Engineering a photo-switch for nerve cells in the eye and brain

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(Medical Xpress)—Chemists and vision scientists at the University of Illinois at Chicago have designed a light-sensitive molecule that can stimulate a neural response in cells of the retina and brain—a possible first step to overcoming degenerative eye diseases like age-related macular degeneration, or to quieting epileptic seizures.

Their results are reported online in the journal *Nature Communications*.

Macular degeneration, the leading cause of vision loss in people over 50, is caused by loss of light-sensitive cells in the retina—the rods and cones.

"The rods and cones, which absorb light and initiate visual signals, are

the broken link in the chain, even though what we call the 'inner cells' of the retina, in many cases, are still potentially capable of function," says David Pepperberg, professor of ophthalmology and visual sciences in the UIC College of Medicine, the principal investigator on the study.

"Our approach is to bypass the lost rods and cones, by making the inner cells responsive to light."

Pepperberg and his colleagues are trying to develop light-sensitive molecules that—when injected into the eye—can find their way to inner retinal cells, attach themselves, and initiate the signal that is sent to the brain.

The researchers synthesized new compounds built upon the well-known anesthetic agent propofol, a small molecule that binds to a receptor-protein on nerve cells. The receptor is ordinarily activated by the neurotransmitter GABA, and when so activated it opens a channel in the membrane of the cell to initiate a signal that propagates to other nerve cells.

Chemists led by Karol Bruzik, professor of medicinal chemistry and pharmacognosy in the UIC College of Pharmacy, succeeded in adding-on a light-sensitive chemical component to the propofol molecule. When struck by light of different wavelengths, the molecule changes shape and functions as a light-triggered, on-off switch for these receptors.

The research team tested the new compound, code name MPC088, in three different types of cells: retinal ganglion cells, the nerve cells that send visual signals from the retina to the brain via the optic nerve; Purkinje neurons from the cerebellum; and non-nerve cells that were specially engineered to produce and install the GABA receptor in their membrane.

MPC088 binds to the receptor and makes it far more responsive to GABA. Light of appropriate wavelengths converts the MPC088 to an inactive form and back again, reducing and then restoring the high sensitivity to GABA, which opens the membrane channel to initiate the neural signal.

"Putting it all together, we have a compound that dramatically regulates, in light-dependent fashion, the GABA receptors of both an engineered receptor system and native receptors of retinal ganglion cells and brain neurons," Pepperberg said.

The experiments on the Purkinje neurons of the cerebellum, conducted in collaboration with neurobiologist Thomas Otis at the University of California at Los Angeles, "showed we were able to go beyond visual systems," Pepperberg said, and demonstrate that "photo-regulation may also have potential as a therapeutic for epilepsy, a class of diseases that involves abnormal excitatory activity in the brain."

Epileptic seizures begin in a defined region of the brain, and it may become possible to introduce a photo-switching compound and a very thin light-guide into this region, Pepperberg said.

"Because GABA receptors are typically inhibitory, introducing light of the appropriate wavelength into the region as the seizure begins and activating the GABA receptors could have the effect of turning off the seizure."

The researchers also created a molecular switch related to MPC088 that can permanently anchor a genetically engineered GABA receptor, demonstrating the possibility that a light-sensitive molecule could be introduced into the eye or brain to modify GABA receptors and act as a photo-switch.

"Our work opens up new avenues for not only the retinal application but also diseases of the central nervous system where a dysfunction or deficiency of GABA activity is a key problem," Pepperberg said.

Provided by University of Illinois at Chicago