This Week in The Journal

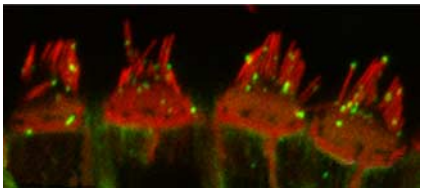
● Cellular/Molecular

Hair-Cell Tip-Link Anchors

Zhigang Xu, Anthony W. Peng, Kazuo Oshima, and Stefan Heller

(see pages 11269–11276)

Mechanical deflection of the stereocilia on hair cells opens transduction channels and thus modulates neurotransmitter release. Each stereocilium is connected to an adjacent stereocilium by a rigid structure called a tip link, which is composed of cadherin 23 and protocadherin 15. Deflection of stereocilia increases tension in the tip link, which is thought to interact with intracellular scaffolding proteins to pull open a transduction channel. Few of the intracellular proteins involved in hair-cell mechanotransduction have been identified. By screening for proteins that interact with the intracellular domain of cadherin 23, Xu et al. have found a scaffolding protein that may help to structure the intracellular transduction complex. The protein, MAGI-1, is a membrane-associated guanylate kinase that has multiple protein-binding domains. In other cells, MAGI-1 interacts with cytoskeletal proteins to form a strong mechanical backbone. In stereocilia, it could couple the tip link to the actin core.



MAGI-1 (green), a tip-link-associated scaffolding protein, is expressed in a punctate pattern in mouse cochlear outer hair cells. See the article by Xu et al. for details.

▲ Development/Plasticity/Repair

Linking Extracellular Cues to Cytoskeletal Changes

Catherine Pawson, Benjamin A. Eaton, and Graeme W. Davis

(see pages 11111–11123)

Synaptic development is regulated by extracellular cues that bind to receptors on axon terminals and trigger localized changes in actin and microtubules. Many of the extracellular cues, receptors, and cytoskeletal proteins involved in this process have been identified. In comparison, little is known about the molecules that link membrane-associated cues to cytoskeletal changes. Using genetic manipulations and a newly developed technique in which active microtubule tips are selectively labeled with GFP, Pawson et al. have identified the protein encoded by the *diaphanous* gene as one such link. Diaphanous protein is expressed presynaptically in *Drosophila* motor neurons, and *diaphanous* knock-out reduced the number of synaptic boutons at the neuromuscular junction. Genetic rescue experiments suggested that the receptor tyrosine phosphatase Dlar (which is activated by extracellular proteoglycan molecules) activates the guanine nucleotide exchange factor Trio, which activates the GTPase that activates Diaphanous, which promotes actin assembly and stabilizes microtubules.

■ Behavioral/Systems/Cognitive

No Evidence of Human Mirror Neurons

Ilan Dinstein, Justin L. Gardner, Mehrdad Jazayeri, and David J. Heeger

(see pages 11231–11239)

Mirror neurons, which respond both when an action is observed and when the same action is performed, were discovered using single-cell recordings in premotor cortex of monkeys. Mirror neurons are thought to be involved in action understanding and imitation. They have been hypothesized to underlie the evolution of language, and their dysfunction has been proposed to underlie autism. Direct evidence of mirror neurons—which requires recording from single neurons during action observation and performance—has not been obtained in humans, however, so assigning them a role in human cognitive functions may be premature. Seeking indirect evidence for human mirror neurons, Dinstein et al. have performed multivariate pattern classification on functional magnetic resonance imaging data. Specific, repeatable patterns of activity were detected in the presumptive mirror-neuron region of human cortex in response to observed or performed actions. Importantly, however, observation and performance regions did not overlap, suggesting that relatively few mirror neurons were present.

♦ Neurobiology of Disease

Cannabinoids and Cancer Pain

Iryna A. Khasabova, Sergey G. Khasabov, Catherine Harding-Rose, Lia G. Coicou, Bryan A. Seybold, Amy E. Lindberg, Christopher D. Steevens, Donald A. Simone, and Virginia S. Seybold

(see pages 11141–11152)

The endocannabinoid anandamide is derived from postsynaptic membrane precursors and diffuses retrogradely across the synapse to activate presynaptic cannabinoid receptors, leading to reduced presynaptic calcium influx and decreased neurotransmitter release. In nociceptive pathways, cannabinoid-mediated inhibition modulates sensitivity to pain. This week, Khasabova et al. show that reduction of endogenous anandamide levels contributes to cancer-related pain in mice. Injection of bone cancer cells increased expression of the enzyme that catabolizes anandamide, fatty acid amide hydrolase (FAAH), in the dorsal root ganglion. Increased FAAH activity reduced the levels of anandamide in sensory neurons and skin, and it increased sensitivity to pain. Injection of an FAAH inhibitor increased anandamide levels and produced long-lasting reduction of pain responses. Although cannabinoids are also effective analgesics, their usefulness is limited by their rapid catabolism by FAAH. Therefore, FAAH inhibitors may provide a more effective treatment for neuropathic and cancer-related pain.