This Week in The Journal

Inflammation Alters the Distribution of a Ca^{2+} Exchanger

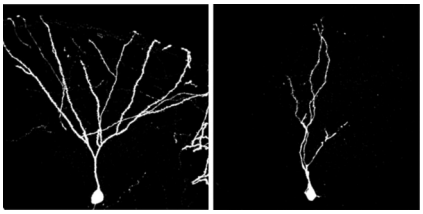
Nicole N. Scheff and Michael S. Gold

(see pages 8423–8432)

Tissue damage causes the release of various inflammatory molecules that not only promote healing, but also sensitize nociceptors, so normally innocuous stimuli become painful. Many cellular and molecular mechanisms contribute to nociceptor sensitization. Most of these involve alterations in the expression, distribution, or function of ligand- or voltage-gated ion channels that regulate membrane excitability. But some changes induced in nociceptors by inflammation remain unexplained. For example, the amplitude and duration of somatic Ca^{2+} transients evoked by depolarization of dorsal root ganglion (DRG) nociceptors increases during inflammation, but the most likely explanations for this effect—increases in Ca^{2+}-induced Ca^{2+} release or in voltage-gated Ca^{2+} channel (VGCC) conductance—have been ruled out. In fact, VGCC current density decreased in nociceptor somata after inflammation was induced (Lu et al., 2010, Pain 151:633).

Scheff and Gold have now identified one mechanism contributing to the inflammation-induced increase in the duration of evoked Ca^{2+} transients: reduced extrusion of Ca^{2+} by the Na^{+}/Ca^{2+} exchanger (NCX). Like inflammation, blocking NCX increased the duration of evoked Ca^{2+} transients in dissociated DRG nociceptors. The effect was occluded in nociceptors from inflamed rats, however. Western blots confirmed that NCX levels were lower in DRG from inflamed rats than in control DRG. Interestingly, however, NCX levels were higher in the peripheral axons of nociceptors in inflamed rats than in controls, apparently as a result of increased trafficking of the protein from the soma to the periphery.

Does this change in NCX trafficking contribute to nociceptor sensitization? Changes in the duration of evoked Ca^{2+} transients in nociceptor somata appeared later and returned to baseline sooner than behavioral hypersensitivity, making it unlikely that the decreased expression of NCX in the soma contributes to the induction or persistence of nociceptor sensitization, although it may contribute to the magnitude of sensitization. However, elevated NCX expression in the periphery may contribute to nociceptor sensitization by reducing the duration of Ca^{2+} transients and thus affecting the gating of Ca^{2+}-sensitive K^{+} and Cl^{-} channels. To better evaluate the roles of NCX, future research should focus on changes occurring at nociceptor terminals both in the periphery and in the spinal cord.



Adult-born dentate granule cells normally generate branched dendritic arbors within 8 weeks of exiting the cell cycle (left). Knockout of BDNF from such neurons stunts dendritic growth (right). See the article by Wang et al. for details.

Newborn Neurons Make BDNF to Help Their Dendrites Grow

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(see pages 8384–8393)

The continual generation of new neurons in the subgranular zone of the adult dentate gyrus is thought to be essential for learning, memory, and mood stabilization. Adult-born neurons extend dendrites toward the dentate molecular layer and extend axons toward hippocampal area CA3, where they make synapses with older neurons, thus becoming incorporated into neural circuits. This process requires neuronal activity and the expression of receptors for brain-derived neurotrophic factor (BDNF) in newborn neurons.

In fact, BDNF is important for neuron survival, growth, and synaptogenesis throughout development and into adulthood. BDNF is generally thought to be secreted by neuronal targets, but some developing neurons secrete the BDNF that activates receptors on their own neurites. This autocrine action has been shown, for example, to promote the growth of nascent axons in cultured hippocampal neurons (Cheng et al., 2011, PNAS 108:18430). Wang et al. now report that BDNF also regulates dendritic growth of adult-born neurons via autocrine signaling.

Retrovirally mediated deletion of BDNF selectively in newborn hippocampal neurons caused these neurons to develop shorter, less branched dendritic arbors than newborn neurons in control animals. Moreover, deletion of BDNF in a subset of newborn neurons did not affect dendritic growth in neighboring newborn neurons that continued to express BDNF. In addition, expressing BDNF selectively in newborn neurons in otherwise BDNF-lacking hippocampus restored dendritic growth, and overexpressing BDNF selectively in newborn neurons caused these neurons' dendrites to grow longer in wild-type animals. Notably, the latter effect was prevented by coexpressing the inward-rectifier K^{+} channel to prevent depolarization of newborn neurons, suggesting the autocrine action of BDNF required neuronal activity. Finally, BDNF deletion prevented the enhancement of dendritic growth that normally occurs in adult-born neurons when mice are given access to a running wheel.

All together, these results indicate that the growth of dendrites in newborn hippocampal neurons depends on their own production of BDNF. This autocrine action appears to underlie the ability of physical activity to promote the incorporation of newborn neurons into existing circuits, and thus is likely to be essential for such activity to enhance cognitive function and elevate mood.

This Week in The Journal is written by Teresa Esch, Ph.D.