This Week in The Journal

● Cellular/Molecular

Glutamate Binding Is Required for AMPA Receptor Trafficking

Sarah K. Coleman, Tommi Möykkynen, Annukka Jouppila, Susanna Koskelainen, Claudio Rivera, Esa R Korpi, and Kari Keinänen

(see pages 303–312)

Many quality-control mechanisms prevent expression of mutated or misfolded proteins in cells. For transmembrane proteins, regulation of folding and assembly occurs in the endoplasmic reticulum (ER), where chaperone proteins bind to misfolded proteins and prevent further transport along the secretory pathway. Chaperones are thought to recognize misfolded proteins by binding to domains that are hidden when the protein is properly folded. Conformationally unstable proteins that fluctuate between properly and improperly folded states are more likely to expose these domains, and thus are inefficiently trafficked through the ER. For some such proteins, binding of "pharmacological chaperones" increases stability and facilitates exit from the ER. This week, Coleman et al. report that point mutations that eliminate glutamate binding prevented delivery of AMPA receptors to the plasma membrane in neurons. Because previous studies showed that glutamate binding increases stability of AMPA receptors, these data suggest glutamate is a pharmacological chaperone required for trafficking of AMPA receptors.

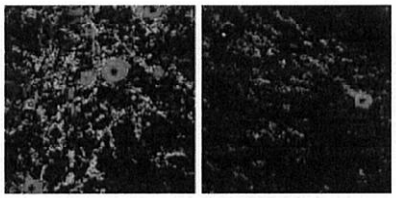
▲ Development/Plasticity/Repair

Neurotrophins Differentially Affect Neuronal Firing

María A. Davis-López de Carrizosa, Camilo J. Morado-Díaz, Juan J. Tena, Beatriz Benítez-Temiño, María L. Pecero, Sara R. Morcuende, Rosa. R. de la Cruz, and Angel M. Pastor

(see pages 575–587)

Neurotrophins act throughout life to promote cell survival, synaptogenesis, and synaptic maintenance. Muscle-derived neurotrophins not only affect innervating motor neurons, but also act transsynapitically, influencing efferent inputs to motor neurons. Davis-López de Carrizosa et al. now show that individual neurotrophins can differentially affect efferent inputs to motor neurons *in vivo*. After the abducens nerve was detached from its target muscle, abducens motor neurons lost synaptic inputs and fired at lower rates. Both tonic spiking, triggered by prepositus hypoglossi nucleus (PHN) inputs and associated with fixed gaze, and burst firing, triggered by pontine reticular formation inputs and associated with saccades, were reduced. Brain-derived neurotrophic factor (BDNF) and/or neurotrophin-3 (NT-3) restored synaptic inputs but produced different effects on spiking. BDNF restored tonic firing, but not bursting, suggesting that it restored inputs from the PHN but not from the reticular formation. NT-3 had complementary effects, suggesting that it restored reticular inputs but not PHN inputs.



Synaptophysin-labeled presynaptic boutons (green) are present throughout the neuropil and surround motor neuronal cell bodies (red) in the abducens nucleus (left). In the absence of externally supplied neurotrophins, axotomy reduces the number of boutons (right). See the article by Davis-López de Carrizosa et al. for details.

■ Behavioral/Systems/Cognitive

Reconsolidation and Extinction Activate CREB in Distinct Areas

Nori Mamiya, Hotaka Fukushima, Akinobu Suzuki, Zensai Matsuyama, Seiichi Homma, Paul W. Frankland, and Satoshi Kida

(see pages 402–413)

Contextual fear memory is produced in mice by administering a foot shock shortly after introducing a mouse to a new environment. If the mouse is returned to the feared environment for a brief period without shock, the initial fear memory is reconsolidated; but if the mouse is re-exposed for a longer period without shock, the fear is extinguished. According to Mamiya et al., reconsolidation and extinction depend on gene expression in distinct brain areas. With reconsolidation, cAMP-responsive element-binding protein (CREB) was activated in the hippocampus and amygdala, and expression of at least one CREB target, activity-regulated cytoskeleton-associated protein (Arc), increased in these areas. After extinction, CREB activity and Arc expression increased in amygdala and prefrontal cortex. Distinct roles of these brain regions were further demonstrated by blocking protein synthesis: blocking synthesis in hippocampus blocked reconsolidation, but not extinction, whereas blocking synthesis in prefrontal cortex had the opposite effect.

◆ Neurobiology of Disease

Loss of Doublecortin Alters Cortical Network Activity

James B. Ackman, Laurent Aniksztejn, Valérie Crépel, Hélène Becq, Christophe Pellegrino, Carlos Cardoso, Yehezkel Ben-Ari, and Alfonso Represa

(see pages 313–327)

Mutations in the microtubule-associated protein doublecortin disrupt migration of cortical neurons in humans, producing an ectopic layer of neurons beneath the normal cortex and resulting in mental retardation and epilepsy. To examine neuronal activity associated with such defects, Ackman et al. knocked down *doublecortin* expression in nascent layer 2/3 (L2/3) neurons of rats using *in utero* RNA interference. Neurons transfected with shRNAs targeting *doublecortin* formed ectopic clusters in white matter and deep cortical layers. Although the frequency of spontaneous EPSCs and IPSCs in these neurons was much lower than in normal L2/3, their spontaneous activity was higher. Interestingly, the presence of ectopic neurons also had consequences for untransfected L2/3 neurons. These migrated to the appropriate layer, but had much higher spontaneous EPSC frequency than neurons in normal L2/3. Ectopic and overlying L2/3 neurons were interconnected and were frequently coactive, and perfusion with magnesium-free medium induced epileptiform activity that was correlated across the two populations.