This Week in The Journal

Cellular/Molecular

$GABA_B$ Receptors Enhance $GABA_A$-Mediated Tonic Currents

Wucheng Tao et al.

(see pages 3738–3743) and

William M. Connelly et al.

(see pages 3780–3785)

GABA can influence neuronal activity through several pathways. Activation of synaptic ionotropic $GABA_A$ receptors ($GABA_A$Rs) containing the α subunit produces rapid, transient inhibition, whereas activation of extrasynaptic $GABA_A$Rs containing the δ subunit (δ-$GABA_A$Rs) produces tonic inhibition that influences neuronal excitability. Activation of presynaptic metabotropic $GABA_B$Rs reduces GABA release, and activation of postsynaptic $GABA_B$Rs produces slow inhibition. Now two groups report that activation of postsynaptic $GABA_B$Rs also enhances tonic inhibition by δ-$GABA_A$Rs. Tao et al. found that the $GABA_B$R agonist baclofen increased currents induced by a δ-$GABA_A$R agonist in rat dentate granule cells, and that this enhancement required G-protein-mediated signaling. Baclofen did not affect synaptic GABA currents or tonic currents in neurons that do not express δ-$GABA_A$Rs. Connelly et al. found that baclofen enhanced tonic currents in thalamocortical neurons and cerebellar granule cells, as well as dentate granule cells. The enhancement required postsynaptic, G-protein-mediated inhibition of protein kinase A, and it did not occur in mice lacking δ-$GABA_A$Rs.

Systems/Circuits

Amygdala Neurons Encode Safety Signals

Susan Sangha, James Z. Chadick, and Patricia H. Janak

(see pages 3744–3751)

In healthy individuals, fear responses are influenced by context. For example, the approach of a strange man on a dark street might provoke fear unless that man is wearing a police uniform. In this case, the uniform is a safety signal, indicating the absence of threat. Sangha et al. reveal that neurons in the basal amygdala respond differentially to cues indicating shock, safety, or reward. Rats learned that one cue signaled impending reward and that another cue signaled impending shock unless it was paired with a third, "safety" cue. The responses of amygdala neurons changed as rats learned the associations. Some were similarly modulated by all three cues, and others responded when one cue was present regardless of whether another cue was presented simultaneously. Importantly, some neurons responded when the shock and safety cues were presented together, but not when the shock cue was presented alone. Thus, the pattern of neuronal activity in the amygdala can discriminate reward, safety, and fear-provoking cues.

Behavioral/Cognitive

Photosensitive Hindbrain Neurons Trigger Movement in Fish

David Kokel, Timothy W. Dunn, Misha B. Ahrens, Rüdiger Alshut, Chung Yan J. Cheung, et al.

(see pages 3834–3843)

Although photoreceptors are best known for their role in vision, nonvisual photoreceptors also exist. In mammals, nonvisual ocular photoreceptors are important for circadian entrainment, and in other vertebrates, nonvisual photoreceptors in the pineal, deep brain, and skin trigger color changes and phototaxis, as well as regulating circadian rhythms. This week, Kokel et al. describe a nonvisual photomotor response (PMR) that occurs transiently in zebrafish embryos. Stimulating dark-adapted embryos with flashes of light any time between 28 and 60 hours after fertilization (hpf) increased coiling and swimming motor patterns; this PMR occurred long before the development of visual pathways (~68 hpf). Although similar behavioral responses were evoked by tactile stimuli, the PMR occurred with a much longer latency and, unlike tactile responses, required supraspinal input. Removal of the hindbrain eliminated the PMR, whereas focally illuminating the hindbrain evoked the response. Inhibiting synthesis of 11-*cis*-retinal inhibited the PMR, suggesting it requires one of the many opsin-family proteins expressed in zebrafish.

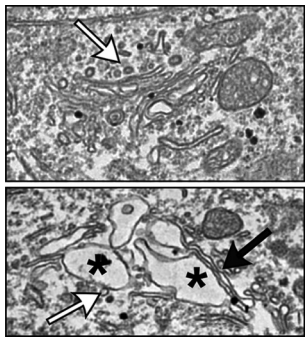
Neurobiology of Disease

Golgi Neutralization Might Underlie Angelman Syndrome

Kathryn H. Condon, Jianghai Ho, Camenzind G. Robinson, Cyril Hanus, and Michael D. Ehlers

(see pages 3799–3814)

After passage through the endoplasmic reticulum, membrane-associated and secreted proteins are transported to the Golgi apparatus, where they become glycosylated and are sorted into vesicles for transport to their final destinations. Golgi compartments are acidic, and loss of acidification disrupts Golgi structure and function. Sialyltransferases, which add sialic acid residues to various proteins and lipids, are particularly sensitive to changes in Golgi pH. Condon et al. have discovered that loss of Golgi acidification may underlie pathology in Angelman syndrome, a neurodevelopmental disorder caused by neuronal loss of the E3 ubiquitin ligase Ube3a. In Ube3a-deficient mice, Golgi compartments were swollen; although Golgi swelling can result from disruption of vesicular trafficking or elevation of intralumenal pH, only the latter was detected in Ube3a-deficient neurons. Consistent with elevated Golgi pH, sialylation of membrane proteins was reduced in the cortex of Ube3a-deficient mice. Notably, protein and/or lipid sialylation is required for several functions disrupted in Angelman syndrome, including neurite outgrowth, synaptogenesis, and myelination.



The Golgi apparatus (white arrows) normally has tightly stacked cisternae with narrow intralumenal spaces (top). But in Ube3a-deficient neurons (bottom), the Golgi has enlarged and distended cisternae (asterisks), often alongside normal-looking cisternae (black arrow). See the article by Condon et al. for details.