Shutting down brain cells with light to study and treat disease

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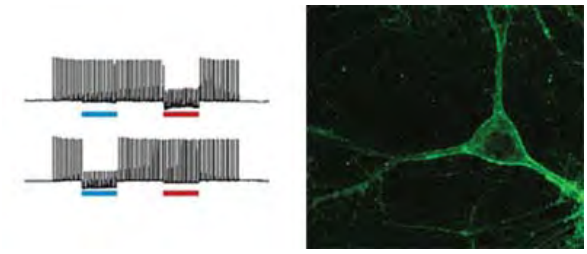
CAMBRIDGE, Mass. – By taking a lesson – and some genes – from nature, researchers at MIT have selectively shut down specific brain cells using different colors of light. One application of this new capability could be a better understanding of the abnormal brain activity linked to chronic pain, epilepsy, brain injury, Parkinson's disease and other disorders.

Another use could be clinical, said research team leader Edward S. Boyden. "These ultraprecise neuromodulation strategies might be useful for treating serious disorders very precisely. Last year, we published the first such preclinical study in the journal *Neuron* on nonhuman primates and are heading toward trials."

Boyden, an assistant professor of biological engineering, was part of a multigroup collaboration some years ago that took an algae gene called ChR2, inserted it into neurons using standard methods and created nerve cells that could be activated by pulses of blue light. A few years later, Boyden and his team used another gene to make neurons that could be shut down by yellow light.



This mouse neuron is expressing the Arch gene. As shown in the inset, the neuron shuts down in response to red light, not blue, while one expressing Mac behaves oppositely. Courtesy of Brian Y. Chow, Xue Han and Edward S. Boyden, MIT.

For research purposes, the ability to silence two groups of selected neurons independently of one another was important. However, the performance in terms of stopping neural activity of the yellow-sensitive reagent was not that good. So the group began searching through a list of 18 candidates for a better one. The screening process was laborious and took years to complete, Boyden said.

The researchers finally identified a gene, archaerhodopsin-3 (Arch), from *Halorubrum sodomense*, a photosynthetic bacterium found in very salty water. Arch has about 10 times the silencing power of the old reagent. The researchers reported in the Jan. 7, 2009, issue of *Nature* that it enabled a nearly 100 percent silencing of cortex neurons of an awake mouse when inserted into the neurons and illuminated with yellow light.

Arch also responded quickly to light, rising to near-complete nerve cell-silencing levels in less than 10 ms. Finally, it recovered quickly when the light was removed, falling to an unexcited level in about 20 ms.

In the same paper, the researchers revealed the complementary *Leptosphaeria maculans* (Mac), a blue-light-driven silencer. Boyden noted that both Arch and Mac work well with the older reagents to make up a new tool that can be used in neuroscience research. They plan to start applying them to the study of how cognitive and emotional processes take place, and they are looking into clinical benefits.

They also are investigating other advances. Some are technological, such as the use of inexpensive LEDs instead of costly xenon lamps for microscope light sources. Others are potential ways to speed up the search for additional brain cell-silencing and light-sensitive genes. Such an innovation could really pay off, Boyden noted.

"We've screened only a tiny, tiny fraction of the species in the world, so almost certainly there are many treasures out there to be found."

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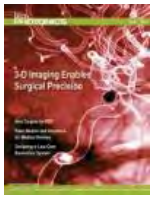
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