This Week in The Journal

Excitatory Effects of Cortical Dendritic SK Channels

Tobias Bock, Suraj Honnuraiah, and Greg J. Stuart

(see pages 7826–7839)

When the dendrites of cortical pyramidal neurons are sufficiently depolarized by synaptic activation or back-propagating action potentials, voltage-gated calcium channels open and can generate dendritic calcium spikes. These spikes contribute to synaptic integration and plasticity, and they shift the pattern of neuronal output from tonic spiking to bursts. Calcium influx also opens large- and small-conductance calcium-activated potassium channels (BK and SK channels), which typically counteract depolarization and close voltage-gated channels. Indeed, the activation of dendritic BK channels limits the generation and duration of calcium spikes. Surprisingly, however, Bock et al. report that dendritic SK channels have the opposite effect: they promote the generation of dendritic calcium spikes in rat layer 5 pyramidal neurons.

As expected from previous work, bath application of apamin, an SK channel blocker, reduced the hyperpolarization that occurs after dendritic calcium spikes and somatic action potentials. It also increased neuronal firing as expected. But when apamin was applied selectively to dendrites, the calcium spike afterhyperpolarization was unchanged and the width and number of dendritic calcium spikes unexpectedly decreased, rather than increased. Also contrary to expectations, blocking dendritic SK channels decreased somatic burst firing induced by dendritic depolarization and increased the critical frequency at which back-propagating action potentials elicited dendritic calcium spikes. Blocking R-type calcium channels—which underlie dendritic calcium spikes and SK channel activation—mimicked and occluded the effects of apamin, whereas pharmacological enhancement of dendritic SK channels had the opposite effects. Notably, blocking dendritic, but not somatic, SK channels increased the input resistance of cells, suggesting that dendritic SK channels are open at rest. Computer simulations suggested that such constitutive activation of SK channels can facilitate calcium spike

generation by reducing calcium channel inactivation.

These results suggest that the activation of dendritic SK channels in cortical pyramidal neurons increases, rather than decreases, dendritic excitability and promotes the production of calcium spikes. Nonetheless, blocking or enhancing somatic SK channels had the expected effects on afterhyperpolarization and spiking. The mechanisms underlying these opposing effects of dendritic and somatic SK channels, and how these mechanisms might be modulated to influence synaptic integration and plasticity, should be elucidated in future studies.

Dendritic current injection (bottom) elicits dendritic calcium spikes (top). These spikes are narrower when dendritic SK channels are blocked (red traces) than in controls (blue). Current injection switches neuronal output to burst mode in control conditions, but not after SK channels are blocked (middle traces). See Bock et al. for details.

Persistent Injury-Induced Changes in Spinal Interneurons

Jie Li and Mark L. Baccie

(see pages 7815–7825)

The superficial laminae of the spinal cord dorsal horn contain a diverse population of excitatory and inhibitory interneurons, as well as the somata of projection neurons that transmit sensory information to the brain. Dorsal horn neurons receive input from multiple types of somatosensory afferents, and local processing of this in-

put, shaped by descending input from the brainstem, influences whether the stimulus is ultimately perceived as painful, itchy, or innocuous. Tissue injury during the neonatal period can lead to persistent changes in dorsal horn circuitry, resulting in reduced sensitivity to innocuous somatosensory stimuli along with hypersensitivity to pain in adulthood in both humans and rodents.

Increased afferent input to dorsal horn projection neurons, reduced inhibitory input to these neurons, and changes in the excitability of sensory afferents and dorsal horn interneurons are all thought to contribute to altered pain sensitivity after neonatal injury in mice (Walker et al., 2016, *Exp Neurol* 275:253). Li and Baccie now show that neonatal injury also produces persistent changes in afferent synapses with dorsal horn GABAergic interneurons. GABAergic interneurons of adult mice that had undergone neonatal surgical incision received fewer inputs from high-threshold C-fiber afferents and more input from A β - and A δ -fibers than neurons in control mice. Neonatal injury also led to reductions in polysynaptic EPSCs and spiking evoked in GABAergic interneurons by dorsal root stimulation. These changes may have stemmed partly from reduced afferent drive to glutamatergic interneurons that provide feedforward excitation to GABAergic neurons. Finally, pairing dorsal root stimulation with postsynaptic action potential generation induced long-term depression in a smaller proportion of GABAergic interneurons, and induced long-term potentiation in a greater proportion of neurons, in mice that had undergone neonatal incision than in controls. These changes may have resulted from increased expression of calcium-permeable AMPA receptors in GABAergic interneurons in previously injured mice.

The reduction in excitatory drive to GABAergic interneurons may contribute to the reduced inhibitory input to projection neurons that occurs after neonatal injury, but how these changes and the changes in the direction of synaptic plasticity relate to changes in pain sensitivity remains unclear. The first step for future work will be to determine which subtypes of GABAergic neurons exhibit these changes.

This Week in The Journal was written by Teresa Esch, Ph.D.
<https://doi.org/10.1523/JNEUROSCI.twij.39.40.2019>