This Week in The Journal

Cellular/Molecular

D5 Goes beyond the Synapse
Constantinos D. Paspalas and Patricia S. Goldman-Rakic
(see pages 5292–5300)

Dopamine and some other neuromodulators are thought to act by volumetric signaling (i.e., gradient diffusion of neurotransmitter to receptors beyond a synaptic release site). In this issue, Paspalas and Goldman-Rakic outline such a signaling pathway involving the D5 dopamine receptor. They used immunogold labeling and electron microscopy in pyramidal neurons of monkey prefrontal cortex. Specific signaling cascades presumably require cytosolic compartmentalization of signaling molecules and a physical scaffold for downstream effector molecules. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors. The authors report a tight anatomical link between membrane D5 receptors in the perisomatic region and subsurface cisterns (SSCs) containing calcium and inositol 1,4,5-trisphosphate (InsP) receptors. SSCs were confined to the perisomatic region and subsurface cisterns of monkey prefrontal cortex. These receptors inhibit somatodendritic calcium influx and are activated by InsP receptors.

Development/Plasticity/Repair

Gene Wakeup Calls from the Locus Ceruleus
Chiara Cirelli and Giulio Tononi
(see pages 5410–5419)

The role of sleep in brain function continues to draw our attention. In addition to the obvious behavioral differences between sleep and waking states, differences in brain function are seen at multiple levels, including gene-expression patterns. The factors dictating gene expression while asleep and awake are unknown but presumably reflect distinct patterns of brain function. Previous studies have revealed both sleep- and wake-associated genes. This week, Cirelli and Tononi examine the role of the central noradrenergic (NA) system on sleep–wake gene expression patterns. Locus ceruleus neurons widely innervate the cortex and are active during waking but mostly silent during sleep. The authors used the neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) to selectively remove noradrenergic inputs. Expression of ~20% of wake-associated genes decreased with DSP-4 treatment, whereas one sleep-associated gene, translation elongation factor 2, was upregulated. The results are consistent with an important role for NA in the regulation of state-dependent genes.

Behavioral/Systems/Cognitive

Oscillating with a Silicon Neuron and a Heart Interneuron
Michael Sorensen, Stephen DeWeerth, Gennady Cymbalyuk, and Ronald L. Calabrese
(see pages 5427–5438)

The motor pattern generator of the medicinal leech heartbeat is made up of “half-center oscillators” (pairs of mutually inhibitory neurons that alternately fire). Sorensen et al. have now created an oscillator made of one heart interneuron (HN) and one model silicon neuron (SiN), a unique beast like a half-leech, half-robot. The result is a synthetically connected hybrid oscillator that mimics the biological pair. They focused on the role of the hyperpolarization-activated inward current Ih, which influences the pattern of the half-center oscillator. They varied the Ih maximal conductance (gH) and its time course of activation and deactivation in the silicon neuron and also manipulated gH in the heart neuron with the dynamic-clamp technique. These changes in both neurons affected the cycle period. The role of Ih in the model neuron mirrored that of the endogenous current, illustrating the silicon model neuron and dynamic clamp as a powerful combination with which to study the dynamics of rhythmically oscillating neurons.

Neurobiology of Disease

Prozac and 5-HT1A Receptor Internalization
Mustapha Riad, Luc Zimmer, Latifa Rhah, Kenneth C. Watkins, Michel Hamon, and Laurent Descarries
(see pages 5420–5426)

Selective serotonin reuptake inhibitors (SSRIs) increase extracellular serotonin, a presumed mechanism for their antidepressant action. However, this apparently simple mechanism is made more complicated by 5-HT1A autoreceptors expressed on the soma and dendrites of serotonergic neurons. These receptors inhibit serotonin release, but they are also subject to desensitization by agonist-dependent internalization. The action of 5-HT1A autoreceptors could underlie the observed delay of several weeks before SSRIs exert their maximal effect in patients. A single dose of a 5-HT1A receptor-specific agonist in rats leads to internalization of autoreceptors in the nucleus raphe dorsalis (N RD) but not of 5-HT1A receptors in hippocampal neurons. Riad et al. sought to determine whether internalization also occurs immediately in response to the SSRI fluoxetine (Prozac). A single injection caused a shift of autoreceptors from plasma membrane to cytosol. Furthermore, autoreceptor internalization could be detected with the 5-HT1A radioligand [3H]MPPF and positron emission tomography, which they propose could be used as a molecular assay of SSRI treatment.