This Week in The Journal

● Cellular/Molecular

A Gating Domain and Kainate Receptor Biogenesis

Pornpun Vivithanaporn, Laura Leanne Lash, William Marszalec, and Geoffrey T. Swanson

(see pages 10423–10433)

Kainate receptors come with a built-in operating manual of sorts. That is, instructions regarding intracellular trafficking and subcellular localization are contained within the amino acid sequence of the subunits. This week, Vivithanaporn et al. examined the linker region between the M3 and S2 domains involved in channel gating. The authors focused on conserved glutamate–arginine (E662–R663) residues. As expected, substitutions for the two residues in GluR6a affected channel desensitization, but in several of the R663 substitutions, glutamate-evoked currents in heterologous cells were markedly reduced. In cells expressing these homomeric mutant receptors, only a small fraction reached the channel membrane. The mutations apparently prevented channels from assembling dimers into functional tetrameric channels. In a charge-swapping double mutation that normalized desensitization, membrane localization was somewhat restored, and multimerization was intact. These results add gating domains to the ligand-binding and intracellular domains as affecting glutamate receptor assembly and trafficking.

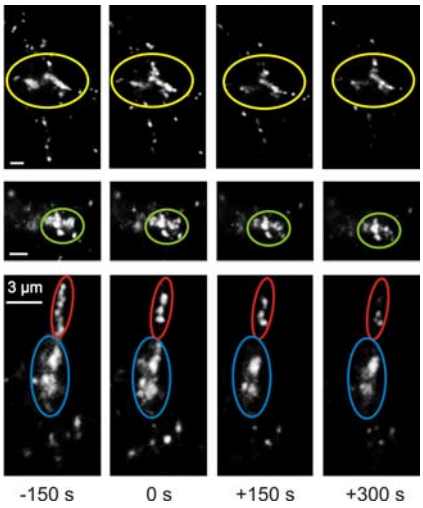
▲ Development/Plasticity/Repair

Tracking Postsynaptic Neurotrophin Secretion

Richard Kolarow, Tanja Brigadski, and Volkmar Lessmann

(see pages 10350–10364)

In this week's *Journal*, Kolarow et al. investigated the signaling pathway driving postsynaptic release of neurotrophins (NTs). The authors reasoned that the mechanism of release of NTs at synapses might provide insights into their activity-dependent effects on synaptic plasticity. In cultured hippocampal neurons transfected with fluorescently labeled BDNF or NT-3, the authors outlined a signaling cascade leading to NT release, which has a number of well known elements. After strong potassium-stimulated depolarization (50 mM, 300 s), calcium entering through either NMDA glutamate receptors or through L-type voltage-gated calcium channels triggered intracellular release of calcium from ryanodine-sensitive internal stores and downstream activation of ryanodine receptors. Postsynaptic CaMKII (α-calcium–calmodulin-dependent kinase II) was also required for NT release, as was protein kinase A activity, but postsynaptic TrkB or TrkC was not. Interestingly, a fusion pore-permeable dye revealed protracted, diffusion-limited release of NTs.



Postsynaptic BDNF-GFP vesicle clusters gradually decreased in intensity after stimulation with extracellular potassium, consistent with BDNF release. See the article by Kolarow et al. for details.

■ Behavioral/Systems/Cognitive

An α7 Nicotinic Agonist and Cognitive Performance

Robert S. Bitner, William H. Bunnelle, David J. Anderson, Clark A. Briggs, Jerry Buccafusco, Peter Curzon, Michael W. Decker, Jennifer M. Frost, Jens Halvard Gronlien, Earl Gubbins, Jinhe Li, John Malysz, Stella Markosyan, Kennan Marsh, Michael D. Meyer, Arthur L. Nikkel, Richard J. Radek, Holly M. Robb, Daniel Timmermann, James P. Sullivan, and Murali Gopalakrishnan

(see pages 10578–10587)

Enhancing cognitive function through better chemistry is not a new idea but is still a topic of considerable import. This week, Bitner et al. explored the potential benefits and mechanism of action of an α7 nicotinic receptor agonist that goes by the name of A-582941, or 2-methyl-2–5-(6-phenyl-pyradazin-3-yl)-octahydro-pyrrolo[3.4-c] pyrrole, for those of you who actually enjoyed organic chemistry. This compound has improved CNS penetration compared with earlier α7 agonists; thus, the authors tested it in a battery of neurochemical and behavior assays. A-582941 bound with nanomolar affinity to rat and human α7 receptors and showed positive effects on several behavior tasks that tested cognitive performance in mice, rats, and monkeys. Parenteral administration of the compound increased ERK1/2 and CREB phosphorylation in mouse cingulate cortex and hippocampus, which the authors suggest is a possible signaling pathway for the effects of α7 receptor activation.

♦ Neurobiology of Disease

Progranulin, TDP-43, and Neurodegeneration

Yong-Jie Zhang, Ya-fei Xu, Chad A. Dickey, Emanuele Buratti, Francisco Baralle, Rachel Bailey, Stuart Pickering-Brown, Dennis Dickson, and Leonard Petrucelli

(see pages 10530–10534)

Frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTDL-U) and amyotrophic lateral sclerosis (ALS) show inclusions containing the TAR DNA binding protein-43 (TDP-43). TDP-43 normally is involved in alternative exon splicing in the nucleus. In this week's *Journal*, Zhang et al. sought a pathophysiological link between TDP-43 and the growth factor progranulin (PGRN). In cell lines, small interfering RNA reduced expression of PGRN and promoted proteolytic cleavage of TDP-43 into 35 and 25 kDa fragments, similar to those seen in familial FTDL-U. Staurosporine, which activates caspase-3 and induces apoptosis, produced similar results. Either staurosporine treatment or PGRN reduction resulted in translocation of TDP-43 (or its cleavage products) from the nucleus to the cytoplasm, as seen in FTDL-U and ALS. A mutant TDP-43 containing a disrupted caspase cleavage site protected TDP-43 from proteolytic cleavage and cytoplasmic redistribution. The authors speculate that progranulin acts as part of a complex that protects TDP-43 from cleavage by caspase-3.