This Week in The Journal

● Cellular/Molecular

Appoptosin Induces Apoptosis Unless Restrained by APP

Han Zhang, Yun-wu Zhang, Yaomin Chen, Xiumei Huang, Fangfang Zhou, et al.

(see pages 15565–15576)

Apoptosis, the programmed cell-death pathway, depends on interactions between signaling molecules, not all of which have been identified. Zhang et al. have now identified one of those factors as appoptosin. They identified the proapoptotic molecule, a mitochondrial solute carrier until now known as SLC25A38, through a yeast two-hybrid screen of a human fetal cDNA library. As bait, they used amyloid precursor protein (APP) intracellular domain (AICD), because AICD has neurotoxic and proapoptotic effects and was thought to interact with proapoptotic molecules. The authors determined that appoptosin regulates the intrinsic type of caspase-dependent apoptosis through its role in biosynthesis of heme, which is disrupted in Alzheimer's disease (AD) and other neurodegenerative diseases. In brains of human AD patients and stroke victims, appoptosin levels were much higher than in healthy brains, indicating a proapoptotic role in AD- and stroke-related processes. Overexpression of appoptosin led to activation of caspases, and reduction was protective against Aβ, suggesting it as a therapeutic target.

▲ Development/Plasticity/Repair

Thalamic Molecules Promote Cortical Dendrite Growth

Haruka Sato, Yuma Fukutani, Yuji Yamamoto, Eiichi Tatara, Makoto Takemoto, et al.

(see pages 15388 –15402)

The scientific endeavor known as fate mapping—that is, tracing the origins of mature neurons back to their neonatal progenitors in the developing brain—has grown increasingly complex in recent years. Not only intrinsic genetic factors, but also extracellular factors with time, space, and dose dependence, influence developing neurons. Afferent-derived factors are also delivered by inputs from distant brain regions. This week, Sato et al. further our understanding of these external factors by examining those produced by neurons in sensory nuclei of the thalamus that send projections to the multipolar stellate neurons in cortical layer 4. Using microarray data, they first identified a set of thalamus-enriched genes encoding extracellular guidance factors. Neuritin-1 (NRN1) and VGF emerged as instrumental molecules. The factors were transported to axon terminals, where they could potentially be released in developing cortex. In culture, the molecules spurred dendritic growth, and in organotypic slices, stellate but not pyramidal neurons responded to the factors with process outgrowth and improved survival.

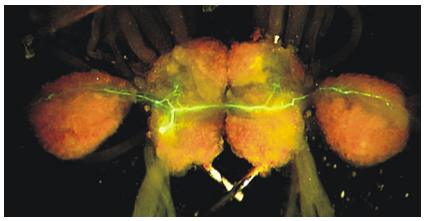
■ Behavioral/Systems/Cognitive

Blocking Axonal Conduction Mediates Prepulse Inhibition

Anne H. Lee, Evgenia V. Megalou, Jean Wang, and William N. Frost

(see pages 15262–15270)

In behavioral terms, "prepulse inhibition" (PPI) describes the phenomenon of a blunted startle response when another stimulus—even from a different modality—precedes the scare. In humans, PPI is thought to help focus attention in the midst of distraction. PPI deficits have been linked to the psychosis of schizophrenia. Mitigating fright might seem like complex sensory processing, but this fast inhibition emerges even in the very simplest nervous systems, like that of the marine invertebrate *Tritonia diomedea*. Lee et al. previously identified an inhibitory interneuron called Pleural-9 (Pl-9) that dampened the startle response in *Tritonia* by decreasing presynaptic neurotransmitter release from an afferent onto its target cell. Now these authors describe another way the Pl-9 interloper shorts the circuit: by blocking conduction of propagating action potentials in the afferent axon at an axoaxonic connection. Though not the first description of this powerful inhibitory trick, the unusual axoaxonic action potential block might underlie network gating in other pathways as well.



A Pleural-9 inhibitory interneuron filled with carboxyfluorescein sends a bilateral axonal process to either side of the brain of the invertebrate *T. diomedea*. See the article by Lee et al. for details.

♦ Neurobiology of Disease

Reducing Polyphosphoinositide Phosphatase Levels May Treat AD

Laura Beth J. McIntire, Diego E. Berman, Jennifer Myaeng, Agnieszka Staniszewski, Ottavio Arancio, et al.

(see pages 15271–15276)

Although Alzheimer's disease (AD) pathology has been closely linked to accumulation of amyloid-β (Aβ), the root of the peptide's toxicity remains elusive. Mounting evidence suggests disruption of lipid metabolism contributes to synaptic dysfunction and cognitive impairment. In particular, synaptic pools of the signaling phospholipid phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) become depleted in AD. McIntire et al. asked whether targeting synaptojanin 1 (Synj1), a phosphatase that tightly regulates levels of PI(4,5)P2, might be beneficial in AD. In mice expressing an AD-linked mutant of amyloid precursor protein, genetic reduction of Synj1 by half rescued learning and memory deficits. Neurons develop visible dendritic spine abnormalities with increasing Aβ levels; these changes were attenuated in cultured hippocampal neurons from Synj1-haploinsufficient mice. Importantly, the benefits arose independently of amyloid load, suggesting protection from synaptotoxic signaling rather than from Aβ per se. The authors conclude that not only PI(4,5)P2, but phosphoinositides in general, may represent a new class of therapeutic targets in AD.