This Week in The Journal

Cellular/Molecular
The Ins and Outs of NMDA Receptors
Derek B. Scott, Ioannis Michailidis, Yuanyue Mu, Diomedes Logothetis, and Michael D. Ehlers
(see pages 7096–7109)

Although the trafficking of AMPA receptors has received much recent fanfare as a mechanism for synaptic plasticity, NMDA receptors have received less attention in this regard. However, Scott et al. now show that independent regions within the cytoplasmic domains of NMDA receptor type 1 (NR1) and NMDA receptor type 2 (NR2) subunits target NMDA receptors for internalization. Interestingly, the receptors can be sentenced differentially to separate fates, either receptor cycling back to the plasma membrane or degradation. In the NR1 subunit, two independent motifs, one tyrosine-based and one lysine-based, were necessary and sufficient for endocytosis. A similar domain was identified in the NR2A subunit. These internalization sequences, found in the membrane-proximal C0 domain of the C terminus, directed the receptors to late endosomes for speedy degradation. In contrast, the NR2B subunit contains a distal C-terminal domain that caused rapid recycling of receptors back to the plasma membrane. These alternative pathways provide flexible signals to control surface expression of NMDA receptors.

Behavioral/Systems/Cognitive
Getting Control of the Pain
Tim V. Salomons, Tom Johnstone, Misha-Miroslav Backonja, and Richard J. Davidson
(see pages 7199–7203)

The perception of pain is influenced by many factors, some of which have nothing to do with the physical stimulus itself, as anyone who has feared a trip to the dentist can attest. Cognitive and emotional states can contribute to our tolerance for pain, particularly intractable pain. In this issue, Salomons et al. used functional magnetic resonance imaging to examine how perceived control of a painful stimulus changes the perception of pain. During brain imaging, subjects used a joystick that they were told could reduce the duration of a painful thermal stimulus. However, this control was illusory because the physical stimulus remained constant. Nonetheless, most subjects reported that they had reduced the length of the painful stimulus under the “controllable” condition. Brain areas commonly associated with pain processing, the anterior cingulate, insular and secondary somatosensory cortex, had attenuated activation. Thus, these regions must not be strictly nociceptive but rather are influenced by the context in which the pain is perceived.

Neurobiology of Disease
Neuronal Nicotinic Receptor Antibodies and Autonomic Neuropathy
Steven Vernino, Leonid G. Ermilov, Lei Sha, Joseph H. Szurszewski, Phillip A. Low, and Vanda A. Lennon
(see pages 7037–7042)

Several classical neurological disorders involve autoimmune-mediated disruption of peripheral synapses, the best known being myasthenia gravis that is caused by circulating antibodies to the muscle nicotinic receptor. In this issue, Vernino et al. examine such a disease mechanism in a disorder involving peripheral autonomic ganglia, autoimmune autonomic neuropathy (AAN). This disorder is manifest by disruption of autonomic functions such as pupillary light responses, gastrointestinal motility, and bladder function. Clues point to neuronal nicotinic dysfunction in AAN, because animals lacking the α3 nicotinic subunit have severe dysautonomia and symptoms in AAN patients correlate with anti-α3 antibody titers. The authors injected mice with IgG from rabbits immunized with an α3 fusion protein to test a requirement for an antibody-mediated disorder: passive transfer. The recipient mice had impaired cholinergic ganglionic transmission and signs of autonomic failure. Likewise, mice injected with serum from human AAN patients also developed a similar phenotype.