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AAQ chemical makes blind mice see; compound holds promise for treating humans

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A team of University of California, Berkeley, scientists in collaboration with researchers at the University of Munich and University of Washington in Seattle has discovered a chemical that temporarily restores some vision to blind mice, and is working on an improved compound that may someday allow people with degenerative blindness to see again.

The approach could eventually help those with retinitis pigmentosa, a genetic disease that is the most common inherited form of blindness, as well as age-related macular degeneration, the most common cause of acquired blindness in the developed world. In both diseases, the light sensitive cells in the retina — the rods and cones — die, leaving the eye without functional photoreceptors.

The chemical, called AAQ, acts by making the remaining, normally "blind" cells in the retina sensitive to light, said lead researcher Richard Kramer, UC Berkeley professor of molecular and cell biology. AAQ is a photoswitch that binds to protein ion channels on the surface of retinal cells. When switched on by light, AAQ alters the flow of ions through the channels and activates these neurons much the way rods and cones are activated by light.

"This is similar to the way local anesthetics work: they embed themselves in ion channels and stick around for a long time, so that you

stay numb for a long time," Kramer said. "Our molecule is different in that it's light sensitive, so you can turn it on and off and turn on or off neural activity."

Because the chemical eventually wears off, it may offer a safer alternative to other experimental approaches for restoring sight, such as gene or stem cell therapies, which permanently change the retina. It is also less invasive than implanting light-sensitive chips in the eye.

"The advantage of this approach is that it is a simple chemical, which means that you can change the dosage, you can use it in combination with other therapies, or you can discontinue the therapy if you don't like the results. As improved chemicals become available, you could offer them to patients. You can't do that when you surgically implant a chip or after you genetically modify somebody," Kramer said.

"This is a major advance in the field of vision restoration," said co-author Dr. Russell Van Gelder, an ophthalmologist and chair of the Department of Ophthalmology at the University of Washington, Seattle.

Kramer, Van Gelder, chemist Dirk Trauner and their colleagues at UC Berkeley, the University of Washington, Seattle, and the University of Munich will publish their findings Thursday, July 26, in the journal *Neuron*.

The blind mice in the experiment had genetic mutations that made their rods and cones die within months of birth and inactivated other photopigments in the eye. After injecting very small amounts of AAQ into the eyes of the blind mice, Kramer and his colleagues confirmed that they had restored light sensitivity because the mice's pupils contracted in bright light, and the mice showed light avoidance, a typical rodent behavior impossible without the animals being able to see some light. Kramer is hoping to conduct more sophisticated vision tests in

rodents injected with the next generation of the compound.

"The photoswitch approach offers real hope to patients with retinal degeneration," Van Gelder said. "We still need to show that these compounds are safe and will work in people the way they work in mice, but these results demonstrate that this class of compound restores light sensitivity to retinas blind from genetic disease."

From optogenetics to implanted chips

The current technologies being evaluated for restoring sight to people whose rods and cones have died include injection of stem cells to regenerate the rods and cones; "optogenetics," that is, gene therapy to insert a photoreceptor gene into blind neurons to make them sensitive to light; and installation of electronic prosthetic devices, such as a small light-sensitive retinal chip with electrodes that stimulate blind neurons. Several dozen people already have retinal implants and have had rudimentary, low vision restored, Kramer said.

Eight years ago, Kramer, Trauner, a former UC Berkeley chemist now at the University of Munich, and their colleagues developed an optogenetic technique to chemically alter potassium ion channels in blind neurons so that a photoswitch could latch on. Potassium channels normally open to turn a cell off, but with the attached photoswitch, they were opened when hit by ultraviolet light and closed when hit by green light, thereby activating and deactivating the neurons.

Subsequently, Trauner synthesized AAQ (acrylamide-azobenzene-quaternary ammonium), a photoswitch that attaches to potassium channels without the need to genetically modify the channel. Tests of this compound are reported in the current Neuron paper.

New versions of AAQ now being tested are better, Kramer said. They

activate neurons for days rather than hours using blue-green light of moderate intensity, and these photoswitches naturally deactivate in darkness, so that a second color of light is not needed to switch them off.

"This is what we are really excited about," he said.

Provided by University of California - Berkeley

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