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Clap on! Clap off!

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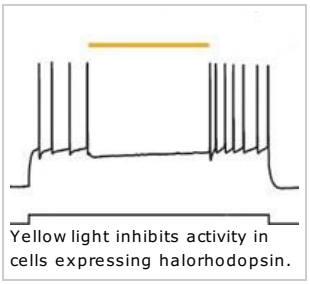
Different wavelengths of light stimulate and inhibit neurons expressing complementary light-activated proteins.



Yellow light inhibits activity in cells expressing halorhodopsin.

Although researchers cannot yet use The Clapper to activate and deactivate neurons with a clap of their hands, recent advances in light-activated membrane proteins promise to allow researchers to turn neurons on and off at whim. Within milliseconds, light activates neurons expressing channelrhodopsin-2, an opsin found in algae. Now Zhang *et al.* and Han and Boyden report an opsin activated by a different wavelength of light that inhibits cellular activity in recent articles in *Nature* and *PLoS ONE*, respectively.

Channelrhodopsin-2 is a cation channel that helps algae move toward better conditions for photosynthesis. Channelrhodopsin-2 depolarizes cells in response to blue light. Halorhodopsin is a light-activated chloride pump expressed in archaea, which are prokaryotes that share some similarities with eukaryotes. In response to yellow light, halorhodopsin pumps chloride in, hyperpolarizing the cell.

Yellow light inhibits endogenous activity in halorhodopsin-expressing neurons. Han and Boyden expressed halorhodopsin in hippocampal neurons. In these neurons, a one-second pulse of yellow light induced transient hyperpolarization. Neurons repolarized quickly after light exposure ended. Repeated pulses of yellow light induced a series of inhibitory postsynaptic currents. Yellow light inhibited action potentials induced by current injection, and short pulses of yellow light inhibited single action potentials, sparing the action potentials occuring immediately after the end of yellow illumination. In contrast, Zhang *et al*. inhibited evoked activity for as long as 10 minutes with extended yellow illumination.

Cells expressing both channelrhodopsin-2 and halorhodopsin can be activated and inhibited by different wavelengths of light. Han and Boyden alternated 50-millisecond pulses of yellow and blue light and found comparable alternations between inhibitory and excitatory postsynaptic currents in hippocampal neurons expressing both proteins.

Zhang *et al*. injected mouse pups with lentiviral vectors containing the light-activated proteins. In hippocampal slices from these mice, blue light transiently increased intracellular calcium concentration. Simultaneous exposure to yellow light blocked the blue-light mediated increase, suggesting that light can activate and deactivate neurons expressing these proteins *in vivo*.

In *C. elegans* expressing light-activated proteins, light controlled behavior. Zhang *et al.* generated *C. elegans* expressing halorhodopsin targeted to either muscle cells or cholinergic motor

neurons. *C. elegans* normally swim in liquid media. However, yellow light stopped swimming behaviors in the transgenic nematodes. Muscle contraction and relaxation can be observed in *C. elegans* placed on a solid substrate. *C. elegans* expressing both channelrhodopsin-2 and halorhodopsin targeted to either muscle cells or cholinergic motor neurons contracted in response to blue light and relaxed in response to yellow light.

Clinicians currently use deep brain stimulation to treat depression, Parkinson disease and Tourette syndrome, and surgeons remove brain areas that cause seizures in epilepsy. Perhaps light-activated membrane proteins could be used eventually instead of more invasive techniques to stimulate or silence diseased parts of the human brain.

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1. Zhang, F. *et al.* Multimodal fast optical interrogation of neural circuitry. *Nature* **446**, 633–639 (2007). | Article | PubMed | ChemPort |
2. Han, X. and Boyden, E. S. Multiple-color optical activation, silencing, and desynchronization of neural activity, with single-spike temporal resolution. *PLoS ONE* **2**, e299– (2007). | Article | PubMed |