This Week in The Journal

● Cellular/Molecular

GIPC and Extrasynaptic NMDA Receptors

Zhaohong Yi, Ronald S. Petralia, Zhanyan Fu, Catherine Croft Swanwick, Ya-Xian Wang, Kate Prybylowski, Nathalie Sans, Stefano Vicini, and Robert J. Wenthold

(see pages 11663–11675)

The usual textbook view is that synaptic receptors, particularly NMDA receptors, are stably anchored at synapses, whereas extrasynaptic receptors are wandering freely in the hinterlands. Not so simple, say Yi et al. The authors used a yeast two-hybrid screen to turn up an interaction between the NMDA receptor subunit NR2B and a novel protein with the well-chosen name GIPC (GAIP-interacting protein, C terminus). The association required the GIPC PDZ (PSD-95/Dlg/ZO-1) domain and the NR2B PDZ binding domain. A chimera consisting of the single transmembrane domain protein Tac and the distal cytoplasmic region of NR2B, TacNR2B, colocalized with GIPC on the cell surface and in the cytoplasm. The expression level of GIPC had no effect on total NMDA receptor expression, but surface expression in hippocampal neurons fluctuated with GIPC expression. GIPC colocalized with NR2B but was excluded from synapses, suggesting that GIPC contributes to trafficking and stabilization of extrasynaptic NMDA receptors.

The domain structure of the PDZ protein GIPC that interacts with extrasynaptic NMDA receptors. See the article by Yi et al. for details.

▲ Development/Plasticity/Repair

Deadly Ganglionic α7 Nicotinic Receptors

Martin Hruska and Rae Nishi

(see pages 11501–11509)

Culling of select neurons is a fundamental characteristic of brain development, but the target-derived and intrinsic factors that determine cell fate are still being mapped. This week, Hruska and Nishi propose a cell-autonomous action of α7-nicotinic acetylcholine receptors (nAChRs) in the developmental death of avian ciliary ganglion neurons. Half of these neurons die between embryonic day 8 (E8) and E14. Because nAChR antagonists prevent this cell death, the authors examined the site and mechanism of antagonist-mediated rescue. Labeling of α7 nAChRs at E8 with α-bungarotoxin (αbtx)–Alexa 488 revealed heterogeneity in surface receptor density of these calcium-permeable channels. Nicotine induced greater calcium influx in receptor-dense neurons, which was blocked by nicotinic antagonists. The intracellular calcium signal was reduced by expression of αbtx tethered to the membrane by a glycosylphosphatidylinositol linkage similar to externally applied toxin. Moreover, toxin expression rescued neurons from impending death.

■ Behavioral/Systems/Cognitive

κ Opiates and Aversion to Stress

Michael R. Bruchas, Benjamin B. Land, Megumi Aita, Mei Xu, Sabiha Barot, Shuang Li, and Charles Chavkin

(see pages 11614–11623)

Chronic stress activates the endogenous opioid system and produces dysphoria, an umbrella term that includes depression and associated behaviors. This behavioral response may be mediated in part by the dynorphin-κ-opioid system. In this week's *Journal*, Bruchas et al. examined the link between activation of the G-protein-coupled κ-opioid receptor (KOR) and downstream activation of the mitogen-activated protein kinase (MAPK) signaling system, specifically the stress kinase p38. In mice subjected to a repeated swim-stress test, KOR and p38 were activated in inhibitory neurons of the nucleus accumbens, cortex, and hippocampus, visualized by phosphospecific antibodies. The p38 inhibitor SB203580 alleviated the immobility resulting from repeated stress, as well as another behavior associated with KOR activation, conditioned place aversion. Activation of p38 depended on phosphorylation of KOR by the G-protein receptor kinase GRK3.

♦ Neurobiology of Disease

BDNF Depletion as a Model of Huntington's Disease

Andrew D. Strand, Zachary C. Baquet, Aaron K. Aragaki, Peter Holmans, Lichuan Yang, Carine Cleren, M. Flint Beal, Lesley Jones, Charles Kooperberg, James M. Olson, and Kevin R. Jones

(see pages 11758–11768)

Fourteen years after discovery of the disease gene, huntingtin, the pathophysiology of Huntington's disease (HD) remains an enigma. This week Strand et al. decided to compare striatal gene expression in mouse models of HD with human HD. The genetic model, the R6/2 mouse, expresses a fragment of huntingtin (htt) containing a long CAG repeat. Other mice, such as those treated with 3NP, an inhibitor of mitochondrial electron transport that causes striatal degeneration, were also examined. Finally, the authors tested mice with conditional deletion of brain-derived neurotrophic factor (BDNF) from cortical neurons (*Emx-BDNF*) or with a heterozygous null BDNF mutation. Surprisingly, BDNF-deficient mice showed the best concordance with human HD. Because corticostriatal axons are the major source of striatal BDNF, the data suggest that dysfunction in the cortex could contribute to striatal degeneration in HD. BDNF depletion is a plausible mechanism because mutant htt allows nuclear translocation of the neuronal suppressor REST, thus suppressing BDNF transcription. A testable hypothesis it seems.