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Scientists identify new molecules important for vision and brain function

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In a pair of related studies, scientists from the Florida campus of The Scripps Research Institute have identified several proteins that help regulate cells' response to light—and the development of night blindness, a rare disease that abolishes the ability to see in dim light.

In the new studies, published recently in the journals *Proceedings of the National Academy of Sciences* (*PNAS*) and *The Journal of Cell Biology,* Scripps Florida scientists were able to show that a family of proteins known as Regulator of G protein Signaling (RGS) proteins plays an essential role in vision in a dim-light environment.

"We were looking at the fundamental mechanisms that shape our light sensation," said Kirill Martemyanov, a Scripps Research associate professor who led the studies. "In the process, we discovered a pair of molecules that are indispensible for our vision and possibly play critical roles in the brain."

In the PNAS study, Martemyanov and his colleagues identified a pair of regulator proteins known as RGS7 and RGS11 that are present specifically in the main relay neurons of the retina called the ON-bipolar cells. "The ON-bipolar cells provide an essential link between the retinal light detectors—photoreceptors and the neurons that send visual information to the brain," explained Martemyanov. "Stimulation with light excites these neurons by opening the channel that is normally kept shut by the G proteins in the dark. RGS7 and RGS11 facilitate the G protein inactivation, thus promoting the opening of the channel and

allowing the ON-bipolar cells to transmit the light signal. It really takes a combined effort of two RGS proteins to help the light overcome the barrier for propagating the excitation that makes our dim vision possible."

In the Journal of Cell Biology study, Martemyanov and his colleagues unraveled another key aspect of the RGS7/RGS11 regulatory response—they identified a previously unknown pair of orphan G protein-coupled receptors (GPCRs) that interact with these RGS proteins and dictate their biological function.

GPCRs are a large family of more than 700 proteins, which sit in the cell membrane and sense various molecules outside the cell, including odors, hormones, neurotransmitters, and light. After binding these molecules, GPCRs trigger the appropriate response inside the cell. However, for many GPCRs the activating molecules have not yet been identified and these are called "orphan" receptors.

The Martemyanov group has found that two orphan GPCRs—GPR158 and GPR179—recruit RGS proteins and thus help serve as brakes for the conventional GPCR signaling rather than play an active signaling role.

In the case of retinal ON-bipolar cells, GPR179 is required for the correct localization of RGS7 and RGS11. Their mistargeting in animal models lacking GPR179 or human patients with mutations in the GPR179 gene may account for their night blindness, according to the new study. Intriguingly, in the brain GPR158 appears to play a similar role in localizing RGS proteins, but instead of contributing to vision, it helps RGS proteins regulate the □-opioid receptor, a GPCRs that mediates pleasurable and pain-killing effects of opioids.

"We are really in the very beginning of unraveling this new biology and

understanding the role of discovered orphan GPR158/179 in regulation of neurotransmitter signaling in the brain and retina," Martemyanov said. "The hope is that better understanding of these new molecules will lead to the design of better treatments for addictive disorders, pain, and blindness."

More information: The first study was published in the May 15, 2012 issue of the journal *Proceedings of the National Academy of Sciences*. The second study was published June 11, 2012 by *The Journal of Cell Biology*.
See www.pnas.org/content/109/20/7905.long
See jcb.rupress.org/content/197/6/711.abstract

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