This Week in The Journal

● Cellular/Molecular

Activity-Dependent Regulation of a Chloride Transporter

Claudio Rivera, Juha Voipio, Judith Thomas-Crusells, Hong Li, Zsuzsa Emri, Sampsa Sipilä, John A. Payne, Liliana Minichiello, Mart Saarma, and Kai Kaila
(see pages 4683–4691)

The chloride conductance of $GABA_A$ receptors usually hyperpolarizes cells because of the tireless activity of the K–Cl cotransporter, KCC2, which keeps intracellular chloride low. In the absence of cotransporter activity, $GABA_A$ responses become depolarizing, as occurs in hippocampal neurons under conditions of intense stimulation. Now Rivera et al. present a molecular explanation for rapid activity-dependent shifts in the chloride gradient. After interictal-like activity in the hippocampus, they observed downregulation of KCC2 mRNA and protein that resulted from endogenous BDNF binding at TrkB receptors. Using transgenic mice with mutations to the phospholipase Cγ docking site and the Shc binding site, they determined that both of these signaling pathways were activated. Given the rapid turnover rate of membrane-bound KCC2, downregulation of the transporter may act as a dynamic mechanism for regulation of neuronal excitability.

▲ Development/Plasticity/Repair

Neurotrophin Receptors and Motoneuron Survival In Vivo

Thomas W. Gould and Ronald W. Oppenheim
(see pages 4668–4682)

Approximately 50% of motoneurons (MNs) die during development. This programmed cell death (PCD) culls ~50% of the neurons because they apparently fail to compete for a limited supply of muscle-derived neurotrophic factors (NTFs). The question is which growth factor (and which of the growth factor receptors) is expressed on motoneurons or closely associated Schwann cells. To address this issue, Gould and Oppenheim examined the specific pool of MNs that innervates a pair of thigh adductor muscles in chick embryos. They examined expression of seven growth factors and their cognate receptors. Neurons within the adductor pool homogeneously expressed a set of growth factor receptors. Furthermore, combined treatment with BDNF, GDNF, CNTF, and HGF was required to completely prevent PCD. The authors also provide evidence of rescue *in trans* from other motoneurons. The results underscore the complexity of signals that mediate the life and death struggle of developing motoneurons.

■ Behavioral/Systems/Cognitive

Sleeplessness and Task Complexity

Michael W. L. Chee and Wei Chieh Choo
(see pages 4560–4567)

Even a single night without sleep dulls our mental performance. Seems obvious, right? Well, what's less obvious is that complex task performance is better preserved after sleep deprivation than simple tasks. In this issue, Chee and Choo use functional magnetic resonance imaging to examine brain activity after 24 hr without sleep to probe the regions responsible for this task dependence. Not surprisingly, sleep deprivation slowed the subjects' responses to tasks requiring either maintenance or manipulation and maintenance of memory. Both tasks activated bilateral, left hemisphere-dominant frontoparietal areas, as expected for verbal working memory tasks. After sleep deprivation, some brain areas showed reduced activation (medial parietal), and others showed reduced deactivation (anterior medial frontal and posterior cingulate). In addition, increased activation was apparent in the left dorsolateral prefrontal cortex and thalamus, which the authors suggest represents compensatory activity required for complex task performance.

◆ Neurobiology of Disease

Pyramidal Cell Activity in APP-Sw Mice

Edward A. Stern, Brian J. Bacskai, Gregory A. Hickey, Frank J. Attenello, Julianne A. Lombardo, and Bradley T. Hyman
(see pages 4535–4540)

A number of studies suggest that the accumulation of amyloid-β peptide in plaques in Alzheimer's disease (AD) can affect the cellular and synaptic properties of neurons as well as the circuitry of neuronal networks. Stern et al. approached this issue by recording *in vivo* from neocortical pyramidal neurons in one of the most commonly used animal models of AD, APP-Sw mice that overexpress the amyloid precursor protein (APP). They examined mice at two stages, 8–9 months, when there is soluble amyloid accumulation but no plaques, and 14 months, when there is significant plaque formation. As amyloid-β plaques accumulated, neuronal processes coursing in the vicinity were distorted, but the overall level of synaptic activity was similar to control animals. However transcallosal stimulation revealed considerably more variability in responses in the AD mice, suggesting that temporal synchrony was reduced. The authors suggest that the effect of amyloid-β on synaptic transmission in these mice involves disruption of the normal networks, in part because of the distortion of neurites by plaques.

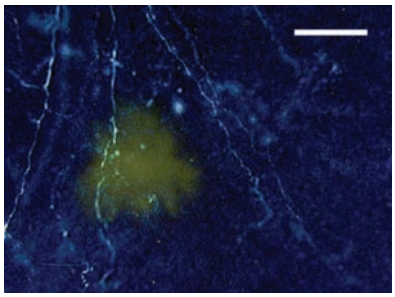

Image of neurites deflecting around an amyloid-β plaque that is labeled in yellow with thioflavine-2. Scale bar, 20 μm. See the article by Stern et al. for details.