This Week in The Journal

● Cellular/Molecular

Role of Voltage-Gated Sodium Channels in Neurite Outgrowth

William J. Brackenbury, Tigwa H. Davis, Chunling Chen, Emily A. Slat, Matthew J. Detrow, Travis L. Dickendesher, Barbara Ranscht, and Lori L. Isom

(see pages 3246–3256)

The β1 subunit of the voltage-gated sodium channel participates in homophilic and heterophilic cell adhesion and increases neurite outgrowth *in vitro*, in addition to modulating electrical excitability. It interacts with several other cell adhesion molecules (CAMs), and these CAMs activate two signaling pathways: one that involves fyn kinase and one that involves the fibroblast growth factor receptor (FGFR). To determine whether the β1 subunit relies on these same signaling pathways, Brackenbury et al. examined the growth of dissociated cerebellar neurons on β1-expressing and control cell lines. β1 expression enhanced neurite outgrowth from wild-type neurons, as expected, and FGFR antagonists did not diminish this effect. But β1 expression did not enhance outgrowth from *Fyn* null neurons, suggesting that fyn kinase, but not FGFR, is involved in β1 potentiation of neurite growth. Examination of axon growth in β1 null mice suggested that β1 is involved in axon fasciculation *in vivo*.

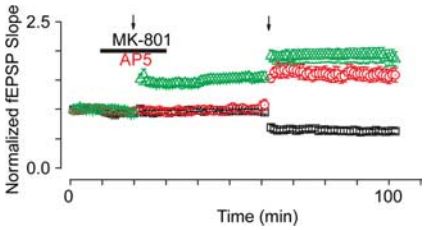
▲ Development/Plasticity/Repair

Effects of NMDA Receptor Lateral Diffusion on Synaptic Plasticity

Jiang Zhao, Yi Peng, Zhuo Xu, Rongqing Chen, Qin-hua Gu, Zheng Chen, and Wei Lu

(see pages 3060–3070)

Synaptic plasticity depends on the receptors present at the synapse; the response to a stimulus can change if the receptors change. For example, the subunit composition of NMDA receptors (NMDARs) influences whether long-term potentiation (LTP) or long-term depression (LTD) is produced by a given stimulus. Zhao et al. show that the composition of synaptic NMDARs can change as a result of lateral diffusion of NMDARs in the membrane. When only synaptic NMDARs were blocked, EPSC amplitude recovered after washout. But when both synaptic and extrasynaptic NMDARs were blocked, EPSCs did not recover. This suggests that the recovery after synaptic block depended on diffusion of extrasynaptic NMDARs into the synapse. The decay time of spontaneous and evoked NMDAR-mediated EPSCs was longer after recovery, suggesting a change in the subunit composition of synaptic receptors. This change was paralleled by a change in synaptic plasticity: a stimulus that normally produced LTP instead induced LTD.



A stimulus (arrows) that induced LTP in control rat hippocampal slices (green) also induced LTP after recovery from reversible block of NMDA receptors (AP-5; red), but induced LTD after irreversible block (MK-801; black). See the article by Zhao et al. for details.

■ Behavioral/Systems/Cognitive

Olfactory Learning in Drosophila

Michael J. Krashes and Scott Waddell

(see pages 3103–3113)

Learning often requires multiple training sessions spaced over time. This is true of aversive, but not appetitive, olfactory conditioning in *Drosophila*. When an odor is paired with sucrose, flies learn to follow that odor after a single training session, whereas 5–10 sessions are required to avoid an odor paired with shock. Despite this difference, Krashes and Waddell now report that appetitive long-term memory (LTM) involves many of the same neural processes previously shown to underlie aversive LTM. Like aversive LTM, appetitive LTM requires protein synthesis and activation of cAMP response element-binding protein (CREB) in mushroom bodies (MBs). Both require activity in DPM and MB $\alpha'\beta'$ neurons for consolidation and require MB $\alpha\beta$ neurons for retrieval. The main difference between aversive and appetitive LTM appears to be that appetitive LTM requires the *radish* gene, which is expressed in mushroom body $\alpha\beta$ neurons and produces a protein of unknown function.

♦ Neurobiology of Disease

Endocannabinoids and Epilepsy

Anikó Ludányi, Loránd Erőss, Sándor Czirják, János Vajda, Péter Halász, Masahiko Watanabe, Miklós Palkovits, Zsófia Maglóczky, Tamás F. Freund, and István Katona

(see pages 2976–2990)

CB_1 endocannabinoid receptors are expressed on presynaptic terminals, where they decrease transmitter release and are thought to help control hyperexcitability. In this week's *Journal*, Ludányi et al. present evidence of decreased endocannabinoid signaling in people with intractable epilepsy. Compared to controls, hippocampi removed from epileptic brains had dramatically reduced levels of CB_1 mRNA. Levels of the CB_1-associated protein cannabinoid receptor interacting protein 1a and of diacylglycerol lipase, which synthesizes an endocannabinoid, were significantly reduced in sclerotic hippocampi (i.e., those with principal cell loss), but not in nonsclerotic epileptic hippocampi. Immunostaining indicated that CB_1 expression was reduced throughout sclerotic and nonsclerotic hippocampi. Ultrastructural analysis revealed that in epileptic dentate gyrus, a smaller fraction of glutamatergic terminals expressed CB_1 than in controls, whereas the fraction of GABAergic terminals with CB_1 was comparable across samples. These results support the hypothesis that loss of cannabinoid signaling in glutamatergic neurons contributes to epilepsy in humans.