This Week in The Journal

Cellular/Molecular

Doc2b Ensures Synchronous Vesicle Release in Two Ways

Paulo S. Pinheiro, Heidi de Wit, Alexander M. Walter, Alexander J. Groffen, Matthijs Verhage, et al.

(see pages 16459–16470)

In synaptic terminals, vesicles are held in different pools distinguished by how likely member vesicles are to be released by calcium entry. Many proteins associate with vesicles in these pools and regulate movement between pools. This regulation not only ensures that many vesicles are released simultaneously when an action potential occurs, but also ensures that some vesicles are reserved for release by the next spike. Synaptotagmins are thought to maintain vesicles in a readily releasable pool (RRP) until calcium enters the terminal, but the function of a group of closely related calcium-binding proteins—the Doc2 family—has remained elusive. By measuring release of dense core vesicles from chromaffin cells, however, Pinheiro et al. have identified two roles for Doc2b. At resting calcium levels, Doc2b promotes filling of the RRP. But when calcium levels increase during repeated stimulation, Doc2b inhibits this vesicle priming. Because primed vesicles are immediately released when calcium concentration is high, inhibition of priming limits sustained release and prevents vesicle depletion.

Development/Plasticity/Repair

Actin and Drebrin Promote Microtubule Invasion of Spines

Elliott B. Merriam, Matthew Millette, Derek C. Lumbard, Witchuda Saengsawang, Thomas Fothergill, et al.

(see pages 16471–16482)

Synaptic plasticity is often accompanied by changes in the shape of dendritic spines. Although spine shape is primarily regulated by the actin cytoskeleton, microtubules sometimes enter spines. Such entries increase after activation of synaptic NMDA receptors (NMDARs), suggesting that microtubules contribute to synaptic plasticity. Merriam et al. have discovered some of the molecular mechanisms linking NMDAR activation to microtubule invasion of spines. In cultured mouse hippocampal neurons, NMDAR activation caused increases in calcium and f-actin in some spines. Microtubules preferentially entered spines that had the largest increases in calcium and f-actin. Chelating calcium or depolymerizing actin filaments reduced microtubule entry, whereas stabilizing actin filaments increased microtubule invasion. NMDAR activation also increased expression of drebrin, a protein that interacts not only with actin but also with a protein at microtubule tips. Drebrin overexpression increased, whereas knockdown decreased microtubule invasion of spines. Together, these data suggest that calcium influx through activated NMDARs causes local increases in f-actin, which, through drebrin, promotes microtubule entry.

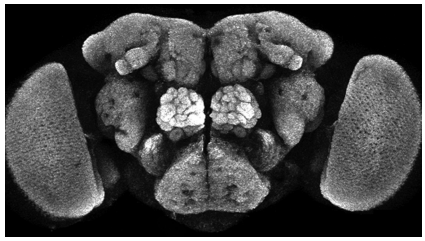
Behavioral/Cognitive

Presynaptic Mechanism Underlies Short-Term Odor Habituation

Madhumala K. Sadanandappa, Beatriz Blanco Redondo, Birgit Michels, Veronica Rodrigues, Bertram Gerber, et al.

(see pages 16576–16585)

Drosophila olfactory sensory neurons (OSNs) project to the antenna lobe, where they synapse on projection neurons (PNs) and local interneurons (LNs). LNs also receive inputs from PNs and they inhibit PNs and afferents in the same and other glomeruli. Potentiation of GABAergic synapses between LNs and PNs leads to olfactory habituation, in which avoidance of an odor decreases with repeated exposure. Sadanandappa et al. provide evidence that the potentiation underlying short-term odor habituation (STH) is presynaptic, involving phosphorylation of synapsin. Although synapsin-null flies did not exhibit STH, STH was rescued by expressing wild-type synapsin—but not nonphosphorylatable synapsin—selectively in LN1-type interneurons. Furthermore, inhibiting calcium/calmodulin-dependent kinase II (CaMKII) in LN1 interneurons reduced STH. Synapsin phosphorylation by CaMKII is thought to enable vesicles in the reserve pool to move to the active pool, which is expected to result in increased



Whole-mount fly brain labeled with antibodies against synapsin. Phosphorylation of synapsin in LN1 interneurons in the antenna lobe is required for short-term olfactory habituation. See the article by Sadanandappa et al. for details.

GABA release and thus increased inhibition of PNs. Interestingly, synapsin-null flies exhibited normal long-term habituation (LTH) indicating that LTH can occur without STH.

Neurobiology of Disease

Stress-Inducible Phosphoprotein Reduces Aβ Toxicity

Valeriy G. Ostapchenko, Flavio H. Beraldo, Amro H. Mohammad, Yu-Feng Xie, Pedro H. F. Hirata, et al.

(see pages 16552–16564)

β-amyloid (Aβ) oligomers, the likely culprit in Alzheimer's disease (AD), appear to exert some of their toxic effects by binding to the cellular prion protein (PrP^C). Aβ also affects cholinergic signaling (which is disrupted in AD), in part through interactions with α7 nicotinic acetylcholine receptors (α7nAChRs). Interestingly, stress-inducible phosphoprotein 1 (STI1), a protein secreted by astrocytes, binds to PrP^C near the Aβ binding site and exerts neuroprotective effects by activating α7nAChRs. Therefore, Ostapchenko et al. hypothesized that STI1 would inhibit the toxic effects of Aβ. Indeed, STI1 reduced binding of Aβ both to PrP^C and to mouse hippocampal neurons in culture. Whereas Aβ reduced the number of synaptic puncta, STI1 increased puncta and blocked the effect of Aβ. STI1 also prevented Aβ-induced reductions in long-term potentiation in hippocampal slices and reduced Aβ-induced neuron death. STI1 did not increase survival of neurons from α7nAChR-null mice, however. Interestingly, STI1 levels were elevated in AD brains, possibly representing an endogenous attempt to counteract Aβ accumulation.