This Week in The Journal

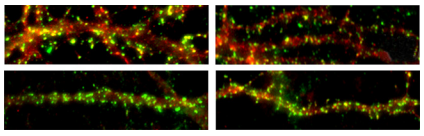
● Cellular/Molecular

Synaptic Calcineurin Affects LTP and LTD

Jennifer L. Sanderson, Jessica A. Gorski, Emily S. Gibson, Philip Lam, Ronald K. Freund, et al.

(see pages 15036–15052)

Homomeric AMPA receptors (AMPARs) composed solely of GluA1 subunits are permeable to Ca^{2+}, whereas heteromeric receptors containing GluR2 are not. Phosphorylation of GluA1 by cAMP-dependent protein kinase (PKA) in hippocampal neurons stabilizes Ca^{2+}-permeable AMPARs in extrasynaptic membranes, where they can move into synapses during long-term potentiation (LTP). Dephosphorylation of GluA1 by calcineurin and other phosphatases causes endocytic removal of homomeric AMPARs, and this contributes to long-term depression (LTD). Calcineurin is ubiquitously expressed and must interact with A-kinase anchoring protein 150 (AKAP150) to remain near synapses. To selectively examine the synaptic role of calcineurin, therefore, Sanderson et al. generated knock-in mice in which normal AKAP150 was replaced by a form lacking the calcineurin-binding domain. Hippocampal LTD was disrupted in these mice, but LTP induced by strong stimulation was enhanced. Although LTD caused dephosphorylation of GluA1 in knock-in mice, phosphorylation recovered more quickly than normal, suggesting synaptic calcineurin is required for persistent dephosphorylation of GluA1, which in turn is required for LTD.



GluA1 (red) and postsynaptic density protein PSD-95 (green) were colocalized at synapses in wild-type mice before (top left), but not after (bottom left), an LTD-inducing stimulus was applied. In knock-in mice expressing mutant AKAP150, these proteins were synaptically localized before (top right) and after (bottom right) the same stimulus. See the article by Sanderson et al. for details.

▲ Development/Plasticity/Repair

NOS1 Is Required for LTP Only in Male Mice

James Dachtler, Neil R. Hardingham, and Kevin Fox

(see pages 14994–14999)

Differences between male and female brains extend far beyond the neural circuitry underlying sex-specific behaviors. They include differences in stress responses, disease susceptibility, learning, and memory. Some sex differences in learning are attributable to differences in brain structures, including the hippocampus, or to the effects of sex hormones—most notably estrogen, which increases dendritic spine density and enhances long-term potentiation (LTP). Surprisingly, sex differences in learning exist even at the molecular level. For example, some kinases and transcription factors appear to be required for particular forms of learning exclusively in male mice. Similarly, Dachtler et al. now report that nitric oxide synthase 1 (NOS1) is required for LTP in barrel cortex of male, but not female, mice. Although LTP produced at layer IV-II/III synapses was similar in wild-type male and female mice, αNOS1 knock-out had much greater effects in males, in which LTP was rarely detected. Furthermore, plasticity induced by whisker stimulation was far more impaired in male than female mice lacking αNOS1.

■ Behavioral/Systems/Cognitive

Stimulating the Fusiform Gyrus Distorts Face Perception

Josef Parvizi, Corentin Jacques, Brett L. Foster, Nathan Withoft, Vinitha Rangarajan, et al.

(see pages 14915–14920)

Functional imaging in humans has identified several cortical areas that respond more to faces than to other visual stimuli. These areas are thought to be specialized for perceiving components of faces (eyes, nose, mouth, etc.), recognizing individual faces, and inferring emotions from facial expressions. Behavioral studies of patients with lesions in these regions, and other studies using transcranial magnetic stimulation, have led to the hypothesis that the fusiform gyrus (FG) is involved at early stages of face processing and recognition. This hypothesis is strengthened by Parvizi et al., who studied a man implanted with intracranial electrodes, two of which were centered on face-selective regions of the lateral FG. Stimulation of these sites temporarily distorted the patient's perception of faces, such that the person being viewed looked like a different person. Perception of other objects was affected to a lesser degree. How exactly the facial appearance changed was unclear, however, and the patient's ability to identify famous people in photographs was not impaired.

♦ Neurobiology of Disease

Shank3 Causes Presynaptic Effects via Neuroligin and Neurexin

Magali H. Arons, Charlotte J. Thynne, Andreas M. Grabrucker, Dong Li, Michael Schoen, et al.

(see pages 14966–14978)

Autism, which is characterized by communication deficits and repetitive movements, is a component of a spectrum of disorders. Mutations in several genes involved in cellular growth or synaptic function have been linked to autism. The latter group includes the postsynaptic scaffolding protein Shank3, the postsynaptic adhesion molecule neuroligin, and neuroligin's presynaptic partner, neurexin. Shank3 interacts with multiple postsynaptic proteins, including glutamate receptors, cytoskeletal proteins, and, intriguingly, neuroligin. Shank3-deficient mice show abnormal social behaviors, reduced synaptic levels of glutamate receptors, an overabundance of immature spines, and impaired synaptic transmission. Arons et al. show that Shank3 also affects presynaptic function via interactions with neuroligin. Overexpressing Shank3 in a subset of cultured rat hippocampal neurons led to increases in presynaptic protein levels and in the size of the recycling vesicle pool in terminals contacting transfected cells. These effects were blocked by preventing neuroligin–neurexin interactions. Furthermore, synapses onto Shank3-deficient neurons showed more paired-pulse facilitation than those onto Shank3-overexpressing neurons, suggesting the release probability was greater at the former.