This Week in The Journal

Cellular/Molecular

Piccolo Stimulates Activity-Dependent Actin Polymerization

Clarissa L. Waites, Sergio A. Leal-Ortiz, Till F. M. Andlauer, Stefan J. Sigrist, and Craig C. Garner

(see pages 14250–14263)

A dense matrix of cytoskeletal, scaffolding, and other proteins compose the active zones of presynaptic boutons; they control docking, priming, and fusion of synaptic vesicles and mediate activity-dependent changes in vesicle release probability. One important protein is filamentous actin, which acts as a barrier that limits vesicle fusion, facilitates vesicle endocytosis during recycling, and slows refilling of the readily releasable pool of vesicles during sustained synaptic activity, thus conserving vesicles. Profilin-2 promotes actin assembly in synaptic boutons by catalyzing ATP/ADP exchange. Waites et al. show that Piccolo, a large protein localized to boutons, regulates vesicle release by acting upstream of profilin-2 to stimulate activity-dependent actin assembly, thus inhibiting translocation between reserve and readily releasable vesicle pools. In cultured mouse hippocampal neurons, synaptic activity induced clustering of actin filaments around active zones and synaptic vesicle pools in presynaptic boutons. Knockdown of Piccolo reduced activity-dependent clustering of actin and profilin-2 and increased synaptic vesicle release.

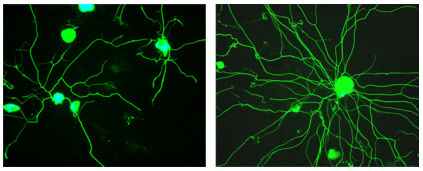
Development/Plasticity/Repair

CSPGs Inhibit Axon Growth via LAR Phosphatase

Daniel Fisher, Bin Xing, John Dill, Hui Li, Hai Hiep Hoang, et al.

(see pages 14051–14066)

Chondroitin sulfate proteoglycans (CSPGs) are extracellular matrix proteins that inhibit axonal growth. Secretion of CSPGs by reactive astrocytes increases after injury and helps form the glial scar that hinders axonal regrowth in the adult CNS. Although CSPGs may inhibit axonal growth partly through interactions with other growth-regulating proteins, their primary effectors are likely to be receptor protein tyrosine phosphatases, which have recently been identified as CSPG receptors. As shown by Fisher et al., one such receptor is the leukocyte common antigen-related phosphatase (LAR). CSPGs increased LAR phosphatase activity in transfected COS-7 cells. Knockdown of LAR, which is expressed by neurons in mouse brain and spinal cord, reduced the inhibitory effect of CPSGs on neurite growth in cultured dorsal root ganglion (DRG) and cerebellar granular neurons. More importantly, subcutaneous injection of LAR function-blocking peptides increased the number of axons growing beyond a dorsal spinal cord transection and enhanced functional recovery in injured mice.



Growth of DRG neurites is inhibited by CSPGs (left). This inhibition is reduced by function-blocking peptides against LAR (right). See the article by Fisher et al. for details.

Behavioral/Systems/Cognitive

5HT$_{1A}$ Receptor Desensitization Causes Learned Helplessness

Robert R. Rozeske, Andrew K. Evans, Matthew G. Frank, Linda R. Watkins, Christopher A. Lowry, et al.

(see pages 14107–14115)

Exposure to inescapable stress reduces an animal's subsequent effort to escape when it is possible, and it also reduces aggression, social interactions, and attempts to escape unrelated stressors. These effects, collectively termed learned helplessness, generally do not occur when animals can control stress exposure. Learned helplessness is thought to result from sensitization of serotonergic neurons in the dorsal raphe nucleus (DRN), leading to excess serotonin release over subsequent days. Rozeske et al. hypothesized that serotonin released during inescapable stress desensitizes inhibitory 5HT$_{1A}$ autoreceptors on DRN serotonergic neurons, thus reducing inhibitory feedback. Inhibition of serotonergic neurons by a 5HT$_{1A}$ agonist was reduced in rats after inescapable, but not escapable tail shock. Moreover, inhibiting prefrontal cortex while delivering escapable shock—a condition under which learned helplessness develops—reduced 5HT$_{1A}$-mediated inhibition, whereas after pretreatment to reduce learned helplessness, inescapable stress did not reduce autoinhibition. These data support the hypothesis that 5HT$_{1A}$ receptor desensitization underlies learned helplessness.

Neurobiology of Disease

Trigeminovascular Thalamic Neurons Project Widely to Cortex

Rodrigo Noseda, Moshe Jakubowski, Vanessa Kainz, David Borsook, and Rami Burstein

(see pages 14204–14217)

Trigeminal ganglion neurons that innervate blood vessels of the dura and pia maters converge with cutaneous nociceptors of the neck and forehead onto second-order neurons in the trigeminal nucleus and cervical dorsal horn. Stimulation of any of these nociceptors produces generalized headache, and activation of the trigeminovascular pathway in particular is thought to underlie migraine. Second-order trigeminovascular neurons project primarily to the posterior (Po) and ventral posteromedial (VPM) thalamic nuclei. Noseda et al. now report that thalamic trigeminovascular neurons have widespread and diverse cortical projection patterns. Although VPM neurons projected primarily to primary and secondary somatosensory cortex, some also arborized in motor and insular cortices. Higher-order relay neurons of the Po also projected to somatosensory cortex, but also had major projections to various other cortical areas, including primary auditory, visual, parietal association, and motor cortices. These projections may account for the diverse symptoms, such as visual disturbances and noise intolerance, experienced during migraine headache.