This Week in The Journal

● Cellular/Molecular

A MAGUK Enhances EAG Potassium Channel Function

Daniel D. Marble, Andrew P. Hegle, Eric D. Snyder II, Spiros Dimitratos, Peter J. Bryant, and Gisela F. Wilson
(see pages 4898 – 4907)

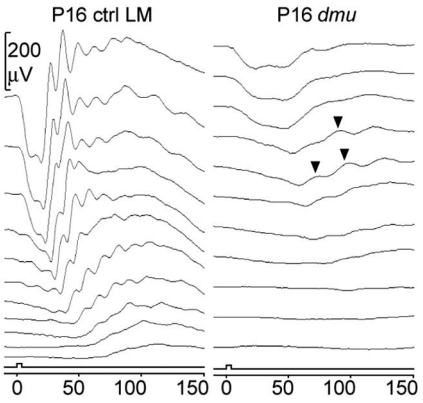
Adaptor proteins, by bringing together kinases and other effectors, form a submembrane scaffold of signaling molecules. One such adaptor, *Drosophila* Camguk (CMG), is a member of the membrane-associated guanylate kinase family and associates with calcium- and calmodulin-dependent protein kinase II (CaMKII). This week, Marble et al. describe a signaling complex including CMG, CaMKII, and the Ether-á-go-go (EAG) potassium channel, the *Drosophila* ortholog of KCNH1. Phosphorylation of EAG by CaMKII leads to a significant increase in current. Previous studies have reported that *eag* mutants or CaMKII inhibition cause similar associative learning deficits in *Drosophila*; thus the authors looked for a functional link between the adaptor molecule and the potassium channel. When CMG and EAG were coexpressed in *Xenopus* oocytes, whole-cell currents doubled compared with EAG alone. The increase depended on threonine 787, the residue phosphorylated by CaMKII, although the CMG–EAG interaction itself involved a separate domain. The results suggest that CMG, probably indirectly through CaMKII, enhances EAG phosphorylation and thus increases surface expression.

▲ Development/Plasticity/Repair

Sodium Channels in Photoreceptor Development

Patrice D. Côté, Yves De Repentigny, Stuart G. Coupland, Yannick Schwab, Michel J. Roux, S. Rock Levinson, and Rashmi Kothary
(see pages 5046 –5050)

A null mutation in the mouse *Scn8a* gene encoding the voltage-dependent sodium channel $Na_V1.6$ was initially described as a cause of neuromuscular paralysis, leading to death by postnatal day 20 (P20). The $Na_V1.6$ channel is expressed at nodes of Ranvier in the peripheral nervous system, but its absence also causes abnormal firing in central neurons. This week, Cote et al. unmask a retinal abnormality in *Scn8a* null mice. The mice had apparently normal retinal morphology, but the flash electroretinogram (ERG) was reduced in P16 mice to levels typical of P12. The reduction involved both the initial hyperpolarization attributable to photoreceptor cells (the a-wave) as well as the subsequent positive component attributable to ON bipolar and Müller cells (the b-wave). Because acute block of sodium channels does not interfere with the a-wave of the ERG, the authors suggest that $Na_V1.6$ plays a developmental role in photoreceptor maturation.



An ERG evoked by flashes of white light in a P16 control mouse littermate (P16 ctrl LM) and in an *Scn8a* null mutant mouse [P16 *dmu* (*degenerating muscle*)]. See the article by Côté et al. for details.

■ Behavioral/Systems/Cognitive

Fast and Slow Mesocortical Signaling to Prefrontal Cortex

Antonieta Lavin, Lourdes Nogueira, Christopher C. Lapish, R. Mark Wightman, Paul E. M. Phillips, and Jeremy K. Seamans
(see pages 5013–5023)

When one hears the words ventral tegmental area (VTA), one immediately thinks dopamine and reward pathways. VTA neurons project to the prefrontal cortex (PFC) and encode stimulus salience. However, this week Lavin et al. provide additional evidence that these neurons release a fast-acting transmitter, glutamate, in addition to dopamine. Although the firing of VTA neurons is considered to carry temporally precise information about reward or stimulus salience, this seemed at odds with the much slower changes in extracellular dopamine as measured in the PFC. The authors found that VTA stimulation produced a fast EPSP in the PFC that was blocked by glutamate receptor antagonists as well as by VTA destruction with 6-hydroxydopamine. Short burst stimulation of the VTA did produce inhibition, presumably by activation of local GABAergic neurons, as well as a long-lasting, dopamine-dependent potentiation of excitability. As expected, burst stimulation evoked transient dopamine release lasting a few seconds, as detected by voltammetry.

♦ Neurobiology of Disease

Subthalamic Nucleus Stimulation in the Parkinsonian Rat

François Windels, Carole Carcenac, Annie Poupard, and Marc Savasta
(see pages 5079 –5086)

Neurons in the subthalamic nucleus (STN) show increased neural activity in Parkinson's disease. Yet lesioning or high-frequency stimulation of the STN (HFS-STN) alleviates motor symptoms in parkinsonian patients. How does that work? In this week's *Journal*, Windels et al. approach the question by using microdialysis to monitor the effects of HFS-STN in hemiparkinsonian rats. STN neurons exert their effects by projections to the output nuclei of the basal ganglia, the globus pallidus (GP), and the substantia nigra pars reticulata (SNr). Glutamate and GABA are normally elevated in these structures by HFS-STN. However, after a unilateral 6-hydroxydopamine lesion, the authors report that basal levels of glutamate and GABA doubled in the rats. HFS-STN failed to evoke additional increases in glutamate, but stimulation did increase GABA in the SNr. Lesioning of the GP prevented the SNr GABA elevation, suggesting that stimulation of pallidonigral GABAergic pathways may be part of the benefit derived from HFS.