Neuroscience tool's structure may lead to next gen versions

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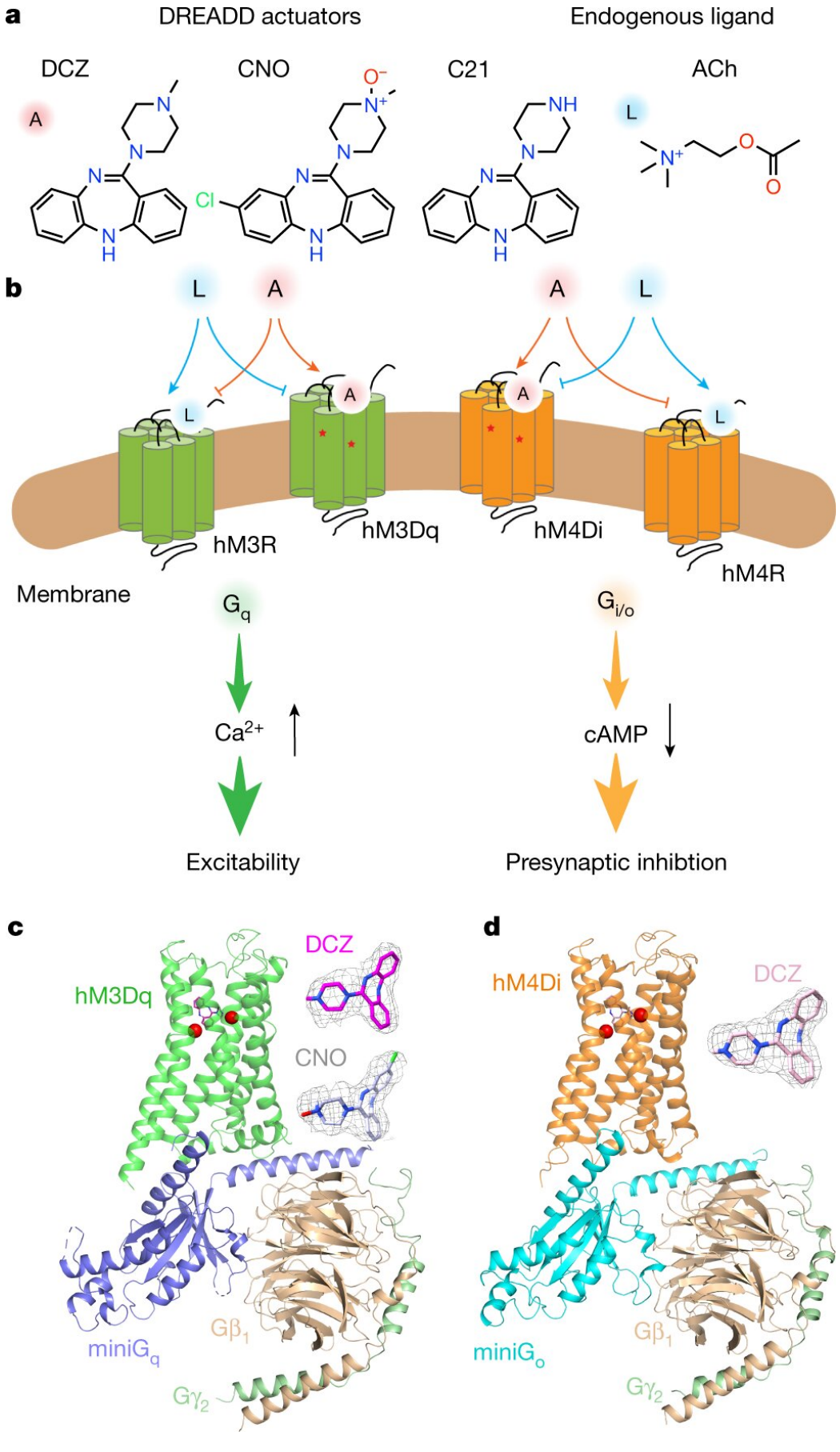
a
DREADD actuators
Endogenous ligand
DCZ
CNO
C21
ACh
A
L
b
hM3R
hM3Dq
hM4Di
hM4R
Membrane
G_q
$G_{i/o}$
Ca^{2+}
cAMP
Excitability
Presynaptic inhibtion
c
hM3Dq
DCZ
CNO
$miniG_q$
$G\beta_1$
$G\gamma_2$
d
hM4Di
DCZ
$miniG_o$
$G\beta_1$
$G\gamma_2$

Overall structures of the DREADD complexes. Credit: *Nature* (2022). DOI: 10.1038/s41586-022-05489-0

In order to more fully understand how diseases arise in the brain, scientists must unravel the intricate way neurons relay messages (either chemical or electrical) along a complex web of nerve cells. One way is by using a tool called DREADDs, which stands for **D**esigner **R**eceptors **A**ctivated by **D**esigner **D**rugs.

When introduced to a nerve cell or neuron, DREADDs acts like a specialized lock that only works when a key—in the form of a synthetic designer drug—fits into that lock. DREADDs can enable researchers to turn specific cell functions on or off to examine groups of neurons in circuits more precisely. (see Animations)

Now, a University of Maryland School of Medicine researcher and his colleagues at the University of North Carolina Chapel Hill (UNC) have unveiled the structure of these DREADDs that will pave the way for creating the next generation of these tools. This step ultimately will bring them closer to an elusive goal—understanding the underpinnings of brain disorders, such as schizophrenia, substance abuse, epilepsy, and Alzheimer's, in order to develop more effective drugs to treat them.

The research team published their findings in a recent issue of *Nature*.

"These findings provide atomic clarity into the nature of DREADD receptors bound to their drugs, resulting from the culmination of all these technologies converging at the right place and right time," said study author Jonathan Fay, Ph.D., Assistant Professor of Biochemistry

and Molecular Biology at UMSOM. "This knowledge will allow this tool to be further refined and optimized. We were previously limited in how to upgrade their designs because we didn't fully understand how they worked at the structural level."

Hundreds of labs around the world now use the DREADD tool, which was developed at UNC. Scientists there designed these receptor proteins to react only to uniquely designed drugs that are pharmacologically inert because they only bind to the DREADD protein receptor.

For this new study, researchers used a newer imaging technology, known as cryogenic electron microscopy, to determine the molecular structure of DREADD receptors with the drugs. This process flash-freezes the DREADDs in a way that does not form traditional ice crystals, but instead creates a sort of slurry that allows some movement in the molecules. This technique allowed researchers to determine the DREADD's structure when other older molecular imaging methods failed. The researchers observed inhibitory (turning off cell functions) or stimulatory (turning on cell functions) DREADD receptors bound to each of two different designer drugs.

The researchers also compared the structure of the natural brain receptor from which DREADDs originated to see how it differed from DREADDs. The original brain receptor, found in the cell membrane of neurons, traditionally binds to a molecule involved in learning and memory. By changing two of the natural receptor's building blocks, the engineered DREADD receptor binds better to its own laboratory-designed drugs rather than to the original memory molecule—a process they visualized through their experiments.

"With this imaging technique, we could see that the genetic changes in the DREADDs opened up the space where the memory molecule normally binds, allowing the new designer drugs to slip in. We could see

that shape of the space changed as well, contributing to why the new drugs fit better," said Dr. Fay.

The class of receptors from which DREADDs originated are often the intended targets of many therapeutics. However, various drugs bind to several kinds of receptors or activate others in unintended ways. The result might be a beneficial effect, but also can result in side effects.

"Because of the precise way in which these designer drugs in DREADDs bind so specifically, it is likely possible that researchers will one day eventually develop targeted therapies for many of these other similar receptors without the cross-reactivity and unpleasant side effects," said UMSOM Dean Mark T. Gladwin, MD, Vice President for Medical Affairs, University of Maryland, Baltimore, and the John Z. and Akiko K. Bowers Distinguished Professor.

Although the microscopy-related part of this study occurred at UNC, UMSOM also has high-tech structural biology capabilities in their Center for Biomolecular Therapeutics (CBT), where researchers determine the structures of the human body's proteins to better develop new drugs to treat a variety of diseases. Dr. Fay plans to use CBT's facilities to analyze the structure of other brain receptors, as well as to continue his collaboration with UNC on potential DREADD 2.0 versions.

A major focus of UMSOM's research, as evidenced by the launch of the University of Maryland-Medicine Institute for Neuroscience Discovery (UM-MIND) in late 2022 includes neuroscience and brain-related diseases. Dr. Fay's work directly contributes towards these institutional priorities.

More information: Shicheng Zhang et al, Molecular basis for selective activation of DREADD-based chemogenetics, *Nature* (2022).

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