This Week in The Journal

● Cellular/Molecular

Synaptotagmin IV and Hippocampal Synapses

Jonathan T. Ting, Brooke G. Kelley, and Jane M. Sullivan

(see pages 372–380)

Calcium binding to synaptotagmin serves as the presumed calcium sensor for Ca^{2+} dependent neurotransmitter release. However in the family of synaptotagmin molecules synaptotagmin IV (Syt IV) stands out because it has much reduced Ca^{2+} binding to its C2A domain. Syt IV is usually expressed at low levels in the brain, but it is upregulated following intense activity such as seizures. Thus, one idea has been that Syt IV serves a dominant negative function. To test this idea in neurons, Ting et al. overexpressed Syt IV in cultured hippocampal neurons. Overexpressed Syt IV was trafficked to synaptic vesicles, but had no apparent effect on synaptic transmission. However a mutant Syt I with reduced Ca^{2+} binding did reduce release probability and altered Ca^{2+} dependence of release. Thus it appears that Syt IV does not have a dominant negative effect at this hippocampal synapse, although prior studies found that Syt IV altered exocytosis at the *Drosophila* neuromuscular junction and in PC 12 cells.

▲ Development/Plasticity/Repair

Visualizing Axonal Defects in Frizzled3

Yanshu Wang, Jiangyang Zhang, Susumu Mori, and Jeremy Nathans

(see pages 355–364)

This week, Wang et al. compared several new methods for large-scale mapping of axonal tracts. They used as their model the *Frizzled3* ($Fz3^{-/-}$) mouse that lacks the frizzled cell surface receptor. The authors confirmed that $Fz3^{-/-}$ mice have absent or severely reduced major tracts including the corpus callosum, anterior commissure, and fornix. The results highlighted the advantages of each method. Compared to labeling with the carbocyanine dye DiI, magnetic resonance diffusion tensor imaging (uDTI) provided a global assessment of fiber tracts, unprecedented flexibility, a lack of sectioning artifacts and it was quantitative. However, it is limited by 80-μm resolution. Two genetic methods were useful for sparse and selective tract labeling. In one case, the Thy1 promotor drove expression of yellow fluorescent protein in fibers originated from cortical pyramidal cells; in the other the *CreER;ZAP* system was pharmacologically triggered to express human alkaline phosphatase in a subset of cells.

■ Behavioral/Systems/Cognitive

Localizing the Placebo Effect

Jian Kong, Randy L. Gollub, Ilana S. Rosman, J. Megan Webb, Mark G. Vangel, Irving Kirsch, and Ted J. Kaptchuk

(see pages 381–388)

Dagfinn Matre, Kenneth L. Casey, and Stein Knardahl

(see pages 559–563)

The placebo effect can be a blessing for patients and a annoying confound for experimenters. This week, two groups tried to localize the site(s) of action of placebo analgesia. Matre et al. show that spinal processing of pain is altered by placebo. The authors informed subjects that they were testing the efficacy of magnets in alleviating heat pain, whereas in truth they used a specially constructed "sham" magnet. A placebo effect emerged not only in patient reports of initial pain intensity, but also in the subsequent hyperalgesia. The latter is a consequence of central sensitization of spinal nociceptive neurons. In other work, Kong et al. used functional magnetic resonance imaging to visualize brain areas activated by the placebo effect generated by sham acupuncture needles. Interestingly, different regions were activated than previously seen with a placebo cream treatment of the skin, suggesting that placebo effects can arise from different brain pathways.

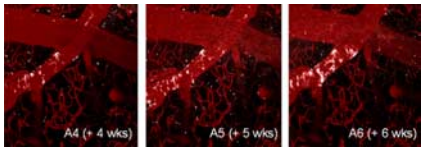
♦ Neurobiology of Disease

Amyloid Angiopathy in an AD Mouse

Elissa M. Robbins, Rebecca A. Betensky, Sarah B. Domnitz, Susan M. Purcell, Monica Garcia-Alloza, Charles Greenberg, G. William Rebeck, Bradley T. Hyman, Steven M. Greenberg, Matthew P. Frosch, and Brian J. Bacskai

(see pages 365–371)

β-amyloid (Aβ) deposits accumulate not only within the brain parenchyma, but also in cerebral arteries The vascular deposits of cerebral amyloid angiopathy (CAA) are often associated with lobar intracerebral hemorrhages in elderly patients, and are recapitulated in mouse models of Alzheimer disease (AD). This week Robbins et al. made use of methoxy-X04, the fluorescent dye that binds amyloid, to visualize the progression of CAA in real time. Using the *Tg2576* mouse model of AD, the authors peered through a small craniotomy window with a multiphoton microscope. Weekly images of leptomeningeal cerebral arteries revealed that Aβ steadily accumulated at a rate of ~0.35% of the total available vessel area per day. The arterial amyloid formed first as band-like deposits, then advanced mainly through propagation of existing deposits rather than formation of new deposits. This approach may be of use in examining treatments that affect the deposition and clearance of Aβ.



Serial *in vivo* images reveal progression of vascular amyloid deposits. Amyloid (white pseudocolor) deposits were labeled with methoxy-X04. See article by Robbins et al. for details.