This Week in The Journal

Cellular/Molecular

Nicotine Can Potentiate Inactive Synapses

Andrew W. Halff, David Gómez-Varela, Danielle John, and Darwin K. Berg

(see pages 2051–2064)

Long-term potentiation (LTP) occurs when spikes in a glutamatergic neuron are paired with depolarization of a postsynaptic neuron, leading to calcium influx through activated NMDA receptors. This ultimately leads to increases in AMPA receptor (AMPAR) levels at postsynaptic sites and thus produces long-lasting increases in EPSP amplitude. Nicotine enhances learning in part by enhancing LTP induction in the hippocampus. But Halff et al. discovered that nicotine (at levels produced by repetitive smoking and transdermal nicotine patches) increased the frequency and amplitude of miniature EPSCs in hippocampal neurons even when action potentials were blocked. Like classic LTP, nicotine-induced potentiation required calcium influx and was accompanied by increases in the density of AMPARs in dendritic spines. Unlike classic LTP, however, it did not require activation of NMDA receptors or insertion of AMPARs. Instead, it required activation of acetylcholine receptors containing α7 subunits, lateral diffusion of GluA1-containing AMPARs within the membrane, and finally, anchoring of AMPARs by scaffolding proteins of the PSD-95 family.

Systems/Circuits

Inhibiting Purkinje Cells Elicits Motor Responses

Shane A. Heiney, Jinsook Kim, George J. Augustine, and Javier F. Medina

(see pages 2321–2330)

The cerebellum is essential for fine-tuning and coordinating movements and for associative conditioning of eye blink and other reflexes. Purkinje cells, the sole output cells of the cerebellar cortex, fire tonically at high rates and inhibit target neurons in the vestibular and deep cerebellar nuclei (DCN). Changes in Purkinje cell firing rates are associated with changes in movement speed and duration, with pauses in firing coinciding with movement. Heiney et al. demonstrated that such pauses shape motor responses by causing disinhibition of DCN neurons. In mice that expressed channelrhodopsin in interneurons that inhibit Purkinje cells, photostimulation led to rapid reductions in Purkinje cell firing and subsequent increases in firing of DCN neurons. Remarkably, photostimulation elicited motor responses, including eye closing, mouth opening, and vibrissal movements, depending on the stimulus location. Furthermore, varying the intensity and duration of photostimulation caused graded reductions in Purkinje cell firing, graded increases in DCN firing, and corresponding increases in the speed or duration of movements.

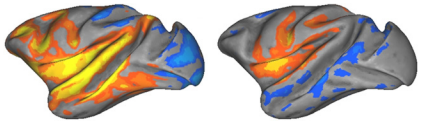
Behavioral/Cognitive

DHA Deficiency Disrupts Cortical Processing

David S. Grayson, Christopher D. Kroenke, Martha Neuringer, and Damien A. Fair

(see pages 2065–2074)

Docosahexaenoic acid (DHA) is a polyunsaturated omega-3 fatty acid that is enriched in the CNS, where it helps maintain the fluidity of membranes, acts as a secondary messenger, and is a precursor for anti-inflammatory molecules. DHA is particularly enriched in the outer segments of rod photoreceptors, and DHA deficiency—which occurs with inadequate dietary intake—impairs vision and has been linked to macular degeneration. To determine whether DHA deficiency also affects subsequent stages of visual processing, Grayson et al. used functional magnetic resonance imaging to examine activity in anesthetized adult macaques that had been fed DHA-enriched or DHA-free diets since birth. Although DHA-deficient monkeys could see, resting-state activity in the lateral geniculate nucleus and superior colliculus was less correlated with that in the primary visual cortex of these monkeys than in DHA-fed monkeys, suggesting functional connections were abnormal. In fact, correlations between many cortical regions were weaker in DHA-deficient than in DHA-fed monkeys, suggesting DHA-deficiency disrupts functional organization throughout the brain.



Correlation between activity in dorsal anterior insula and other association cortices differed between DHA-fed monkeys (left) and DHA-deficient monkeys (right). There was greater correlation among higher-order associational cortical areas and greater negative correlations with primary sensory cortex in the DHA group. See the article by Grayson et al. for details.

Neurobiology of Disease

α-Synuclein Aggregates First Appear in Synaptic Terminals

Kateri J. Spinelli, Jonathan K. Taylor, Valerie R. Osterberg, Madeline J. Churchill, Eden Pollock, et al.

(see pages 2037–2050)

Intracellular inclusions composed primarily of α-synuclein aggregates are found in neurons in several neurodegenerative diseases, such as Parkinson's. α-synuclein is normally present in cytoplasm and associated with cellular membranes, including those of synaptic vesicles. Although α-synuclein has been proposed to have roles in vesicle trafficking and fusion, its functions are poorly understood. To investigate how α-synuclein aggregation might relate to neuropathology, Spinelli et al. examined the mobility of GFP-labeled human α-synuclein (syn-GFP) in mouse cortical layers 2/3 *in vivo*, using fluorescence recovery after photobleaching. In cell bodies, fluorescence recovery was nearly as fast for syn-GFP as for unbound GFP, suggesting most somatic α-synuclein is freely diffusible. In surrounding synaptic terminals, however, fluorescence recovery was slower and its time course suggested the presence of three pools: a freely diffusible pool, a less mobile pool likely bound to synaptic vesicles, and an essentially immobile pool that, like α-synuclein aggregates, was resistant to proteinase degradation. The authors conclude that aggregation of α-synuclein begins in synaptic terminals.