# Optogenetics Illuminates Brain Function

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CHICAGO—An emerging technique that allows scientists to use light-bearing fiberoptics to control select types of brain cells in living animals is helping to elucidate the role played by individual cell types in a pathological state and to identify which type of cell mediates the benefits of brain-targeted therapy.

Nobelist Francis Crick, the codiscoverer of DNA's structure, said the central challenge in neuroscience is the difficulty of controlling just 1 type of neuron at a time (Crick FHC. *Sci Am*. 1979; 241[3]:219-232). The new technique, called optogenetics, helps scientists overcome this challenge, said Karl Deisseroth, MD, PhD, associate professor of bioengineering and psychiatry at Stanford University in California, at the annual meeting of the Society for Neuroscience in Chicago in October.

Deisseroth explained that in the past, many of the tools used in neuroscience, such as electrodes, were not selective enough. He likened a scientist studying the nervous system with such crude tools to a conductor directing an orchestra with strings, brass, woodwinds, and percussion mixed together rather than segregated according to instrument type; when the conductor points his baton to a section and numerous instruments play simultaneously, the result is cacophony. In contrast, optogenetics "allows us to control the individual instruments, or the individual cell types, even though they are intermixed," he said.

## AN UNLIKELY SOURCE

The insights that made the method possible came from an unlikely source—basic research on algae and ancient forms of bacteria that revealed that these microbes produce proteins called opsins that function as light-sensitive ion channels or pumps. Fortuitously, the actions of some opsins translate into signals that can turn on or turn off neural cells, Deisseroth explained. For example, one opsin derived from algae allows sodium ions to enter a cell and activate the neuron, while another opsin allows chloride ions to enter the neuron and inhibit its action.

Raag Airan and Karl Deisseroth

**Blue laser light delivered deep into the brain of a mouse that has been genetically altered to produce light-sensitive proteins in select neurons can influence the animal's behavior.**

Through a series of experiments that at the time Deisseroth thought likely to fail, he and colleagues were able to demonstrate that select neurons in living animals could be induced to produce opsins via techniques similar to those used in gene therapy and that the activity of the opsin-producing cells could be controlled with light delivered through fiberoptic filaments into the brain (Wang H et al. *Proc Natl Acad Sci U S A*. 2007;104[19]:8143-8148).

"It was serendipitous that it all worked well," he said.

The scientists have since refined their techniques and the hardware used for the experiments and expanded the stable of opsins. After they deliver the opsin genes and a gene promoter or other piece of DNA specific to the targeted cell type (often via adeno-associated viral vectors), the researchers implant fiberoptic filaments in the brain of the animal to deliver the appropriate light to stimulate the opsins. This enables them to monitor the resulting activity while still allowing the animals to move freely. Deisseroth and colleagues also have been actively disseminating the tools they have developed, sending them to more than 500 laboratories around the world.

## NEW INSIGHTS

The technique is already yielding new insights. Deisseroth and colleagues recently used optogenetic techniques to systematically activate or deactivate neurons known to play a role in Parkinson disease in an animal model of the disorder in an effort to better understand which cell types might mediate the beneficial effects of deep brain stimulation (Gradinaru V et al. *Science*. 2009;324[5925]:354-359). They found that afferent neurons extending into the animal's subthalamic nucleus appear to play an important role but that the effect is frequency-dependent. Other groups presenting findings at the Society for Neuroscience meeting used optogenetics in their studies to identify potential targets for depression therapy, to help map brain circuits involved in addiction, and to identify cell types important for memory.

"This points to the value of basic research," Deisseroth said. "It would have been impossible to predict that studying algae would give us insights into Parkinson disease."