This Week in The Journal

● Cellular/Molecular

Location of Thalamocortical Synapses Affects Their Influence

Robert J. Richardson, Jay A. Blundon, Ildar T. Bayazitov, and Stanislav S. Zakharenko

(see pages 6406 – 6417)

The electrotonic properties of dendrites attenuate individual postsynaptic potentials before they reach the spike-initiating zone. A given neuron can increase its impact on spiking of postsynaptic neurons by forming more simultaneously activated, bigger synapses, with high release probability, closer to the spike-initiating zone. To explore how thalamocortical sensory inputs strongly drive layer 4 pyramidal neurons although they comprise only a small percentage of the total input to these cells, Richardson et al. studied inputs to layer 4 auditory cortical neurons in slices. Focal glutamate uncaging paired with whole cell recording revealed that synapses on stubby spines that were near the soma produced greater somatic depolarization than those on nearby mushroom-shaped spines and more distal spines. Calcium imaging paired with electrical stimulation of thalamocortical or intracortical inputs showed that thalamocortical afferents synapsed only within 100 μm of the soma, and primarily on stubby spines, whereas intracortical inputs showed no preference for spine shape or location.

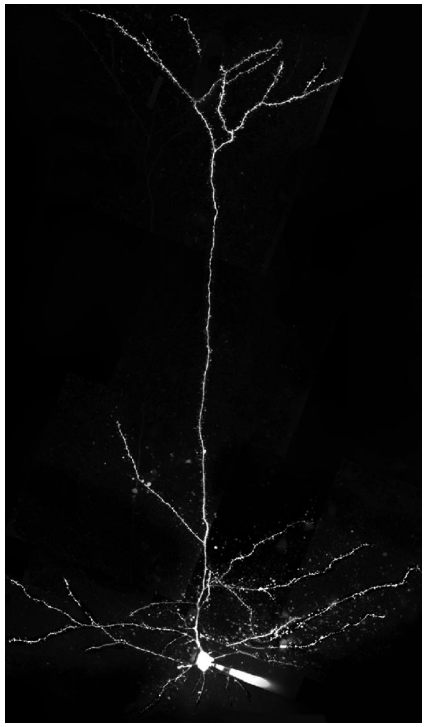
▲ Development/Plasticity/Repair

PHR Prevents Excessive Microtubule Stabilization

Michael Hendricks and Suresh Jesuthasan

(see pages 6593– 6598)

Neurite growth requires interactions between continually polymerizing and depolarizing actin and microtubules, and these interactions are influenced by extracellular guidance cues. PHR (Phr1, Esrom, Highwire, RPM-1), a ubiquitin ligase that tags proteins for proteasomal degradation, appears to be required at specific points in axonal growth. In *phr* mutants, although most axonal growth is normal, growth is halted at specific choice points, and microtubules accumulate and form loops in the stalled axons. Whether altered microtubule dynamics are a cause or effect of stalled growth is unknown, but Hendricks and Jesuthasan suggest the former based on imaging of microtubule dynamics in neurons from zebrafish *phr* mutants. Microtubules depolymerized less frequently in mutant neurons than in wild type. Moreover, stabilizing microtubules replicated the *phr* phenotype, whereas promoting depolymerization in mutants reduced microtubule defects *in vitro* and reduced the number of stalled axons *in vivo*. Surprisingly, none of the downstream effectors previously linked to PHR appeared to mediate its effects on microtubule dynamics.



A cortical thalamorecipient neuron. Thalamocortical inputs preferentially target stubby spines within 100 μm of the soma. See the article by Richardson et al. for details.

■ Behavioral/Systems/Cognitive

Humans Adapt to Within-Task Visuomotor Transforms

Daniel A. Braun, Ad Aertsen, Daniel M. Wolpert, and Carsten Mehring

(see pages 6472– 6478)

Motor control theories propose that we develop internal models to predict the optimal muscle forces required to successfully perform an action. Sensory feedback initiates error correction if, for example, the target of the action moves unexpectedly. Error correction is inadequate, however, if the relationship between motor force and effect changes, e.g., if pushing down unexpectedly makes an object move up. With practice one can learn new motor transforms and perform new tasks effectively, but how well can people adapt when the transform changes randomly and unexpectedly during a task? To address this question, Braun et al. instructed subjects to move a cursor to a target using a pendulum-suspended controller. On some trials, the visuomotor transform was rotated after the movement was initiated. Over many trials, subjects' movements on rotation trials became more accurate, faster, and less variable, suggesting they learned strategies to compensate for the unexpected within-trial transform. The characteristics of their later trajectories matched those predicted by an adaptive optimal feedback control model.

◆ Neurobiology of Disease

Mitochondrial Glutathione Depletion Increases Aβ Toxicity

Anna Fernández, Laura Llacuna, José C. Fernández-Checa, and Anna Colell

(see pages 6394 – 6405)

High cholesterol levels have been implicated as a possible susceptibility factor for Alzheimer's disease (AD). Although cholesterol-influenced modulation of secretases that produce plaque-forming amyloid β (Aβ) may contribute to this increased susceptibility, Fernández et al. suggest that depletion of mitochondrial glutathione (GSH) also plays a role. GSH is an antioxidant that controls the generation of reactive oxygen species and regulates cell-death pathways. Increased cholesterol alters mitochondrial membrane fluidity and thus inhibits mitochondrial uptake of GSH. In two transgenic mouse lines, increased mitochondrial cholesterol levels were associated with decreased mitochondrial GSH, increased generation of reactive oxygen species and pro-apoptotic proteins, and increased neuronal susceptibility to Aβ-induced death. Intracerebroventricular infusion of Aβ into one of these lines led to multiple AD-like pathologies, including amyloid deposition, activation of microglia and astrocytes, release of pro-inflammatory cytokines, accumulation of oxidized proteins, reduced synaptophysin levels, and increased apoptosis. Co-infusion of a membrane-permeable GSH increased mitochondrial GSH levels and attenuated all Aβ-induced pathologies.