This Week in The Journal

Cellular/Molecular

Cold, Icilin, and PI(4,5)P_2 Act Directly on TRPM8 Channels

Eleonora Zakharian, Chike Cao, and Tibor Rohacs

(see pages 12526–12534)

The transient receptor potential channel TRPM8 is the principal sensor for innocuous cold. Its open probability greatly increases when temperature falls below ~25°C, and subsequent influx of sodium and calcium causes depolarization, which further activates the channel. But TRPM8 activity requires the presence of phosphatidylinositol 4,5-bisphosphate [PI(4,5)P_2] in the inner leaflet of the plasma membrane, and if the temperature remains low, activation of phospholipase C by elevated calcium depletes PI(4,5)P_2, thus desensitizing the channel. TRPM8 is sensitized by menthol and icilin, which shift the channel's activation threshold to higher temperatures. Although much evidence indicates that cold and menthol act directly on TRPM8 channels, it has been suggested that auxiliary proteins are required for these effects and for regulation of TRPM8 by PI(4,5)P_2. After reconstituting purified rat TRPM8 channels in planar lipid bilayers, however, Zakharian et al. found that TRPM8 activation by cold, menthol, icilin, and PI(4,5)P_2 occurred in the absence of other proteins.

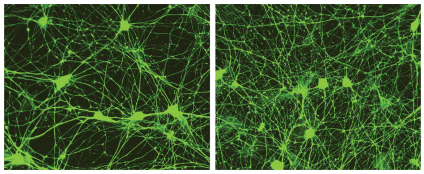
Development/Plasticity/Repair

Norepinephrine Inhibits Neurite Growth via β1 Autoreceptors

Gwenaëlle L. Clarke, Aritra Bhattacherjee, Sarah E. Tague, Wohaib Hasan, and Peter G. Smith

(see pages 12446–12454)

β-Adrenergic receptor antagonists ("β-blockers") inhibit the effects of the sympathetic nervous system and are widely used to treat hypertension, heart arrhythmias, heart failure, and performance anxiety. Although β-blockers are generally considered safe, abrupt discontinuation can increase hypertension, arrhythmia, and risk of myocardial infarction. Results by Clarke et al. suggest that these effects result in part from increased sympathetic innervation of the heart. Rats treated with β_1-selective antagonists showed increased innervation, and 2 days after treatment was stopped, these rats had greater-than-normal increases in blood pressure in response to startling stimuli and tyramine-induced release of endogenous norepinephrine. Cardiac response to β-adrenergic receptor agonist was no different from control responses, however, indicating that receptor levels were unchanged. β_1-Antagonists also increased neurite outgrowth from cultured rat sympathetic neurons, as did blocking norepinephrine synthesis, whereas β_1-agonist eliminated the latter effect. Together, these results suggest that norepinephrine released by sympathetic neurons acts on β_1 autoreceptors to inhibit neurite growth.



β-Adrenergic receptor antagonist increased neurite outgrowth in cultures of superior cervical sympathetic ganglion neurons. Left, Control; right, treated. See the article by Clarke et al. for details.

Behavioral/Systems/Cognitive

Brood Contact Suppresses Circadian Rhythm in Bees

Yair Shemesh, Ada Eban-Rothschild, Mira Cohen, and Guy Bloch

(see pages 12517–12525)

Circadian rhythms are driven by oscillations in gene expression in clock pacemaker cells, but they are entrained by environmental factors such as light and social interactions. Forager honey bees search for food only during the day and show normal cyclic oscillations in clock genes, but nurse bees, which tend the brood day and night, exhibit neither circadian activity patterns nor normal oscillations in gene expression. Shemesh et al. suggest that circadian oscillations in nurse bees are suppressed by contact with the brood. Nurse bees caged within the hive—and thus exposed to all normal hive cues except direct brood contact—were more active during the light period and showed gene expression oscillations similar to those in foragers. When caged in constant darkness outside the hive, nurse bees soon showed circadian activity in phase with that of foragers, suggesting that their clocks were set to the proper phase, even when oscillations were suppressed.

Neurobiology of Disease

Lysosome Biogenesis Reduces Degeneration in Parkinson's Disease Model

Benjamin Dehay, Jordi Bové, Natalia Rodríguez-Muela, Celine Perier, Ariadna Recasens, et al.

(see pages 12535–12544)

Macroautophagy is a principal cellular mechanism for degrading organelles, proteins, and other macromolecules. Components to be degraded are first sequestered in an autophagosome, which later fuses with a lysosome, forming an autolysophagosome, the contents of which are degraded by lysosomal enzymes. The number of autophagosomes is elevated in brains of patients with Parkinson's disease, leading some to hypothesize that macroautophagy is upregulated. But Dehay et al. show that in a toxin-based mouse model of Parkinson's disease, increases in autophagosome number result in part from depletion of lysosomes. Based on additional studies in dopaminergic neuroblastoma cells, they propose that mitochondrial dysfunction leads to accumulation of reactive oxygen species that permeabilize lysosome membranes, causing lysosomal breakdown. This causes accumulation of undegraded proteins and releases lysosomal enzymes into the cytoplasm, where they can degrade healthy components. Promisingly, stimulating lysosome biogenesis stimulated autophagosome–lysosome fusion, increased clearance of autophagosomes, and reduced toxin-induced neurodegeneration in mice.