

This Week in The Journal

● Cellular/Molecular

Dynorphins Interact With Acid-Sensing Ion Channels

Thomas W. Sherwood and Candice C. Askwith

(see pages 14371–14380)

Cation-selective acid-sensing ion channels (ASICs) are activated by large, rapid reductions in pH but are desensitized by smaller, gradual decreases in pH. During ischemia, elevated CO₂ and reduced O₂ concentrations cause acidosis, and the subsequent activation of ASIC1a leads to excitotoxic cell death. Steady-state desensitization, which is enhanced by the tarantula toxin peptide PcTx1, protects neurons from ischemia-induced death. Sherwood and Askwith found that the opioid peptides dynorphin A and big dynorphin (which comprises dynorphin A and dynorphin B) shifted the threshold for induction of steady-state desensitization of ASIC1a toward lower pH, closer to the activation threshold. Pretreatment with PcTx1 reduced the effects of dynorphin and vice versa, suggesting that dynorphin, like PcTx1, binds directly to the extracellular domain of ASIC1a. Dynorphin and ASIC1a are expressed in overlapping regions of CNS, and both are thought to be involved in nociception and emotional learning, suggesting their interaction might modulate these processes.

▲ Development/Plasticity/Repair

Turtle Helps Segregate Fly Axons Into Columns

Kerry Ferguson, Hong Long, Scott Cameron, Wen-Tzu Chang, and Yong Rao

(see pages 14151–14159)

In the *Drosophila* visual system, projections from photoreceptors of different ommatidia terminate in separate columns in the optic lobe. Studies have suggested that segregation of axons from R7 photoreceptors is mediated by parallel pathways—one involving transcriptional regulation by Activin (a member of the transforming growth factor β family), and another involving repulsive interactions be-

tween cells in different columns. Ferguson et al. provide evidence that the repulsive interactions are mediated in part by homophilic interactions of Turtle, a member of the immunoglobulin superfamily. Mutating Turtle in a subset of cells resulted in abnormal lateral extension both of mutant R7 axons into adjacent wild-type columns and of wild-type R7 axons into columns containing mutant axons. Removing some R7 axons, which increases lateral extension of neighboring axons in wild-type and Activin mutants, decreased abnormal extension in Turtle mutants. Moreover, mutating Turtle along with components of the Activin signaling pathway increased the frequency of mistargeting, suggesting these pathways operate in parallel.

■ Behavioral/Systems/Cognitive

Not-So-Loud Noise Damages Hearing

Sharon G. Kujawa and M. Charles Liberman

(see pages 14077–14085)

It has long been thought that exposure to loud noises damages hearing primarily by killing hair cells, and therefore, that noise levels that do not kill hair cells do not damage hearing. Kujawa and Liberman show that this is not true. They exposed mice to noise that induced

a moderate elevation in the sound level required to activate cochlear afferents but did not kill hair cells. Although neural response thresholds recovered within two weeks, response amplitudes remained lower than those in unexposed mice. The number of presynaptic ribbons in inner hair cells was reduced after noise exposure, and many remaining ribbons were unapposed by afferent terminals. Fiber density in the cochlear nerve was reduced, and gradual degeneration of these axons over the subsequent 2 years ultimately led to death of spiral ganglion neurons. These data indicate that noise can permanently impair hearing without damaging hair cells. So turn that music down!

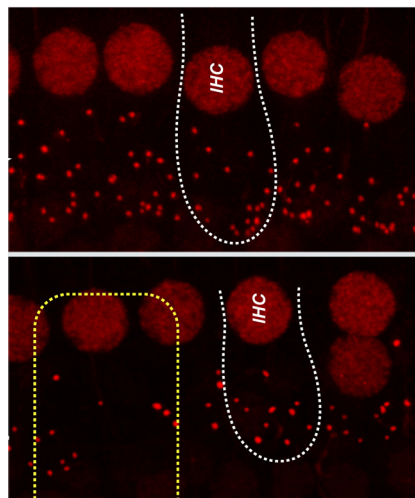
◆ Neurobiology of Disease

Gut Hormone Protects Neurons by Strengthening Mitochondria

Zane B. Andrews, Derek Erion, Rudolph Beiler, Zhong-Wu Liu, Alfonso Abizaid, et al.

(see pages 14057–14065)

Obesity predisposes people to many diseases, including Parkinson's disease (PD). The pathological effects of obesity often result from changes in levels of hormones that regulate energy homeostasis. One such hormone is ghrelin, which is normally secreted by the empty stomach, stimulates eating and weight gain, and is chronically reduced in obese individuals. In addition to regulating energy balance, ghrelin increases mitochondrial proliferation and respiration and promotes synaptogenesis. Ghrelin also increases dopamine release and reduces 1-methyl-4-phenyl-1,2,5,6 tetrahydropyridine (MPTP) neurotoxicity of substantia nigra (SN) dopaminergic neurons. Because mitochondrial dysfunction is thought to play a role in PD, Andrews et al. hypothesized that the neuroprotective effects of ghrelin stem from its effects on mitochondria. Indeed, exogenous ghrelin reduced MPTP-induced dopaminergic cell death and increased mitochondrial proliferation and respiration, but these effects were absent in transgenic mice lacking ghrelin, the ghrelin receptor, or uncoupling protein 2 (UCP2), a mitochondrial protein that reduces accumulation of reactive oxygen species and promotes proliferation.



Noise levels that do not kill inner hair cells (IHCs) can damage hearing by causing loss of synapses (red puncta) and subsequent degeneration of afferent neurons. Yellow dashed line shows region of maximal damage. See the article by Kujawa and Liberman for details.