Researchers "smell" new receptors that could underlie the many actions of the anesthetic drug ketamine

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Penn Medicine researchers are continuing their work in trying to understand the mechanisms through which anesthetics work to elicit the response that puts millions of Americans to sleep for surgeries each day. Their most recent study looked at ketamine, an anesthetic discovered in the 1960s and more recently prescribed as an anti-depressant at low doses. Through collaboration with the University of Pennsylvania's department of Chemistry and scientists at the Duke University Medical Center, researchers at Penn's Perelman School of Medicine have identified an entirely new class of receptors that ketamine binds in the body, which may underlie its diverse actions. The work is published in this week's issue of *Science Signaling*.

Ketamine is believed to act through glutamate receptors to produce anesthesia, but this is unlikely to explain the anti-depressant effect; most antidepressants target G-protein coupled receptors (GCPRs), the largest class of druggable receptors, located in the body's central nervous system (CNS). To explore the GCPR class of receptors, the investigators screened proteins present in the mouse nasal epithelium, olfactory receptors (ORs), which typically respond very selectively to compounds in the air, giving rise to smell. It turns out that these ORs are also present throughout the nervous system. ORs make up the largest group of GCPRs, yet they are unexplored as transducing components of general anesthesia or of antidepressants.

"Our hope is that we can visualize the precise molecular interactions between ketamine and ORs, and in turn, learn how this old drug interacts with these and other GCPRs throughout the central nervous system," says the study's senior author, Roderic Eckenhoff, MD, the Austin Lamont Professor of Anesthesiology and Critical Care at Penn.

Eckenhoff and a team at Duke University began their study by screening ORs of mice and found that ketamine activated only two types out of more than several hundred, known as MOR136 and MOR139. They then used computational modeling and simulation approaches with Jeffery Saven, PhD, professor of Chemistry at Penn to generate structural models of these ORs and to understand exactly how they recognize ketamine. Several amino acid residues were identified as critical determinants. The team found that by mutating these amino acids, they could turn ketamine responsiveness both on and off.

They also tested these conclusions in mice by stimulating the olfactory epithelium via intranasal application of ketamine and showed that olfactory sensory neurons that expressed these unique ORs responded to ketamine, suggesting that ORs may truly serve as functional targets for ketamine.

"Here we provide evidence that ketamine has a highly specific interaction with the ORs, indicating that at least some of ketamine's actions may result from these or other GCPRs in the central nervous system," says Eckenhoff, noting that "our rigorous combination of simulation and experiment indicates that we can design receptors to respond specifically to certain drugs, which gets us one step closer to doing the opposite and designing drugs to interact specifically with certain receptors."

More information: *Science Signaling*, stke.sciencemag.org/content/8/370/ra33.abstract

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