This Week in The Journal

Cdk5, MeCP2, and BDNF Link Depolarization to Dendrite Growth

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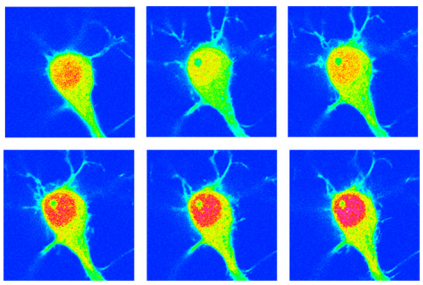
(see pages 15127–15134)

Neuronal activity shapes circuits by strengthening synapses, stabilizing dendritic spines, and stimulating dendritic growth and branching. These effects are mediated through increases in intracellular calcium levels, activation of kinases, and downstream changes in gene transcription. For example, activity-dependent activation of calcium/calmodulin-dependent protein kinase IV leads to activation of the transcription factor CREB, which in turn enhances expression of brain-derived neurotrophic factor (BDNF), thereby promoting dendritic growth. New evidence suggests that activity-dependent activation of cyclin-dependent kinase 5 (Cdk5) also promotes dendritic growth by increasing expression of BDNF.

Liang et al. found that Cdk5 levels increased in cell nuclei in mouse visual cortex after the animals' eyes opened, raising the possibility that increased synaptic activation led to nuclear translocation of Cdk5 in neurons. Consistent with this possibility, KCl-induced depolarization of cultured hippocampal neurons caused cytoplasmic Cdk5 to enter the nucleus. Depolarization also increased the number of dendrites in cultured neurons (as shown previously), but reducing Cdk5 activity attenuated this effect. Furthermore, knocking down Cdk5 reduced the number and length of dendrites, and rescue of this effect required accumulation of Cdk5 in the nucleus, suggesting it required Cdk5-dependent regulation of gene expression.

Microarray analysis revealed that depolarization-induced changes in the expression of many genes were altered in Cdk5-deficient neurons. One of the genes most strongly affected by Cdk5 knockout was *bdnf*: depolarization of wild-type neurons increased levels of *bdnf* mRNA, but this effect was attenuated by Cdk5 knockout. Additional work revealed that neuronal depolarization led to Cdk5-mediated phosphorylation of methyl-CpG–binding protein 2 (MeCP2), a transcriptional repressor that regulates *bdnf* expression. KCl treatment reduced the association of MeCP2 with *bdnf*, and inhibiting Cdk5 attenuated this effect.

These results reveal a new pathway linking neuronal activity to dendritic growth: depolarization causes Cdk5 to enter the nucleus where it phosphorylates MeCP2, causing this repressor to dissociate from the *bdnf* gene. Interestingly, previous work showed that Cdk5 also regulates BDNF-dependent dendritic growth by phosphorylating the BDNF receptor TrkB and remodeling the actin cytoskeleton (Cheung et al., 2007, PLoS Biology 5:e63). Moreover, Cdk5 phosphorylates several other activity-regulated transcription factors. Thus, Cdk5 appears to participate in many pathways linking neuronal activity to dendritic growth.



Time-lapse images show Cdk5 accumulating in the nucleus of a cultured hippocampal neuron after treatment with KCl. Top left image is before treatment, remaining panels are 6, 15, 30, 45, and 60 min after treatment. See Liang et al. for details.

Late Calcium Wave Is Key in Wallerian Degeneration

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(see pages 15026–15038)

When an axon is cut, the detached portion remains intact for several hours before it fragments and degenerates. This process is called Wallerian degeneration. The lag between axonal severing and fragmentation can be extended by many hours by overexpressing a protein called Wallerian degeneration slow (WldS). Intriguingly, overexpression of WldS also extends axon survival in models of Parkinson's disease and glaucoma, indicating that some neurodegenerative diseases may share molecular mechanisms with axotomy-induced degeneration. Fully elucidating the molecular events occurring during Wallerian degeneration might therefore help researchers discover treatments for neurodegenerative diseases.

Increases in intracellular calcium levels are often associated with neurodegeneration, and minimizing calcium elevation delays axon fragmentation after axotomy. At the same time, calcium appears to have protective functions, such as promoting membrane sealing after axonal transection. By monitoring calcium fluctuations in single zebrafish somatosensory axons *in vivo*, Vargas et al. found that two distinct waves of calcium elevation occur after axotomy. The first wave began at the cut site immediately after injury, traveled up to 100 μm in both the detached axon and the proximal stump, and petered out within 5 min. After a long period during which calcium levels remained at baseline, a second wave started somewhere in the detached axon (often at the distal tip), progressed through the entire segment, and was followed within minutes by axon fragmentation and degeneration.

Several experiments suggested that the first calcium wave was benign while the second triggered degeneration. First, WldS did not affect the first wave, but it greatly delayed the second wave, as well as delaying fragmentation. Expressing the calcium buffer parvalbumin in neurons also delayed the second calcium wave and subsequent axonal fragmentation. Finally, in cultured mouse dorsal root ganglion neurons, buffering extracelluar calcium during the first calcium wave did not affect the timing of axonal degeneration, but buffering calcium only during the second wave delayed degeneration.

These data suggest that the late calcium wave is tightly linked to axonal degeneration. Why this wave occurs suddenly after a long baseline period and how it triggers rapid fragmentation of entire axon branches remain unknown. Answering these questions should provide valuable insights into neurodegenerative processes.

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