This Week in The Journal

● Cellular/Molecular

Major New Class of Vomeronasal Stimuli

Francesco Nodari, Fong-Fu Hsu, Xiaoyan Fu, Terrence F. Holekamp, Lung-Fa Kao, John Turk, and Timothy E. Holy

(see pages 6407–6418)

Nodari et al. have discovered a major new class of molecules that activate the accessory olfactory (vomeronasal) system: sulfated steroids. Vomeronasal sensory neurons (VSNs) detect cues that are important for social communication. Mouse urine strongly activates VSNs, but few of its active compounds had been identified. Using fractionation, mass spectrometry, and multielectrode physiological recordings, Nodari et al. found that sulfated steroids account for 80% of the vomeronasal-stimulating activity in female urine. Testing synthetic steroids revealed that individual neurons responded selectively and with different sensitivity to one to four closely related compounds, but, as a population, VSNs detected all classes of steroid hormones known to control mammalian physiology. Sulfation is thought to help clear steroids from the body, and the levels of sulfated corticosterone increased following restraint stress, suggesting that urine levels of sulfated hormones reflect the recent physiological state. Interestingly, sulfated steroids were not detected in males, suggesting another major class of VSN stimuli remains undiscovered.

▲ Development/Plasticity/Repair

Robos and Slits in Inferior Olive Development

Thomas Di Meglio, Kim T. Nguyen-Ba-Charvet, Marc Tessier-Lavigne, Constantino Sotelo, and Alain Chédotal

(see pages 6285–6294)

Diffusible molecules of the Slit family inhibit midline crossing by axons and neurons that express Robo receptors. For example, migrating inferior olive (IO) neurons extend a leading process across the midline, but the somata stop upon reaching the floor plate, which expresses Slits; the leading process forms the axon. Robo3 knock-out prevents midline crossing by the leading process, suggesting that Robo3 may interfere with repulsive signaling by other Slit–Robo pairs. To test this hypothesis, Di Meglio et al. knocked out Slits and Robos individually and in combination. As expected, IO somata crossed the midline in *Slit1/2* and *Robo1/2* knock-outs, confirming that these proteins normally repel neurons. Unexpectedly, however, axons failed to cross the midline in *Robo1/2/3* triple knock-outs, indicating that *Robo3* actively promotes crossing, rather than simply interfering with *Robo1/2* signaling. In addition, the patterning of IO subnuclei was disrupted in knock-outs, suggesting an additional role for Slits and Robos.

■ Behavioral/Systems/Cognitive

Predicting Psychotic Symptoms

Garry D. Honey, Philip R. Corlett, Anthony R. Absalom, Michael Lee, Edith Pomarol-Clotet, Graham K. Murray, Peter J. McKenna, Edward T. Bullmore, David K. Menon, and Paul C. Fletcher

(see pages 6295–6303)

Symptoms of schizophrenia vary widely across patients, making it difficult to predict future symptoms. Symptom variability is thought to reflect underlying variations in the vulnerability of different brain systems. Assuming that more vulnerable brain areas are more active during a cognitive challenge, Honey et al. measured brain activity in healthy subjects performing various cognitive tasks; the tasks challenged functional systems linked theoretically to different psychotic symptoms. Subjects then took the psychotomimetic drug ketamine, and the authors compared ketamine-induced symptoms to brain activity during the cognitive challenges. The expected correlations were found: negative symptoms (social withdrawal, unresponsiveness, apathy) were correlated with increased activation during working memory and attention tasks; thought disorder, a deficit in arranging and communicating thoughts, was correlated with increased activation during a sentence-completion task; and auditory hallucinations were correlated with differential activity during a self-monitoring task. These correlations suggest that similar testing could predict schizophrenics' susceptibility to symptoms.

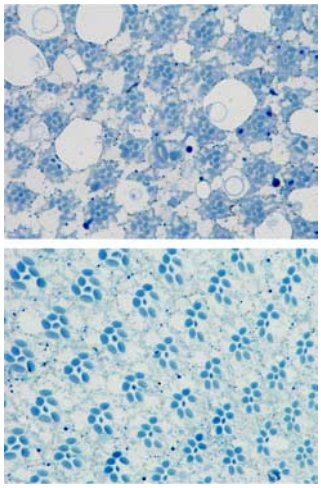
♦ Neurobiology of Disease

Energy Balance and Neurodegeneration

Miloš R. Spasić, Patrick Callaerts, and Koenraad K. Norga

(see pages 6419–6429)

Because neurons continuously consume large amounts of ATP to maintain their membrane potential and to produce action potentials, energy balance is critically important in the nervous system. Norga et al. have demonstrated the importance a well-regulated ATP supply by mutating *Drosophila* AMP-activated protein kinase (AMPK), which regulates energy homeostasis by promoting both production and conservation of ATP. They restricted expression of the nonfunctional mutant AMPK to the eyes, antennae, and optic lobe. Although neurons developed normally in these regions, neurons expressing the mutant protein began degenerating immediately after maturation. As a result, flies showed neither gravitaxis (which depends on antennae) nor phototaxis. Degeneration of photoreceptors was slowed by raising flies in total darkness and was nearly eliminated by blocking phototransduction via a phospholipase C mutation, indicating that neuronal activity is a critical factor in neurodegeneration. Apoptosis inhibitors did not block degeneration, suggesting that another mechanism was responsible for cell death.



Loss of AMPK causes retinal degeneration in flies (top), but rearing in constant darkness (bottom) slows degeneration. See the article by Norga et al. for details.