Researchers develop curious snapshot of powerful retinal pigment and its partners

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Science fiction novelist and scholar Issac Asimov once said, "The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' but 'That's funny.' " This recently rang true for an international team of researchers when they observed something they did not expect.

In a Journal of Biological Chemistry "Paper of the Week," the Berlin-based team reports that it has uncovered surprising new details about a key protein-protein interaction in the retina that contributes to the exquisite sensitivity of vision. Additionally, they say, the proteins involved represent the best-studied model of how other senses and countless other physiological functions are controlled.

"Nearly a thousand different types of these proteins are present in the human body, and nearly half of pharmaceutical drugs are targeted to them," explains Martha E. Sommer, a postdoctoral researcher at the Institute for Medicinal Physics and Biophysics at Charité Medical School and the first author on the JBC paper.

The retina, which is located at the back of the eye, is considered an outgrowth of the brain and is, thus, a part of the central nervous system. Embedded in the retina's 150 million rod-shaped photoreceptor cells are purplish pigment molecules called rhodopsin. It is the rhodopsin protein that is activated by the first glimmer – or photon – of light. Upon activation, the purple molecule binds another protein, known as transducin, to set off a cascade of biochemical reactions that ultimately

results in vision.

"After this signaling event, rhodopsin must be shut off. This task is achieved by a third molecule called arrestin, which binds to light-activated rhodopsin and blocks further signaling," Sommer says. When rhodopsin is not properly shut off, overactive signaling can lead to a decrease in sensitivity to light and ultimately cell death. People who lack arrestin have a form of night blindness called Oguchi disease. "They are essentially blind in low light and can suffer retinal degeneration over time."

It is believed that the arrestin molecule silences rhodopsin's signaling by embracing it and elbowing out transducin.

"Since arrestin was first discovered more than 20 years ago, it was assumed that a single arrestin binds a single light-activated rhodopsin," Sommer says. "However, when the molecular structure of arrestin was solved using X-ray crystallography about 10 years ago, it was observed that arrestin is composed of two near-symmetrical parts – like an open clam shell."

The diameter of each side of the arrestin shell is about equal to that of one rhodopsin, she says, so some researchers wondered if a single arrestin might be able to bind to two rhodopsins.

It seemed like a simple enough question: To how many rhodopsins can a single arrestin bind? But, Sommer explains, little experimental work had been published about the topic, and the few studies that had been done seemed to support the one-arrestin-to-one-rhodopsin theory. That is, until now.

Using photoreceptor cells from cows, Sommer's team set out to shine a light on the rhodopsin-arrestin mystery once and for all. They exposed

the rhodopsin molecules to low light and to bright light and managed to count how many arrestin molecules bound with them. In the end, it took three to tango.

"Increasing the light intensity increases the percentage of rhodopsins that are activated. Although the number of arrestins that bound per activated rhodopsin appeared to change with the percentage of activated rhodopsins -- with one-to-one binding in very low light and one-to-two binding in very bright light -- we hypothesize that arrestin always interacts with two rhodopsin molecules," Sommer says. "In low light, arrestin interacts with one active rhodopsin and with one inactive rhodopsin; whereas, in bright light, arrestin interacts with two active rhodopsins."

It's just a matter of probability, Sommer says: In brighter light, arrestin interacts with two activated receptors simply because there are more of them around.

"Although there were two fairly clear-cut theories regarding how arrestin binds rhodopsin, what was totally unexpected is that both can occur," she says.

But, what does this mean for the other senses and physiological functions controlled by other rhodopsin-like proteins? Rhodopsin is the most-studied member of the large family of G-protein coupled receptors, or GPCRs, and many well-known drugs target GPCRs. For example, when morphine binds to a GPCR, it affects the release of neurotransmitters in the brain and thus reduces pain signals. Meanwhile, beta-blockers, which are used to treat cardiac conditions and hypertension, block the activation of GPCRs by standing in the way of natural activating molecules.

"Nearly all GPCRs are normally bound by arrestin, and arrestin can

greatly influence what happens to the GPCRs when they are acted on by drugs," says Sommer. "For example, many GPCR-targeted drugs become less effective with continued use. Part of this is because of arrestin. Arrestin binds to the activated GPCR and tells the cell to remove it from the cell surface. In other words, arrestin causes the cell to become less sensitive to the drug because it loses the receptors that normally catch the drug molecules."

By understanding how arrestin interacts with receptors like rhodopsin under healthy conditions, she says, researchers will be able to design better drugs that avoid such problems as desensitization.

More information: The resulting "Paper of the Week" appears in the March 4 print issue of the *Journal of Biological Chemistry*.

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