This Week in The Journal

● Cellular/Molecular

Docking and Priming with Munc18

Attila Gulyás-Kovács, Heidi de Wit, Ira Milosevic, Olexiy Kochubey, Ruud Toonen, Jürgen Klingauf, Matthijs Verhage, and Jakob B. Sørensen

(see pages 8676 – 8686)

This week, Gulyás-Kovács et al. unmask a dual role for Munc18 in docking and priming of vesicles in chromaffin cells. *In vitro*, Munc18 binds the "closed" state of syntaxin1 and thus occludes binding of the SNARE proteins SNAP-25 and synaptobrevin. However, Munc18 cannot be simply a negative regulator of exocytosis because vesicles fail to dock in its absence. To address this issue, the authors expressed mutant variants in chromaffin cells from Munc18 null mice and used uncaging of calcium to trigger release of primed vesicles. Expression of the NV mutation that prevents binding to closed syntaxin1 reduced vesicle docking. However, Munc18-1 NV rescued release, albeit to a lesser extent than wild type. Thus, Munc18 regulates a postdocking (priming) step by a mechanism that does not require binding to syntaxin1. In fact, the authors suggest that this second interaction either involves dissociation from syntaxin or a conformational change in the N-terminal domain of Munc18.

▲ Development/Plasticity/Repair

Pak1 and Neuronal Polarity

Tom Jacobs, Frédéric Causeret, Yoshiaki V. Nishimura, Mami Terao, Adele Norman, Mikio Hoshino, and Margareta Nikolić

(see pages 8604 – 8615)

If you want to make axons, you will need some activated p21-activated kinase (Pak1), according to Jacobs et al. The authors found this CdC42 and cofilin effector in all neurites, but it was activated locally in nascent axons. In cultured hippocampal and cortical neurons, the levels of membrane-associated phosphorylated (active) Pak1 peaked at the same time that neurons became polarized with distinct axons and dendrites, at ~2–4 d *in vitro* (DIV). Total Pak1, in contrast, reached a plateau at 4 DIV and beyond. Total and activated Pak1 were evenly distributed among multiple neurites before polarization, but once a neurite emerged as the axon, activated Pak1 was restricted to the soma and the distal part of the nascent axon, where it reorganized the F-actin cytoskeleton. Expression of constitutively active Pak1 disrupted morphological development of dendrites and axons; neurons did not survive past 7 DIV when Pak1 expression was silenced by RNA interference.

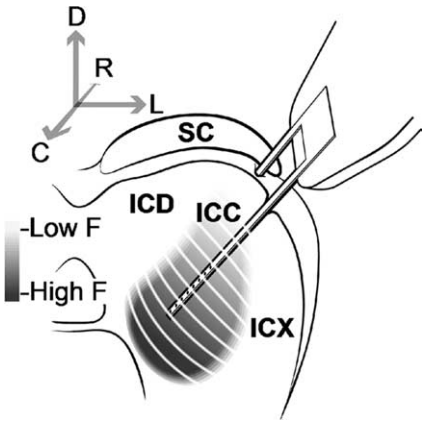
■ Behavioral/Systems/Cognitive

Toward an Auditory Midbrain Implant

Hubert H. Lim and David J. Anderson

(see pages 8733– 8743)

Cochlear implants have revolutionized the treatment of sensorineural hearing loss, but they don't work for everyone, for example, if the auditory nerve is severely damaged. Lim and Anderson propose the inferior colliculus central nucleus (ICC) as an alternative site for auditory prostheses. For such devices to work, it is necessary to stimulate at sites that tap into the tonotopic organization of the auditory system; but there's more. In this week's *Journal*, the authors reveal a previously unappreciated complexity in the functional organization of ICC. In anesthetized guinea pigs, the authors stimulated along the isofrequency or rostrocaudal axis in ICC. They measured responses in primary auditory cortex including threshold, evoked potential magnitude, discriminable level steps, and temporal response patterns. These parameters generally were optimal at rostral and slightly ventral ICC stimulation sites. At least two functional regions emerged, one caudal–dorsal and one rostral–ventral, which will require consideration in designing implants.



The drawing shows a multisite probe positioned along the tonotopic axis of the ICC. SC, Superior colliculus; ICD, inferior colliculus dorsal cortex; ICX, inferior colliculus external cortex. See the article by Lim and Anderson for details.

♦ Neurobiology of Disease

Microglia, Complement, and Neuropathic Pain

Robert S. Griffin, Michael Costigan, Gary J. Brenner, Chi Him Eddie Ma, Joachim Scholz, Andrew Moss, Andrew J. Allchorne, Gregory L. Stahl, and Clifford J. Woolf

(see pages 8699 – 8708)

In this week's *Journal*, Griffin et al. used microarrays to narrow in on genes affected in three peripheral nerve injury models of neuropathic pain. The most highly regulated were involved in the microglial complement cascade. Messenger RNAs for C1qb, C3, and C4 were upregulated in the dorsal horn of the spinal cord after injury and were expressed only in microglia. The complement cascade culminates in C5 and C5a receptor (C5aR) activation and formation of the membrane attack complex (MAC). Both C5 and C5aR were upregulated dramatically after injury. Mice lacking C5 displayed reduced postinjury indicators of neuropathic pain, whereas animals lacking the MAC component C6 did not. Having ruled out C3a and the MAC as major pain effectors, the authors injected naive rats intrathecally with the C5a anaphylatoxin. C5a increased cold pain sensitivity, and a C5a receptor antagonist blocked this effect, consistent with a role for C5a in neuropathic pain.