This Week in The Journal

● Cellular/Molecular

Activation Voltage of $Ca_v1.3$ Underlies Pacemaker Activity

Ilva Putzier, Paul H. M. Kullmann, John P. Horn, and Edwin S. Levitan

(see pages 15414–15419)

$Ca_v1.3$ L-type voltage-sensitive calcium channels are expressed in dopaminergic neurons in the substantia nigra, where they activate at subthreshold membrane potentials and drive slow oscillating potentials that underlie pacemaker activity and tonic dopamine release. This effect has been proposed to require fluctuations in calcium concentration and activation of calcium-sensitive potassium channels. But Putzier et al. demonstrate that calcium influx through these channels is not necessary to produce pacemaker activity. Inhibiting $Ca_v1.3$ channels eliminated pacemaker activity in midbrain slices from rats, but the activity was restored by simulating the current produced by the channels with the dynamic clamp, which does not involve calcium flux. By taking advantage of the ability to alter various electrical properties of the virtual current independently and comparing the pacemaking ability of altered conductances to those of virtual leak channels and NMDA receptors, the authors determined that the half-maximal activation voltage ($V_{1/2}$) of $Ca_v1.3$ is the critical feature that enables them to support pacemaker activity.

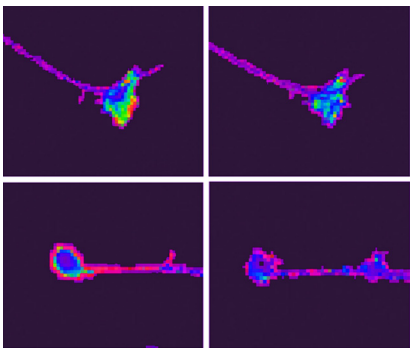
▲ Development/Plasticity/Repair

cAMP Activates Distinct Pathways in Embryonic and Neonatal Neurons

Andrew J. Murray, Steven J. Tucker, and Derryck A. Shewan

(see pages 15434–15444)

Developing axons are guided to their targets by attractive and repulsive cues that act on the growth cone. Some cues, including netrin-1, attract growth cones early in development, but later repel them. This switch in responsiveness is associated with decreasing cAMP levels as development proceeds; artificially increasing cAMP levels late in development switches the response from repulsion back to attraction. Murray et al. identified downstream effectors that mediate the effects of different cAMP concentrations: protein kinase A (PKA) and the guanine nucleotide exchange factor Epac. Epac requires higher cAMP levels for activation than PKA and therefore was activated by netrin-1 in neurons from embryonic, but not neonatal rats. Knockdown of Epac in embryonic neurons caused growth cones to turn away from instead of toward netrin-1, but had no effect on postnatal neurons. In contrast, knockdown of PKA did not alter growth cone responses in embryonic neurons, but switched repulsion to attraction in postnatal neurons.



Fluorescence resonance energy transfer reveals that netrin-1 (right panels) increases (indicated by darker color) activity of Epac in embryonic neurons (top) and of PKA in neonatal neurons (bottom). See the article by Murray et al. for details.

■ Behavioral/Systems/Cognitive

Monkeys Weight Information by Reliability

Christopher R. Fetsch, Amanda H. Turner, Gregory C. DeAngelis, and Dora E. Angelaki

(see pages 15601–15612)

When integrating information from multiple sources to assess a situation, the optimal strategy is to weight information from each source according to its reliability. It has been hypothesized that animals use this strategy when integrating information from multiple sensory modalities. This has been demonstrated for humans in self-motion detection experiments in which the relative reliability of visual and vestibular information is systematically varied. In such cases, people update their estimates of each modality's reliability on each trial and judge heading direction using the updated values. Experiments by Fetsch et al. suggest that monkeys use a similar strategy. Vestibular stimulation was produced by moving the monkey, while visual stimuli simulated movement through clouds of dots. The reliability of visual stimuli was manipulated by varying the coherence of dot movement. The monkeys' report of perceived self-motion showed that they continually updated their weighting of visual and vestibular information, although the vestibular information was given more weight than predicted.

♦ Neurobiology of Disease

BDNF Regulates SORLA Expression

Michael Rohe, Michael Synowitz, Rainer Glass, Steven M. Paul, Anders Nykjaer, et al.

(see pages 15472–15478)

Sorting-protein-related receptor with A-type repeats (SORLA) regulates trafficking of vesicles containing amyloid precursor protein (APP) between the trans-Golgi network and early endosomes. When SORLA levels are low—which occurs in sporadic cases of Alzheimer's disease—more APP is transported to intracellular compartments containing β-secretase, which cleaves APP to form the toxic amyloid-β species, $A\beta_{40}$. Rohe et al. have found that SORLA expression levels are regulated by brain-derived neurotrophic factor (BDNF). BDNF-deficient mice had lower SORLA expression compared to wild-type. Bath application of BDNF increased levels of SORLA and decreased levels of $A\beta_{40}$ in cultured neurons from wild-type mice, but did not reduce $A\beta_{40}$ in SORLA-null mice. Similarly, BDNF reduced $A\beta_{40}$ *in vivo* in wild-type mice but not in SORLA-deficient mice. Because BDNF has been shown to increase APP levels, the authors suggest that simultaneous upregulation of SORLA serves to sequester excess APP in the trans-Golgi network, preventing it from entering the toxic amyloidogenic pathway.