. *Neuron*, April 30, 2015.

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