This Week in The Journal

Changes in Action Potential Waveform during Propagation

Victoria Gonzalez Sabater, Mark Rigby, and Juan Burrone

(see pages 5372–5385)

Synaptic potentials evoked in neuronal dendrites and soma summate and converge at the axon initial segment, where, if sufficient depolarization occurs, an action potential is generated. By sequentially activating clusters of voltage-sensitive sodium channels along the axon shaft, action potentials travel to presynaptic terminals, where they induce opening of voltage-sensitive calcium channels, calcium influx, and neurotransmitter release. The probability of neurotransmitter release depends on the amount of calcium influx, which is influenced by the amplitude and temporal profile of the action potential.

Although action potentials are typically described as all-or-nothing events, their waveform can change as they propagate. Detection of such changes has become possible only recently, thanks largely to the development of fluorescent voltage indicators. Gonzalez Sabater, Rigby et al. show that two recently developed genetically encoded voltage indicators (GEVIs)—Ace-2N-4AA-mNeon and Archon2—are sensitive and fast enough to detect single spikes. They use these indicators to show how voltage-gated potassium channels shape spikes in distal versus proximal axons of cultured hippocampal neurons.

By comparing voltage changes measured with GEVIs and electrodes, the authors demonstrated that GEVIs reliably report variations in action potential waveform produced by altering the activity of voltage-sensitive sodium and potassium channels. GEVIs slightly overestimated spike widths, however, and they could not be used to compare spike amplitudes across cells, likely because of variation in expression levels. Spatial averaging was required to reliably measure action potential waveforms in distal axons.

Action potentials were narrower in distal axons than in the proximal axon and soma of the same cell. As expected, blocking potassium channels broadened spike waveforms, and this effect was greatest in distal axons, where potassium channel

expression is highest. Notably, whereas action potential width in the soma and proximal axon increased by ~20% during high-frequency stimulation, broadening was only ~4% in distal axons. Surprisingly, this broadening was enhanced, not occluded, by blocking potassium channels, suggesting that a second channel type is responsible for the effect.

These results demonstrate that GEVIs can be used to measure changes in action potential waveform as spikes propagate along single axons. Researchers can now investigate activity-induced waveform plasticity and how it might contribute to synaptic function.

Fluorescence imaging of a neuron expressing a GEVI shows that action potential waveforms are narrower in the distal axon (blue) than in the soma (red) or proximal axon (green). See Gonzalez Sabater, Rigby et al. for details.

Movement Suppression by the Hyperdirect Pathway

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(see pages 5502–5510)

The basal ganglia have important roles in learning and controlling complex movements. The striatum, the largest input structure of the basal ganglia, contains two

classes of projection neurons that integrate thalamocortical input and project either directly or indirectly [via the globus pallidus external segment (GPe) and subthalamic nucleus (STN)] to the basal ganglia output nuclei: the substantia nigra pars reticulata (SNr) and the globus pallidus internal segment. The output nuclei tonically inhibit thalamocortical motor circuits to prevent unintended movements, and direct and indirect striatal outputs are thought to modulate portions of this inhibition to allow specific movements to proceed.

Basal ganglia output is also regulated by the so-called hyperdirect pathway, which involves direct cortical input to the STN. This pathway has been proposed to stop ongoing movement, but it is poorly understood compared with the direct and indirect pathways. To elucidate hyperdirect-pathway function, Koketsu et al. selectively killed motor cortical neurons that projected to the STN in mice, using retrogradely transported microbeads conjugated with a molecule that induces phototoxicity. As targeted neurons underwent apoptosis, spontaneous locomotor activity gradually increased, becoming significantly different from control levels after 2–4 weeks. Responses of GPe and SNr neurons to motor cortical stimulation were also altered after 4 weeks. Cortical stimulation normally evoked triphasic responses—fast excitation followed by inhibition and then delayed excitation—in GPe and SNr neurons, but elimination of cortical–STN projections greatly reduced the number of neurons showing a fast excitatory response. In contrast, cortically evoked inhibition and delayed excitation were unaffected.

These results support the hypothesis that the hyperdirect pathway from motor cortex to STN leads to rapid excitation of SNr neurons that can suppress ongoing movement. Because cortically evoked inhibition and delayed excitation—which are likely mediated by direct and indirect striatal pathways, respectively—remained intact, the authors speculate that activation of the hyperdirect pathway resets motor circuitry so it can respond appropriately to subsequent commands. They further suggest that deep brain stimulation of the STN, an effective treatment for motor impairment in Parkinson's disease, might disrupt cortical input, thus releasing the brake on movement.

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