This Week in The Journal

Cellular/Molecular

Acetylcholine Activates GABAergic Projections to Cortex

Chun Yang, James T. McKenna, Janneke C. Zant, Stuart Winston, Radhika Basheer, et al.

(see pages 2832–2844)

Brain activity patterns change throughout the day, switching between REM and non-REM sleep and vigilant and inattentive wakeful states. These states are generated by coordinated action in multiple brain areas. The maintenance of attention, for example, depends on cholinergic neurons in the brainstem and basal forebrain that project throughout the cortex. These cholinergic projections form collaterals within the basal forebrain, and Yang et al. found cholinergic terminals surrounding GABAergic neurons in this structure. Some of these GABAergic neurons project to the cortex, providing another pathway by which acetylcholine might influence cortical activity. Indeed, optical activation of cholinergic terminals induced inward currents in cortically projecting GABAergic neurons, and cholinergic agonists activated mixed cation channels in the neurons, increasing their firing rates. The agonist also increased the frequency of spontaneous EPSCs and IPSCs in GABAergic projection neurons. Thus, acetylcholine can regulate the activity of cortically projecting GABAergic neurons both directly and by increasing the excitability of their local excitatory and inhibitory inputs.

Development/Plasticity/Repair

Wingless Protein from Glia Regulates NMJ Development

Kimberly S. Kerr, Yuly Fuentes-Medel, Cassandra Brewer, Romina Barria, James Ashley, et al.

(see pages 2910–2920)

Reversed polarity (Repo) is a transcription factor that regulates glial maturation in *Drosophila*. Using chromatin immunoprecipitation to identify genes regulated by Repo, Kerr et al. were surprised to find several components of the Wingless (Wg)/Wnt signaling pathway. Wg was previously identified as a protein secreted by motor neurons that regulates development of both presynaptic and postsynaptic compartments at neuromuscular junctions (NMJs). Kerr et al. confirmed that neuronally secreted Wg is required for NMJ development, but found that Wg secreted by glia is also essential. Knocking down Wg in either neurons or subperineurial glia increased the size of glutamate receptor clusters at NMJs and increased the amplitude of miniature excitatory junctional potentials (mEJPs), but reduced the amplitude of evoked EJPs. Interestingly, mEJP frequency was increased only when Wg was knocked down in glia, whereas bouton number was reduced only when neuronal Wg was depleted. Therefore, neuronal and glial Wg have partially overlapping roles, but expression in both is required for normal NMJ development.

Behavioral/Cognitive

Human CT Afferents Respond to Caress-Like Stimuli

Rochelle Ackerley, Helena Backlund Wasling, Jaquette Liljencrantz, Håkan Olausson, Richard D. Johnson, et al.

(see pages 2879–2883)

Tactile discrimination (e.g., edge detection, skin deformation, stretch, and vibration) is mediated by low-threshold cutaneous mechanoreceptors that have large myelinated axons and fast conduction speed. But low-threshold mechanoreceptors with slow-conducting unmyelinated axons (C fibers) also innervate the skin. Unlike high-threshold, nociceptive C-fibers, these C-tactile (CT) afferents respond preferentially to pleasurable, light stroking. Their stimulation causes activation of the insular cortex. These properties suggest that CT afferents may have evolved to encode social touch. Seeking evidence for this hypothesis, Ackerley et al. asked how CT afferents respond to stimuli of various speeds (0–30 cm/s) and temperatures (18, 32, and 42°C). Single-unit recordings from human peripheral nerves revealed that CT afferents responded best to stimuli that most resembled a human caress: those at normal skin temperature (32°C) and moving at 3 cm/s. For warm stimuli, moreover, the firing rate of CT afferents was correlated with participants' pleasantness rating of the stimulus, consistent with the hypothesis that these fibers encode pleasant social touch.

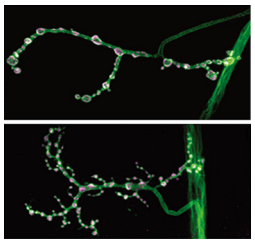
Neurobiology of Disease

Acyl-CoA Synthetase Deletion Impairs Receptor Recycling

Zhihua Liu, Yan Huang, Wen Hu, Sheng Huang, Qifu Wang, et al.

(see pages 2785–2796)

The lipid composition of membranes determines which proteins associate with the membrane, and can also influence protein function. Proper regulation of lipid metabolism and delivery are therefore essential to maintaining cellular function. In fact, several neurological disorders are caused by mutations in proteins that regulate lipid metabolism. For example, mutations in acyl-CoA synthetase long-chain family member 4 (ACSL4), an enzyme important in phospholipid synthesis, causes mental retardation. Several cellular processes, including axonal transport and synaptic transmission, are impaired when the *Drosophila* ortholog of ACSL4 (dAcsl) is knocked out. Liu et al. report that recycling of membrane proteins is also impaired in dAcsl mutants. dAcsl deletion reduced membrane association of Rab11, a GTPase essential in trafficking proteins through recycling endosomes. This in turn curtailed inactivation of BMP receptors, which stimulate growth at neuromuscular junctions. BMP receptor inactivation requires receptor endocytosis and recycling, but after dAcsl deletion, activated BMP receptors accumulated in early endosomes and their continued signaling caused supernumerary synaptic boutons to form.



Motor neurons (green) in anterior segments of fly larvae lacking dAcsl (bottom) have more synaptic boutons (white) than wild-type (top) motor neurons. See the article by Liu et al. for details.