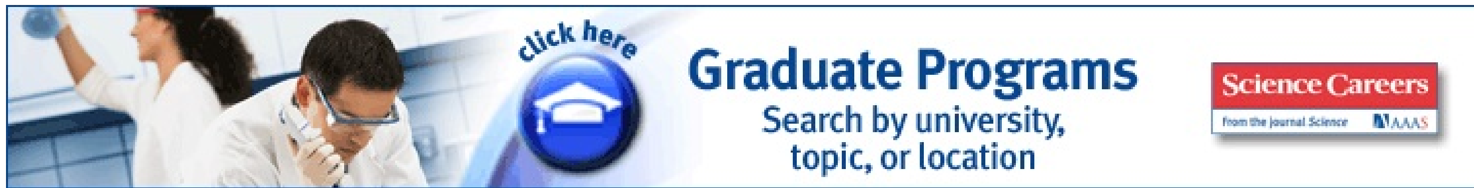

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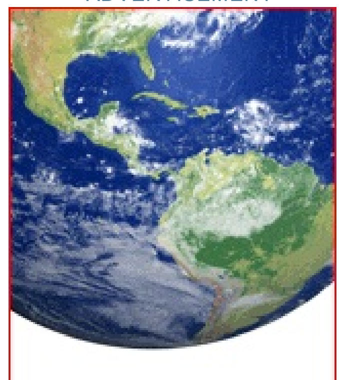

Molecular Tools for Controlling Brain Circuits with Light

Ed Boyden

The brain is composed of many kinds of cells, which differ from one another in molecular composition, shape, physiology, and pattern of connectivity. In order to understand how this diversity of cells works together as a circuit to implement the computations that generate behavior, and how these computations go awry in states associated with neurological and psychiatric disorders, it is important to be able to assess experimentally the causal role that a given kind of cell plays in the emergent dynamics of the circuit in which it is embedded. Such causal assessments cannot rely solely on observational experimental methodologies, but require the ability to perturb the electrical activity of a defined set of cells in a temporally precise way, as well as the ability to observe the impact of such a perturbation on electrical activity in the rest of the circuit and on behavior. My colleagues and I have developed a suite of genetically encoded molecular tools that, when expressed in defined sets of cells in the brain, enable them to be electrically activated or silenced in a temporally precise fashion, using pulses of light. In 2005, in a collaboration with Karl Deisseroth and Georg

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Nagel, I discovered that the algal gene that encodes the light-activated cation channel channelrhodopsin-2, when expressed in neurons, enables them to fire action potentials in response to brief pulses of blue light. This tool has since found widespread use in neurobiology, enabling explorations of the sufficiency of specific classes of neurons to drive neural dynamics and behavior in neuroscience model organisms ranging from *Caenorhabditis elegans* to monkeys, thanks to its high performance and its ease of use in conjunction with transgenic methodologies for targeting cell types and pathways in the nervous system.

Over the past few years, my research group has explored the genomic diversity of molecules related to channelrhodopsin-2, namely the vast group of membrane proteins called microbial opsins, which are found in species throughout the tree of life. Given that a key role of such molecules is to transport ions across cell membranes in response to light, for sensory or energy-capture purposes, we anticipated that many of these molecules could be adapted as tools for the perturbation of specific cellular processes in the brain. We used genomic data to support the synthesis of microbial opsin genes from species from different kingdoms of life, including archaea, bacteria, and fungi. We then characterized the functions of these opsins in neurons, assessing the colors of light that best drove their activity, the kinetics of their ion transport, the magnitude of the electrical changes they could support, and the safety of their expression and operation. From these experiments, a number of classes of molecular tools emerged, each with distinct properties that made it particularly useful for specific kinds of experiment. For example, we found that halorhodopsins, light-driven inward chloride pumps from archaea, could mediate orange-light–driven hyperpolarizations when expressed in neurons, useful for quieting neurons to assess their necessity in neural computations and behaviors. In contrast, fungal opsins such as the opsin from *Leptosphaeria maculans*, a light-driven outward proton pump, could mediate blue-light–driven hyperpolarization of neurons. Thus, these two distinct classes of hyperpolarizing opsin, when expressed in two different neuron types, enable them to be quieted by two different colors of light, opening up new experimental capacities such as the ability to silence multiple projection pathways into a given brain region. The class of light-driven outward proton pumps known as archaerhodopsins, as represented by the molecule archaerhodopsin-3 from *Halorubrum sodomense*, proved to be excellent for in vivo neural silencing with green light, due to their fast kinetics and large-magnitude photocurrents, and could mediate near-100% shutdown of neurons in awake behaving mice, enabling a wide variety of time-resolved cell- and pathway-specific lesion experiments.

We continue this search by broadly surveying genomes for fundamental new kinds of opsins, searching genomic space near opsins that we have already characterized to look for refinements to existing tools and performing mutagenesis (often guided by structure) to alter the color selectivity, speed, and conductance of opsins. This ongoing work is yielding opsins with fundamental new properties, such as an opsin that when illuminated presents a linear current-voltage relationship like that of a GABA receptor, as well as improved opsins, such as a neural silencer with fourfold-improved light sensitivity over earlier reagents. In parallel with our development of molecular tools, we are devising experimental strategies for addressing new neuroscience questions and for deriving clinically relevant insights into how abnormal neural dynamics might be corrected. For example, we have developed hardware for the delivery of molecular reagents, and of light, to three-dimensional circuits in the brain, thus enabling systematic in vivo optical screening for neural targets that are capable of powerfully modulating behaviors or brain states. As another example, we have demonstrated in vitro that the expression of both channelrhodopsin-2 and halorhodopsin in the same neuron enables optical alteration of the timing of action potential firing by that neuron, thus demonstrating a prototype method for probing the role of

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spike timing in neural coding.

Recently, we developed, in collaboration with the labs of Bob Desimone and Ann Graybiel, molecular and hardware strategies for optically driving specific cell classes in the cortex of the macaque, a species important for the neurobiological investigation of the mechanisms of cognition. In this study, we characterized the local circuit dynamics in the cortex downstream of excitatory neuron activation, revealing principles helpful in the interpretation of studies involving microstimulation or optical cortical neuron control. One valuable insight from this study was that expressing opsins in neurons in a brain similar to the human brain appeared to be safe and efficacious, without producing overt damage or obvious immune responses. Although preliminary, this preclinical study opens up the possibility of a class of high-precision cell-specific optical neuromodulation prosthetics. Thus, our inventions may not only enable causal, time-resolved analysis of brain circuit functions, but may in the future directly support novel kinds of therapy.

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