Optical electrophysiology in neuroscience, disease modeling, and drug discovery

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Electrical spiking is the internal language of the nervous system, but membrane voltage is very hard to measure. This difficulty has been a major obstacle to developing therapeutics that affect neural activity. We developed optogenetic tools for all-optical electrophysiology ('Optopatch')—simultaneous optogenetic stimulation and optical readout of membrane potential. In combination with advanced optical systems and specialized software, Optopatch tools permit high-speed characterization of neuronal function. We have applied Optopatch in primary neurons, in human stem cell-derived neurons, and in rodent brain in vivo. In neurons derived from human induced pluripotent stem cells (iPSCs), optical electrophysiology enables detailed functional characterization of many thousands of neurons in a screening-compatible format. Neurons derived from patients with genetically based diseases of the nervous system show characteristic firing anomalies, which in some cases can be reversed by appropriate pharmacological agents.

Optopatch measurements also permit targeted measurements of individual ion channels heterologously expressed in stable cell lines. In HEK cells that express a voltage-gated sodium channel and an inward rectifier potassium channel, optogenetic stimulation activates the sodium channel, which leads to a voltage spike. The spike can be detected by a fluorescent voltage indicator. Compounds that modulate the activity of the sodium channel affect the spike waveform. We have used this technique to screen for activity-dependent modulators of the channels NaV1.7 and NaV1.9, both implicated in pain.

To apply Optopatch in vivo we developed custom optics to compensate for light scattering and to highlight cells embedded within the three dimensional tissue. We studied the dynamics of hippocampal neurons in mice walking on a treadmill. Optopatch experiments revealed the first information about inter-cellular correlations in sub-threshold membrane potentials in the hippocampus, and how changes in brain state (corresponding to walking or resting) affected these correlations. We identified multiple independent subthreshold signals, shared to varying degrees among distinct subsets of neurons.