This Week in The Journal

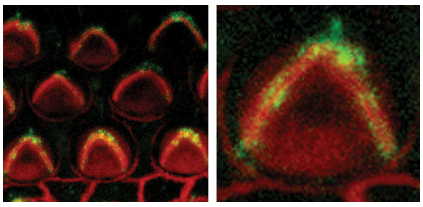
● Cellular/Molecular

Mechanotransduction Requires Cadherin–Protocadherin Interaction

Andrea Lelli, Piotr Kazmierczak, Yoshiyuki Kawashima, Ulrich Müller, and Jeffrey R. Holt

(see pages 11259–11269)

Auditory hair cell stereocilia are connected by thin, stiff filaments called tip links, which extend from the top of each stereocilium to the sides of taller adjacent ones. The filaments are formed by N-terminal interactions between protocadherin 15 (PCDH15), which extends from the shorter stereocilium, and cadherin 23 (CDH23), which extends from the taller one. Disrupting the CDH23–PCDH15 interaction by reducing extracellular calcium makes hair cells unresponsive to mechanical stimulation, and restoring calcium restores normal structure and function, suggesting that tip links are essential for mechanotransduction. But until now, direct physiological evidence linking CDH23 and PCDH15 to mechanotransduction has been lacking. Lelli et al. found that blocking CDH23–PCDH15 interactions with protein fragments during *in vitro* development diminished mechanotransduction in mouse outer hair cells. Likewise, although fragments did not affect mechanotransduction in intact cells, after calcium levels were reduced and then restored, protein fragments prevented both formation of normally oriented tip links and full recovery of mechanotransduction.



Stereocilia of mouse outer hair cells labeled with an actin-binding protein (red) and fragments of PCDH15 (green). The fragments bind to CDH23 filaments after tip links are disrupted, thereby inhibiting both tip link reformation and mechanotransduction recovery. Right panel shows higher-magnification view. See the article by Lelli et al. for details.

▲ Development/Plasticity/Repair

Potassium Channels Prevent Spiking Induced by Asynchronous Release

Hua Yang and Matthew A. Xu-Friedman

(see pages 11466–11475)

Action potentials elicit two phases of vesicle release at nerve terminals: a fast, synchronous phase triggered by a fast calcium transient, and a delayed, asynchronous phase mediated by residual calcium. Asynchronous release that produces superthreshold EPSPs will reduce the precision of postsynaptic spike timing, which would be problematic in systems such as the auditory system that use precise timing to encode information. Nonetheless, prolonged, high-frequency activity in auditory nerves causes presynaptic calcium buildup and significant asynchronous release at the calyx of Held synapse. Yang and Xu-Friedman show that this asynchronous release triggers spiking in postsynaptic neurons in young mice before hearing onset, thus increasing the temporal variability of spikes. After hearing onset, however, although asynchronous release occurs and can elicit spikes if synchronous release is absent, it does not normally trigger postsynaptic spikes. This is because synchronous release activates low-voltage-activated potassium channels, which are upregulated during development and suppress spiking.

■ Behavioral/Systems/Cognitive

Learning to Delay Responses Increases Prelimbic AMPA Currents

Scott J. Hayton, Matthew Lovett-Barron, Eric C. Dumont, and Mary C. Olmstead

(see pages 11493–11500)

It is often necessary to refrain from performing a desired action until an appropriate time: inability to do so contributes to drug addiction, compulsive behaviors, and other psychiatric conditions. Because the activity of medial prefrontal cortex (mPFC) neurons increases while responses are actively inhibited and blocking this activity increases premature responses, the mPFC is thought to mediate response inhibition. Hayton et al. report that as rats learned to withhold responses until a specific cue was given, the AMPA receptor-mediated component of layer II/III-evoked EPSCs in layer 5 pyramidal neurons in the mPFC progressively increased. In contrast, when rats learned that delayed responding was no longer required, response inhibition stopped and AMPA/NMDA ratios returned to baseline. Increases in AMPA/NMDA ratio occurred specifically in neurons in the prelimbic region of mPFC that project to the ventral striatum. Neurons in infralimbic mPFC and prelimbic neurons that projected to the amygdala or dorsal striatum were unaffected.

♦ Neurobiology of Disease

β-Amyloid Inhibits Tumor-Induced Angiogenesis

Daniel Paris, Nowel Ganey, Magdalena Banasiak, Vincent Laporte, Nikunj Patel, et al.

(see pages 11251–11258)

The nervous and circulatory systems are tightly linked: neuronal activity causes vasodilation and vasoconstriction, which alter blood flow; neurons, glia, and endothelial cells cooperate to form the blood–brain barrier; many molecules promote proliferation, migration, differentiation, and survival of both neurons and endothelial cells; and endothelial cells regulate proliferation and survival of neural precursor cells. It is not surprising, therefore, that many neurodegenerative diseases, including Alzheimer's disease (AD), are associated with cerebrovascular dysfunction. For example, patients with AD have more vascular damage and lower microvessel density than do healthy old people. Paris et al. add to increasing evidence that angiogenesis is impaired in AD by implanting glioma cells—which proliferate rapidly and stimulate vascularization—into the brains of mice expressing AD-associated mutations. Tumor volume and vascular density within tumors was greatly reduced in the AD-model mice compared with wild type. This effect was likely caused by soluble β-amyloid, which inhibited capillary formation in culture.