This Week in The Journal

● Cellular/Molecular

Presynaptic LTP Requires RIM1α–Munc13-1 Interaction

Ying Yang and Nicole Calakos

(see pages 12053–12057)

Long-term potentiation (LTP) can arise from presynaptic or postsynaptic changes. Postsynaptic changes include insertion of new neurotransmitter receptors, whereas presynaptic changes involve increased probability of neurotransmitter release. LTP at mossy fiber synapses between dentate granule cells and CA3 pyramidal cells is unusual in that it is driven primarily by presynaptic changes. The mechanisms underlying increased release probability are unclear, but are likely to involve enlargement of the pool of readily releasable vesicles. Yang and Calakos report that a crucial component of mossy fiber LTP in mice is interaction between the presynaptic active zone proteins RIM1α and Munc13-1. Munc13-1 is involved in vesicle priming, in which vesicles docked at the active zone become associated with SNARE proteins and thus join the readily releasable pool. Interaction with RIM1α appears to regulate Munc13-1 function. Disrupting the interaction by mutating the interaction domain of either protein prevented theta-burst LTP at mouse mossy fiber synapses.

▲ Development/Plasticity/Repair

APP Mutation Disrupts NGF/TrkA Signaling

Carmela Matrone, Alessia P.M. Barbagallo, Luca R. La Rosa, Fulvio Florenzano, Maria T. Ciotti, et al.

(see pages 11756–11761)

Amyloid precursor protein (APP) is cleaved to form extracellular and intracellular fragments, and abnormal cleavage leads to accumulation of β-amyloid peptides, which is associated with Alzheimer's disease (AD). The extent to which AD pathology results from β-amyloid accumulation versus disruption of normal APP functions is unclear, however, in part because these functions are poorly understood. Several developmental roles have been proposed, including participation in neuronal degeneration in the absence of trophic support. Matrone et al. have identified an unexpected role for APP in NGF signaling via the TrkA receptor in mice. NGF increased tyrosine phosphorylation of APP, and this was prevented by TrkA inhibitors. APP and TrkA directly interacted, and a mutation that disrupted this interaction prevented NGF-induced activation of TrkA and its downstream signaling molecules. Accordingly, NGF failed to increase survival of dorsal root ganglion neurons in culture. APP mutation reduced membrane levels of TrkA, suggesting APP contributes to TrkA trafficking.

■ Behavioral/Systems/Cognitive

Effects of Maternal Stress Are Transmitted to Second Generation

Christopher P. Morgan and Tracy L. Bale

(see pages 11748–11755)

Chronic stress during pregnancy increases the risk of psychiatric disease in offspring. The effects of stress depend on the gestational age and sex of the fetus. In mice, for example, daily stress exposure during the first week of pregnancy increases depression-like behaviors (e.g., increased immobility during tail suspension) in male, but not female, offspring. Remarkably, the effects of prenatal stress can be passed on to subsequent (F2) generations. Morgan and Bale crossed prenatally stressed F1 males with control females. Although these females were not subjected to stress, their male offspring showed increased immobility during tail suspension. The immobility level of these second-generation offspring was similar to that of normal females, and the expression levels of sexually dimorphic genes was more similar to that of control females than that of control males. These results suggest that prenatal stress causes epigenetic changes resulting in dysmasculinization that can be passed from one generation to the next.

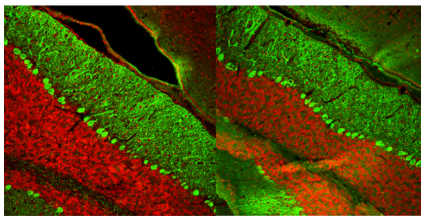
◆ Neurobiology of Disease

Blocking IK_A Ameliorates Spinocerebellar Ataxia

Raphael Hourez, Laurent Servais, David Orduz, David Gall, Isabelle Millard, et al.

(see pages 11795–11807)

Spinocerebellar ataxia type 1 (SCA1) is characterized by progressive loss of coordination. It is caused by a polyglutamine expansion in ataxin-1, which aggregates in intranuclear inclusions in cerebellar Purkinje cells. Affected neurons atrophy and degenerate, but this does not appear to result from inclusion formation per se. Instead, the polyglutamine expansion appears to alter interactions between ataxin-1 and other proteins that regulate gene expression. Hourez et al. suggest that disrupted glutamate signaling contributes to motor impairments in mice expressing SCA1-linked ataxin-1. In these mice, Purkinje cell firing was reduced before the onset of motor impairment and Purkinje cell atrophy. The reduced firing was attributed to decreased strength of glutamatergic synapses onto Purkinje cells and increased A-type potassium current (IK_A), which delayed depolarization-induced spiking. Treating presymptomatic and early symptomatic mice with an IK_A blocker normalized Purkinje cell firing rate and restored motor function. Chronic treatment reduced neuronal atrophy and improved motor performance in old mice.



Cerebellum from 5-week-old control (left) and SCA-1 model (right) mice. At this age, mice show motor deficits but no morphological changes in Purkinje cells. See the article by Hourez et al. for details.