This Week in The Journal

● Cellular/Molecular

Disrupting Astrocyte Calcium Transients Does Not Affect Neurons

Jeremy Petravicz, Todd A. Fiacco, and Ken D. McCarthy

(see pages 4967–4973)

Recent reports have suggested that astrocytes regulate neuronal activity by releasing gliotransmitters (e.g., glutamate and ATP) when intracellular calcium is elevated via release from internal stores. Because calcium release is triggered by activation of an IP_3 receptor, Petravicz et al. examined astrocytic calcium changes and neuronal activity in mice lacking IP_3 receptor type 2 (IP_3R2). G-protein-coupled receptors (GPCRs, which increase IP_3 and activate IP_3Rs) were unable to elicit calcium release from internal stores in hippocampal astrocytes from mutant mice, and the astrocytes had no spontaneous calcium oscillations. Nonetheless, neurons appeared completely normal in these mice: no changes were observed in brain cytoarchitecture; pyramidal cell resting membrane potential, resistance, and capacitance; or AMPA- or NMDA-receptor-mediated sEPSCs; and GPCRs elicited normal calcium transients in neurons. These results, together with previous results from the same laboratory, suggest that widespread increases in astrocytic calcium have no detectable effect on neuronal excitatory synaptic activity.

▲ Development/Plasticity/Repair

Reactive Oxygen Species Promote Axon Degeneration

Craig Press and Jeffrey Milbrandt

(see pages 4861–4871)

Several neurodegenerative diseases, like Parkinson's disease (PD), are linked to mitochondrial dysfunction, which decreases ATP production and increases reactive oxygen species (ROS). Likewise, disrupting mitochondrial function can cause neurodegeneration; for example, the pesticide rotenone, which inhibits mitochondrial electron transport, produces PD-like symptoms in animals and causes axonal degeneration in cultured dorsal root ganglion (DRG) neurons. Press and Milbrandt now report that expression of nicotinamide mononucleotide adenylyltransferase (Nmnat) in DRG neurons slows rotenone-induced axonal degeneration. The protective effects of Nmnat were likely due to reduced accumulation of ROS, since Nmnat had little effect on ATP levels in the neurons. Furthermore, other treatments that increased ROS led to axonal degeneration, treatments that reduced ROS prevented degeneration, and long-term depletion of ATP produced no sign of degeneration. The results support the hypothesis that ROS accumulation is involved in many neurodegenerative processes, including those related to mitochondrial dysfunction.

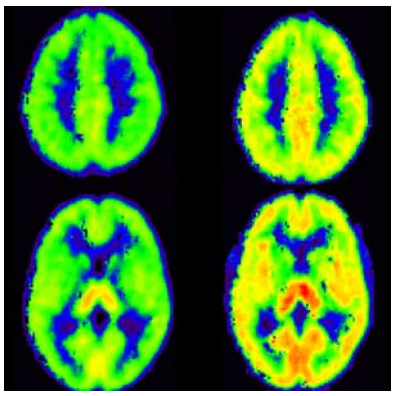
■ Behavioral/Systems/Cognitive

Violent Tendencies Are Linked to Monoamine Oxidase

Nelly Alia-Klein, Rita Z. Goldstein, Aarti Kriplani, Jean Logan, Dardo Tomasi, Benjamin Williams, Frank Telang, Elena Shumay, Anat Biegon, Ian W. Craig, Fritz Henn, Gene-Jack Wang, Nora D. Volkow, and Joanna S. Fowler

(see pages 5099–5104)

Low brain levels of monoamine oxidase A (MAO A)—the enzyme that metabolizes serotonin, dopamine, and norepinephrine—are correlated with an increased disposition toward physical violence, according to this week's report by Alia-Klein et al. The authors used positron emission tomography to measure MAO A activity throughout the brains of healthy men, and compared these levels to the subjects' scores on different traits defined by the Multidimensional Personality Questionnaire. They found an inverse relationship between aggression scores (which are good predictors of future violence) and MAO A activity in many cortical and subcortical regions. MAO A activity explained 30% of the variability across individuals. This relationship held regardless of *MAOA* genotype, consistent with previous studies that found a low-*MAOA* genotype correlated with high aggression scores only in subjects who were abused as children. These results suggest that reduced MAO A activity is associated with abnormal aggressive behavior.



Average brain MAO A activity was lower for the most aggressive subjects (left; $n = 4$) than for the least aggressive patients (right; $n = 5$). See the article by Alia-Klein et al. for details.

♦ Neurobiology of Disease

Cdk5 Regulates the Role of Bcl-2 in Apoptosis

Zelda H. Cheung, Ke Gong, and Nancy Y. Ip

(see pages 4872–4877)

Bcl-2 family proteins, which control permeability of the mitochondrial outer membrane, can promote either cell survival or apoptosis. Cheung et al. now demonstrate that whether Bcl-2 promotes survival or death is regulated partly by its phosphorylation by the cyclin dependent kinase Cdk5. Cdk5, which is active primarily in brain, is involved in neuronal development, and its deregulation is thought to play a role in neurodegenerative diseases. Cheung et al. show that disrupting Cdk5 activity by various means in cultured retinal ganglion cells (RGCs) led to increased apoptosis, and this effect was mediated by phosphorylation of Bcl-2. While overexpression of Bcl-2 in RGCs promoted survival, elimination of the Cdk5 phosphorylation site reversed the protective effects. Furthermore, overexpression of Bcl-2 in HEK293T cells, in which Cdk5 is inactive, induced apoptosis, but this effect was reduced when Cdk5 was activated and was absent when Bcl-2 lacking the Cdk5 phosphorylation site was expressed.