Newly discovered chemical reaction in eye may improve vision

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A light-sensing pigment found in everything from bacteria to vertebrates can be biochemically manipulated to reset itself, an important therapeutic advantage, according to new research out of Case Western Reserve University School of Medicine. In a study just released from the *Proceedings of the National Academy of Sciences*, researchers

successfully used a modified form of vitamin A, called locked retinal, to induce the recycling mechanism and engage proteins central to human vision. The targeted proteins include light-sensing rhodopsin, which belongs to a family of proteins—G protein-coupled receptors, or GPCRs—that sit in cell membranes and transmit external cellular cues into internal cell signaling pathways. The discovery opens a new therapeutic opportunity for modified retinals that help improve vision, and offers a major improvement over current therapeutics designed to perturb cell signaling in the eye.

"Our study demonstrates a complete transition from a one-way activation of a GPCR into a self-renewing, recycling activation mechanism by the mere addition of a cyclohexyl chemical group to the retinal. These findings exemplify the possibility of reprogramming GPCRs into self-renewing machines that can be controlled by external cues. This biochemically induced function will be helpful in treating people with vision impairment, and opens up several avenues for more efficient GPCR-based therapeutics," said Sahil Gulati, first author of the study and graduate student in the department of pharmacology at Case Western Reserve University School of Medicine. Krzysztof Palczewski PhD, professor and chair of the department, served as senior author for the study.

The discovery digs into the biochemistry of vision and why the chemical configuration of the retinal is critical for humans to perceive light. Humans see with the help of an extremely sensitive protein in the back of the eye called rhodopsin, which attaches to a retinal molecule to sense light. Light photons enter the eye and get absorbed by the retinal-rhodopsin complex, activating a cascade of downstream signals that constitute vision. Importantly, the retinal awaits light photons while maintaining a particular chemical configuration—11-cis retinal—and transforms into a second configuration—all-trans retinal—after it absorbs a light photon. But this transformation is a one-way ticket, and

requires an army of specialized proteins to convert all-trans-retinal back to 11-cis-retinal. Inherited mutations in any of these specialized proteins can cause retinal degenerative diseases. Researchers who want to treat such diseases must repair or bypass the mutated proteins to maintain this retinal conversion in humans.

"Our study shows how a chemical modification in the retinal can activate downstream visual signaling in a photocyclic manner. This chemical modification allows retinal to self-renew using thermal energy, and hence does not require any additional enzymes," Gulati said.

The researchers discovered the self-renewing mechanism in bovine rhodopsin, which is exceptionally similar to human rhodopsin. The researchers used purified proteins in their laboratory to show that their modified retinal binds to bovine rhodopsin and successfully activates specific human eye proteins in response to light, and when complete, it uses thermal energy to slowly return to its inactive form that can be repeatedly reactivated with light. The findings suggest that retinal molecules with the specific chemical structure could reversibly stimulate rhodopsin that drives human vision.

Said Gulati, "Although one-way reaction mechanisms of GPCRs enable them to function normally in the human body, they cannot renew their activator molecules, and hence are dependent on continuous administration of drug molecules to treat disease symptoms. Controlled cyclic activation of GPCRs makes them self-sustainable."

The newly discovered mechanism may enhance current approaches to treat retinal degenerative diseases and other nerve cell disorders. Researchers can biochemically tinker with the retinal and the retinal-bound rhodopsin molecules to improve their ability to turn on and off proteins in the eye. Said Gulati, "Our next steps will be to design a new class of modified retinals with faster thermal recovery, and to test their

efficiency as human therapeutic modalities."

More information: Sahil Gulati et al, Photocyclic behavior of rhodopsin induced by an atypical isomerization mechanism, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1617446114

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