This Week in The Journal

● Cellular/Molecular

Role of TRP3C Channels in Motor Control

Fu-Wen Zhou, Shannon G. Matta, and Fu-Ming Zhou

(see pages 473–482)

The basal ganglia help to regulate body movement by providing constant inhibitory input to thalamic and brainstem motor nuclei via GABAergic projection neurons located in the substantia nigra pars reticulata (SNr). The resting potential of these GABAergic neurons (approximately −50 mV) is depolarized relative to most neurons, and this enables the neurons to fire spontaneously and tonically. Zhou et al. have now identified the ion channels responsible for depolarizing SNr GABAergic neurons: type 3 canonical transient receptor potential (TRP3C) channels. The authors used single-cell RT-PCR to screen SNr neurons for all 28 of the TRP channels known in mouse; only TRP3C was present. A thorough investigation of the effects of sodium, calcium, and TRP3C channel blockers demonstrated that inward sodium current through these channels depolarizes SNr neurons. Furthermore, intracellular injection of current-blocking antibodies revealed that the constitutive activity of TRP3C channels is essential for maintaining the regular firing pattern of SNr GABAergic neurons.

▲ Development/Plasticity/Repair

Long-Range Axonal Targeting in the Adult CNS

Kristine S. Ziemba, Nagarathnamma Chaudhry, Alexander G. Rabchevsky, Ying Jin, and George M. Smith

(see pages 340–348)

The use of neuronal implants to treat CNS damage is limited by the inability of the adult CNS to support long-range axonal growth and targeting. This week, Ziemba et al. describe a promising method to circumvent this obstacle by using adenovirus vectors to create a pathway of chemoattractants and chemorepellants in adult rat brain. When the chemoattractant FGF-2 was expressed in the corpus callosum, transplanted postnatal day 1 DRG neurons grew several millimeters along the callosum, and many axons turned to enter a target created by expressing NGF in the striatum. This occurred despite increased expression of the growth-inhibiting molecule chondroitin sulfate proteoglycan (CSPG) in the callosum caused by the injection. Expression of the chemorepellant molecule semaphorin 3A adjacent to the intended axon turning point further increased growth into the striatum. This novel method should be applicable to other neuronal types, provided the appropriate chemoattractants and chemorepellants are used.

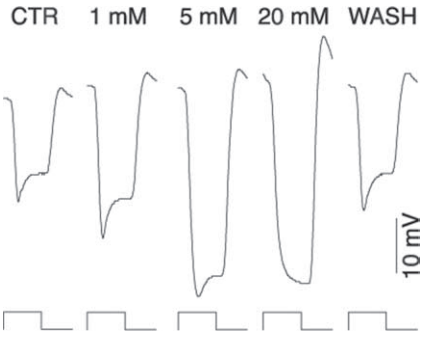
■ Behavioral/Systems/Cognitive

pH-Mediated Negative Feedback in Inhibitory-Surround Formation

Christopher M. Davenport, Peter B. Detwiler, and Dennis M. Dacey

(see pages 456–464)

Despite much investigation, the mechanisms underlying the center-surround receptive fields of retinal neurons remain unclear. Negative feedback from horizontal cells to photoreceptors likely induces cone calcium channels to open at more negative potentials, leading to depolarization; but what is the source of this feedback? The two main contenders are (1) extracellular voltage gradients created by currents through gap junction hemichannels (i.e., an ephaptic mechanism) and (2) a decrease in proton concentration in the synaptic cleft. Davenport et al. now provide strong evidence for the proton hypothesis. In macaque retinas, pH buffers reduced both the inhibitory surround of ganglion cells and the slow depolarization of horizontal cells that is thought to result from negative feedback. A buffer's ability to block the slow depolarization was directly correlated to its buffering capacity. Furthermore, HEPES enlarged horizontal cells' receptive fields, indicating that gap junction blockade was not responsible for the reduction in inhibitory feedback.



HEPES buffer increases the initial hyperpolarization and decreases the slow depolarization of primate horizontal cells responding to light. See the article by Davenport et al. for details.

♦ Neurobiology of Disease

Evidence for Dopamine Toxicity in Neurodegeneration

Linan Chen, Yunmin Ding, Barbara Cagniard, Amber D. Van Laar, Amanda Mortimer, Wanhao Chi, Teresa G. Hastings, Un Jung Kang, and Xiaoxi Zhuang

(see pages 425–433)

The symptoms of Parkinson's disease are caused by loss of dopaminergic neurons in the substantia nigra; therefore, it seems somewhat counterintuitive that dopamine may be a vulnerability factor in the disease. But Chen et al. now provide strong evidence for this hypothesis. Dopamine metabolites are highly reactive species that cause oxidative damage, leading ultimately to degeneration. Dopaminergic neurons sequester dopamine into vesicles, thus protecting these cells from damage. To examine the potential toxic effects of dopamine, Chen et al. engineered transgenic mice to conditionally express the dopamine transporter (DAT) in striatal neurons—targets of dopaminergic neurons that lack the ability to sequester dopamine. When DAT was turned on, the mice exhibited motor dysfunction and neurodegeneration within weeks. These effects depended on the presence of dopamine: if the dopaminergic inputs to the striatum were unilaterally severed, motor function on the contralateral side was spared. In contrast, L-DOPA accelerated neurodegeneration.