This Week in The Journal

Cellular/Molecular

Protons from Synaptic Vesicles Block Calcium Channels

Soyoun Cho and Henrique von Gersdorff

(see pages 15877–15887)

H^+-ATPases pump protons into the lumen of vesicles, creating an electrochemical driving force that is required for neurotransmitter uptake. When synaptic vesicles fuse with the synaptic membrane, protons are released into the synaptic cleft, causing transient acidification. The amount of acidification depends on the number of vesicles released and the size and buffering capacity of the synaptic cleft, and the effects of acidification depend on the pH sensitivity of synaptic proteins. Cho and von Gersdorff report that multivesicular release at ribbon synapses of frog auditory hair cells leads to acidification of the synaptic cleft sufficient to cause a transient block of L-type calcium channels. This effect was reduced by reducing synchronous vesicle release and by increasing the extracellular buffering capacity. Because presynaptic calcium influx drives vesicle release, proton-mediated calcium-channel block affected neurotransmission at these synapses: when hair cells were stimulated at their characteristic frequency, the first spike evoked large EPSCs in postsynaptic fibers, but subsequent EPSCs were strongly depressed.

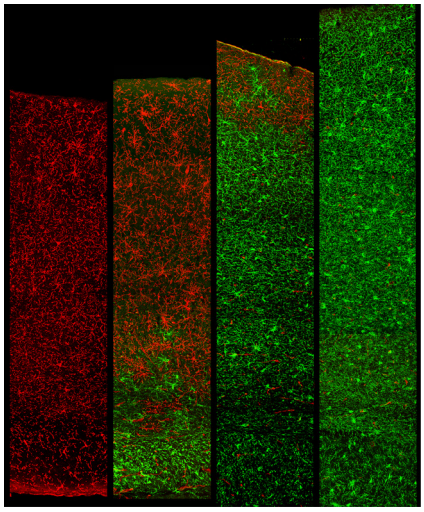
Development/Plasticity/Repair

Human Glial Progenitors Replace Endogenous Glia in Mice

Martha S. Windrem, Steven J. Schanz, Carolyn Morrow, Jared Munir, Devin Chandler-Militello, et al.

(see pages 16153–16161)

Human astrocytes differ morphologically and functionally from rodent astrocytes: human astrocytes are larger, more complex, more numerous, and have faster calcium waves than mouse astrocytes. The significance of such differences has been demonstrated by transplanting human fetal glial progenitor cells (hGPCs) into mice: this leads to enhanced long-term potentiation and improved performance on learning tasks. Windrem et al. now show that when transplanted into periventricular and



Transplanted human GPCs (green) proliferate and expand to populate the cortex, replacing mouse GPCs (red). From left to right: 3 months, no transplant; 3 months after transplant; 8 months after transplant; 12 months after transplant. See the article by Windrem et al. for details.

callosal sites in neonatal mouse forebrain, hGPCs proliferate and spread throughout the CNS from the forebrain to the spinal cord. The advancing front of hGPCs displaced mouse GPCs with little intermingling, and by 12 months, hGPCs had nearly completely replaced mouse GPCs throughout the gray and white matter. Interestingly, the size of glial populations remained stable as hGPCs proliferated and differentiated into astrocytes or oligodendrocytes. hGPC-derived astrocytes gradually replaced mouse astrocytes during the normal turnover process, but few human oligodendrocytes were produced unless mice were genetically deficient in myelin.

Systems/Circuits

IL-6 Induces Fever via Brain Endothelial Cells

Anna Eskilsson, Elahe Mirrasekhian, Sylvie Dufour, Markus Schwaninger, David Engblom, et al.

(see pages 15957–15961)

When circulating macrophages encounter pathogens, they secrete cytokines, which trigger immune responses. Some cytokines, including interleukin-6 (IL-6), bind to receptors in the brain, leading to upregulation of cyclooxygenase-2 (COX-2), the rate-limiting enzyme for prostaglandin E2 synthesis. Prostaglandin E2, in turn, acts on thermoregulatory neurons in the hypothalamic preoptic area, contributing to the generation of fever. Global knockout of IL-6 receptors prevents the induction of fever in response to inflammatory agents such as lipopolysaccharide (LPS). Eskilsson et al. now report that knocking out IL-6 receptors selectively in neural cells did not affect the pyrogenic response to peripherally injected LPS. In contrast, knocking out IL-6 receptors selectively in brain endothelial cells greatly diminished both COX-2 upregulation and temperature elevation after LPS injection. The authors propose that activation of IL-6 receptors on brain endothelial cells leads to COX-2 upregulation via the transcription factor STAT3. Consistent with this, knocking out STAT3 in brain endothelial cells reduced the pyrogenic response to LPS.

Neurobiology of Disease

Dopamine Depletion Affects Firing Patterns in Motor Thalamus

Clémentine Bosch-Bouju, Roseanna A. Smither, Brian I. Hyland, and Louise C. Parr-Brownlie

(see pages 15836–15850)

Motor thalamus has a central role in the control of complex movement, receiving input from motor cortex, basal ganglia, and cerebellum and projecting back to motor cortex. In Parkinson's disease, degeneration of midbrain dopamine neurons disrupts activity in the basal ganglia and cortex, but how these changes affect activity in motor thalamus is unclear. Bosch-Bouju et al. addressed this question by recording from motor thalamus in behaving rats. The overall firing rate of motor-thalamic neurons was higher in rats in which toxin injections had killed dopamine neurons than in controls, both when rats explored an open arena and when they performed a reaching task; yet fewer neurons in dopamine-depleted animals exhibited burst spiking during exploration. In addition, firing patterns during reaching differed in dopamine-depleted rats and controls: in controls, the activity of many neurons increased near the end of the reach and most neurons were inhibited after the reach ended. The inhibition at reach end was greatly reduced in dopamine-depleted rats.