Horizons in Bioscience

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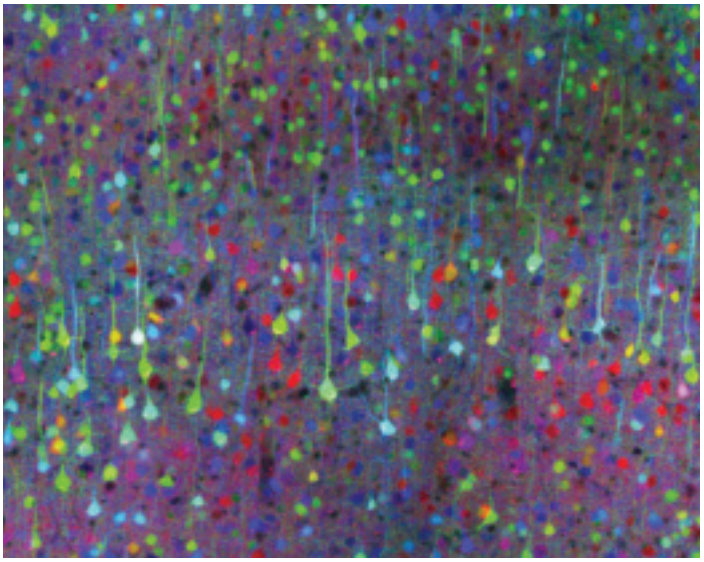
Optogenetics

Illuminating the Brain

Imagine being able to treat and control debilitating neurological disorders with a flash of light! The emerging field of optogenetics represents a promising new approach to the eventual understanding and treatment of a number of devastating neurological and psychiatric disorders. A word first coined in 2006, optogenetics uses light-responsive proteins, genetically introduced into the cells of living organisms, to control the behavior of highly specific cell populations. The technique helps scientists to overcome the phenomenal complexity of the brain by allowing the activity of specific types of cells, distributed among a network of many other cell types, to be precisely controlled in space and time.

The **opto-** of optogenetics describes the use of beams of light, or lasers, to control the desired biological process with precise timing and positioning. The **genetics** part of optogenetics describes the use of opsin genes as well as genes that target the process to specific cells.



Brain tissue of a mouse genetically modified to express differing combinations of fluorescent proteins across its neurons. Each sphere is an individual cell. *Image credit: Stéphane Fouquet and Jean Livet, Institut de la Vision, Paris.*

LIGHT BULB MOMENTS

The key components of optogenetics are proteins known as opsins. In the retina, opsins are joined with a chemical derivative of vitamin A to form molecules that change shape in the presence of light and trigger a cascade of cellular processes that ultimately allows us to see. Certain microorganisms possess a unique type of opsin, which, in response to particular wavelengths of light, moves ions across cell membranes (See sidebar: "Nature's Toolbox"). In neurons, the core cell type of the brain, spinal cord, and other components of the nervous system, the movement of ions across the cell membrane causes the cell to discharge, or "fire," an all or nothing electrical impulse. This nerve cell firing is the basis of all of the brain's activity and allows us to walk, think, and feel. Conversely, when nerve cells exhibit patterns of inappropriate activity or misfiring, serious consequences can occur. This type of malfunctioning of the brain's circuits is thought to be responsible for a number of psychiatric and neurological disorders. Optogenetics pioneers Karl Deisseroth, MD, PhD, and Edward Boyden, PhD, with the support of the National Institutes of Health (NIH) and the National Science Foundation, realized that they could control the movement of ions across the membrane of a neuron, in effect controlling the cells, by harnessing the power of these light-sensitive opsin proteins. They

NATURE'S TOOLBOX

The tools of optogenetics originated from halobacteria, which thrive in extremely salty environments such as the Dead Sea. They are among the most ancient life forms on Earth and about as unrelated to humans as it is possible to be. Researchers noticed that a purple protein on the surface of halobacteria had a structure similar to light-sensitive visual pigment proteins found in the human eye, known as opsins. They eventually discovered that, when excited by green light, the halobacterial protein moved ions, atoms or molecules that carry an electric charge, across the cell membrane.

In their native environments, halobacteria use opsins to produce energy. Other opsins, such as those found in algae, help them move toward light sources to perform photosynthesis. Optogenetics puts opsins to new uses in animal cells with revolutionary results.

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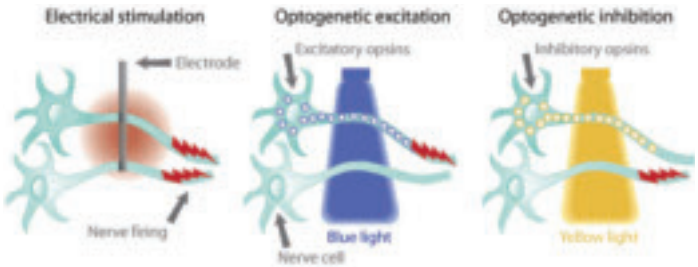
first introduced an opsin gene from single-celled algae into the DNA of neurons in a lab dish and with a flash of light caused the neurons to fire.

Some types of opsins cause nerves to fire. Other types silence nerve cells, preventing them from firing. When an activating opsin and a silencing opsin are expressed in the same neuron, each responding to a different color of light, researchers can turn neuronal activity on or off with the mere flick of a "light" switch.

Researchers realized the potential of optogenetics technology when they moved from the lab dish to experimental animals. In live worms, flies, fish, and mice, optogenetics can activate or inhibit highly select populations of neurons in real time. By turning specific neuron populations on and off and observing how animals respond, researchers can trace neural connections more accurately than ever before. As we gain a greater understanding of the brain's neural circuitry, investigators will be better equipped to develop more effective treatments for neurological and psychiatric disorders.



Schematic representation. Adapted from K. Deisseroth *Nature Methods* 8, 26-29 (2011) *by Corporate Press.*

IDENTIFYING THERAPEUTIC TARGETS

Parkinson's disease (PD), one of the top 15 causes of death in the United States, affects over 500,000 Americans and exerts an annual burden of $23 billion on the United States economy. PD sufferers, the bulk of whom are over the age 50, experience tremors and movement impairment that both decrease quality of life and increase the risk of fatal injury. The disease is caused by the degeneration of a small population of dopamine-producing cells, deep within the brain. At present, there is no cure for PD, but treatments include drugs that replace or mimic dopamine and the surgical implantation of electrodes to block abnormal neurological activity. The problem with both approaches is that they act more widely in the brain, not just within the affected region, potentially leading to very serious side effects. In contrast, optogenetics could precisely target only those brain cells that are within the downstream neural network or the actual malfunctioning neurons themselves. In mice, for example, treated with a chemical that mimics PD, scientists have been able to bypass the dysfunctional neurons and restore normal movement by activating neighboring cells near the surface of the brain. In addition, optogenetic studies in experimental animals are clarifying how current medicines work and thus enabling the improvement of existing treatment options for PD patients.

THINKING OUTSIDE THE BRAIN

As profound as the explosion in optogenetics has been in neurobiology, researchers are also focusing on applications in other areas. Incorporating opsins into signaling molecules can reveal the inner workings of all types of cells, not just neurons. Light can also be used to control the production of specific proteins. For example, researchers working with a mouse model for diabetes have been able to use optogenetics to trigger insulin production and a corresponding decrease in blood glucose levels. Over 25.8 million American's suffer from diabetes. One day, light may replace the needle as a means of controlling blood sugar levels for millions of diabetics.

LIGHTING NEW PATHS

Although optogenetic treatment of disease has not yet reached the clinic, researchers are already demonstrating the feasibility of the approach in nonhuman primates. With NIH support, labs across the nation are now using the technique to study anxiety, aggression, drug addiction, schizophrenia, obsessive-compulsive disorder, stroke, pain, and depression in animal models. Combined with efforts to identify the genes involved in these disorders, researchers could eventually develop targeted new therapies for humans. With the implantation of a light-emitting medical device, analogous to a pacemaker, and the genetic-based targeting of malfunctioning cells or their neural networks, a more effective treatment for schizophrenia may be around the corner. One day, it may be possible to restore sight to the blind by replacing non-functional opsins in the eye. One day, it may be possible to use light signaling at the contact interface to create two-way communication between the prosthesis and brain, and ultimately improve the control of artificial limbs.

"Optogenetics emerged from basic science investigations of how bacteria and plants photosynthesize and sense light. Without those curiosity-driven experiments, done without thoughts of application, these tools would not exist today."
***Edward S. Boyden, PhD,** Neuroscientist*

These are just a few of the possible medical breakthroughs scientists, engineers, and clinicians are working to develop. The overwhelming intricacy, sophistication and inaccessibility of the mammalian brain have long been a shroud, limiting our ability to peer inside the mind to understand and treat psychiatric and neurological disorders. Optogenetics, however, with its humble beginnings in the study of microbial photosensors, is illuminating the brain like never before.

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