This Week in The Journal

● Cellular/Molecular

GABA-Less Tonic Inhibition

Hong-Jin Shu, Lawrence N. Eisenman, Deepani Jinadasa, Douglas F. Covey, Charles F. Zorumski, and Steven Mennerick
(see pages 6667–6675)

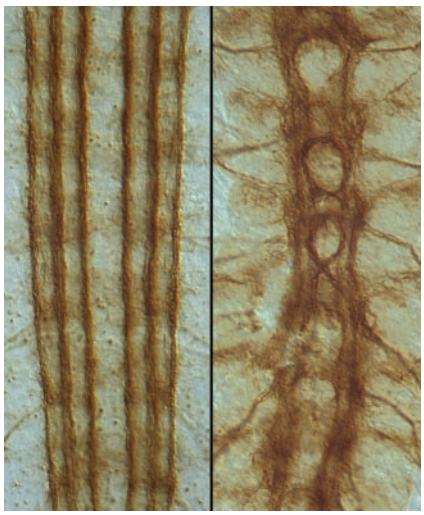
Neuroactive steroids have anesthetic and sedative properties that are attributed to their ability to enhance the activity of $GABA_A$ receptors. However, neurosteroids can also directly gate the $GABA_A$ channel, but supposedly only at concentrations above that required for their behavioral effects. Shu et al. reexamine the functional effects of direct activation by using solitary cultured excitatory hippocampal neurons that express GABA receptors but receive no $GABA_A$-mediated synaptic inputs. In the absence of GABA, the neurosteroid 3α5αP caused a very slowly activating current attributable to direct action on $GABA_A$ channels at concentrations of <1 μM. The authors suggest that the slow rate of current activation and deactivation may have masked this direct effect in previous studies. They were able to speed current decay with cyclodextrins that can "sponge" up neurosteroids from hydrophobic spaces, suggesting that neurosteroids access binding sites within the plasma membrane. A membrane reservoir of neurosteroids could affect GABAergic receptor activity even in the absence of the neurotransmitter.

▲ Development/Plasticity/Repair

cGMP and Sema-1a Signaling in Drosophila *Growth Cones*

Joseph C. Ayoob, Hung-Hsiang Yu, Jonathan R. Terman, and Alex L. Kolodkin
(see pages 6639–6649)

Axonal growth cones, as they approach their targets, are guided by attractant and repellant molecules and surface receptors, which in turn are influenced by second messengers, including cyclic nucleotides. Even subtle fluctuations in the relative amounts of cAMP and cGMP can cause a guidance molecule to flip-flop its directional instructions. Molecules tethering PKA to cell surface guidance receptors have been detected. However, the pathways involved in cGMP signaling remain murky. Now Ayoob et al. describe the interplay between repulsive semaphorin-1A (Sema-1A), its receptor plexin A (PlexA), and the receptor-type guanylyl cyclase Gyc76C in *Drosophila* neurons. The authors generated flies that were deficient in Gyc76C that closely resembled flies that lack Sema-1A or PlexA in terms of their axonal growth pattern. *In vivo*, a mutant that specifically lacked cyclase activity did not appear to support Sema-1A signaling, thus providing evidence that guanylyl cyclase contributes directly to axonal pathfinding and neuromuscular connectivity during development.



A subset of longitudinal axon bundles within the CNS of a wild-type *Drosophila* embryo (left) and an embryo simultaneously overexpressing PlexA and Gyc76C (right). Embryos are stained with an anti-fasciclin II antibody to visualize axon bundles. Anterior is up. See the article by Ayoob et al. for details.

■ Behavioral/Systems/Cognitive

Processing Pitch in the Human Cortex

Hector Penagos, Jennifer R. Melcher, and Andrew J. Oxenham
(see pages 6810–6815)

The perception of sound periodicity (pitch) is a crucial component of our ability to make rhythmic sense of music and language. Although the auditory pathways (the cochlear nucleus, inferior colliculus, and auditory cortex) are the primary substrate for sound processing, some recent reports have uncovered other contributing brain areas. In this week's *Journal*, Penagos et al. use functional magnetic resonance imaging to examine the brain areas activated by varied pitch salience, or perception, while the temporal periodicity of the sound remained constant. They compared four conditions: they filtered harmonic tone complexes into low and high spectral regions to produce strong and weak pitch salience. Two additional conditions had strong pitch saliency but were made up of either low or high spectral regions, thus dissociating pitch saliency from regularity. The neural responses to these varied conditions showed that the anterolateral end of Heschl's gyrus, a nonprimary auditory cortical area, participates in pitch processing.

♦ Neurobiology of Disease

α-Synuclein Rafts to the Synapse

Doris L. Fortin, Matthew D. Troyer, Ken Nakamura, Shin-ichiro Kubo, Malcolm D. Anthony, and Robert H. Edwards
(see pages 6715–6723)

Although the molecules that underlie Parkinson's disease (PD) are emerging, clues to their cellular functions are only slowly following. This week, Fortin et al. focus on the subcellular localization of α-synuclein, which is localized to nerve terminals but appears as a soluble protein in standard biochemical assays. An autosomal dominant form of PD has been traced to the A30P synuclein mutation. The authors report that synuclein binds with high affinity to membrane components that were double-labeled for proteins associated with lipid rafts. The key to the synaptic localization of synuclein thus may be its linkage to rafts. In fact, the A30P mutant was not associated with rafts and no longer confined to synaptic terminals. Mysteriously, the A53T PD-linked synuclein mutation did affect an association with lipid rafts and thus must work through a different mechanism. Although the idiopathic form of PD does not have synuclein mutations, the authors suggest that raft–synuclein interactions may also be important in manifestations of the disease.