This Week in The Journal

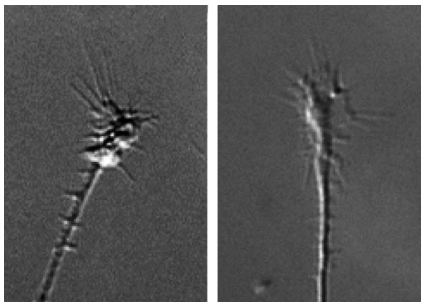
Cellular/Molecular

Asymmetric Endocytosis and Exocytosis Steer Growth Cones

Takuro Tojima, Rurika Itofusa, and Hiroyuki Kamiguchi

(see pages 7165–7178)

As axons grow, the growth cone at their tip explores the environment. Contact with external guidance cues leads to calcium influx, which promotes growth either toward or away from the cue. Attractive cues promote microtubule extension and membrane insertion via exocytosis, whereas repulsive cues trigger microtubule disassembly and membrane endocytosis. Tojima et al. have been investigating how calcium influx leads to these opposite downstream effects. They previously reported that the calcium-dependent phosphatase calcineurin was required to induce asymmetric endocytosis during repulsive responses in chick neurons, whereas attractive cues induced exocytosis. They now demonstrate that attractive and repulsive turning require an imbalance of endocytosis and exocytosis, and that equalizing these processes across the growth cone results in straight growth. They further show that PIPKIγ90, a protein dephosphorylated by calcineurin, was required for endocytosis during repulsive responses. In contrast, attractive cues activated calcium-calmodulin-dependent kinase CaMKII, leading to downstream activation of Cdk5, which phosphorylated and thus inhibited PIPKIγ90. This reduced endocytosis, so exocytosis prevailed.



Axons turn toward a gradient of an exocytosis stimulator (left) or an endocytosis inhibitor (not shown), but if opposing gradients are presented, the axon grows straight (right). See the article by Tojima et al. for details.

Systems/Circuits

Learning Involves Increases and Decreases in Simple-Spike Rate

Yan Yang and Stephen G. Lisberger

(see pages 7077–7090)

Parallel-fiber inputs to Purkinje cells (PCs) modulate simple-spike (SS) rate, thus refining movements. During visual pursuit, for example, increased SS rate in PCs speeds eye movement in the PCs' "on direction", whereas decreases in SS rate are associated with movement in the PCs' "off direction". Inaccurate pursuit is communicated to PCs via climbing fibers, which evoke complex spikes (CSs) that depress SS rate. After repeated stimulation of climbing fibers, long-term depression occurs at parallel-fiber inputs, and this is thought to contribute to motor learning. However, plasticity at other synapses is probably involved as well. Yang and Lisberger examined where and when plasticity occurs over multiple trials of a pursuit task in which the target changed direction at a specific time. They found that when a CS occurred on one trial, the cell's SS rate decreased in anticipation of the direction change on the next. This suppression facilitated long-term learning, which eventually involved potentiation of SS rate in other PCs that exhibited few CSs.

Behavioral/Cognitive

Gut Feelings Can Cause Anxiety

Melanie Klarer, Myrtha Arnold, Lydia Günther, Christine Winter, Wolfgang Langhans, et al.

(see pages 7067–7076)

Feelings of anxiety or dread are often accompanied by unpleasant sensations in the gut, which is a likely origin of the expression "gut feeling". Autonomic outflow from the CNS probably produces some of these gut sensations, but experiments by Klarer et al. suggest that the opposite causative relationship also exists; that is, gut sensations can contribute to feelings of anxiety. Rats that underwent subdiaphragmatic vagal deafferentation (SDA), which eliminates all abdominal vagal afferents to the CNS while sparing half of the vagal efferents, exhibited less anxiety-like behavior than sham-operated rats. Specifically, they spent more time in the open arms of an elevated plus maze, entered the center of an open arena more frequently, and were quicker to eat a novel food. In contrast, extinction of a learned fear response was slower in SDA-treated rats than in controls. Consistent with the latter effect, SDA-treated rats had increased GABA levels in the ventral prefrontal cortex, an area involved in mediating extinction of learned fear.

Neurobiology of Disease

Vitamin D Increases β-Amyloid Clearance in Mice

Matthew R. Durk, Kyung Han, Edwin C. Y. Chow, Rosemary Ahrens, Jeffrey T. Henderson, et al.

(see pages 7091–7101)

The importance of vitamin D in calcium homeostasis and bone growth has long been recognized, but it has other important roles as well, particularly in immune function and cell proliferation. Vitamin D exerts its effects primarily by binding to vitamin D receptors (VDRs), which regulate gene transcription. In the brain, VDRs regulate expression of neurotrophins, calcium-binding proteins, voltage-gated calcium channels, and other genes, thus influencing brain development. Vitamin D deficiency during development has been proposed to increase the risk of several neurodevelopmental disorders, and low vitamin D levels occur in people with some neurodegenerative diseases, including Alzheimer's disease (AD). Durk et al. now report that vitamin D supplements might be beneficial in treating AD. In mice, vitamin D treatment increased the expression of P-glycoprotein, which helps transport β-amyloid across the blood–brain barrier, and it reduced β-amyloid levels in a mouse model of AD, leading to improved performance on a conditioned fear memory test. This effect was blocked by inhibiting P-glycoprotein function.