This Week in The Journal

● Cellular/Molecular

cAMP, FMRP, and mGluRs Form Regulatory Loop

Alexandros K. Kanellopoulos, Ourania Semelidou, Andriana G. Kotini, Maria Anezaki, and Efthimios M. C. Skoulakis

(see pages 13111–13124)

Fragile X mental retardation protein (FMRP) spatially and temporally restricts translation of target mRNAs. Mutations that silence the *FMR1* gene cause dysregulation of FMRP targets, resulting in cognitive deficits. Although loss of FMRP probably affects multiple signaling pathways, effects on metabotropic glutamate receptors (mGluRs) or cAMP signaling are hypothesized to be key contributors to cognitive effects. According to Kanellopoulos et al., these pathways might be linked. Heterozygous *dfmr1*-null ($dfmr^{3/+}$) *Drosophila* exhibited abnormal olfactory learning and memory, increased expression of mGluRA, and reduced cAMP levels. Reducing mGluR activity restored learning, memory, and levels of *dfmr1* mRNA and cAMP. Elevating cAMP also increased FMRP levels and rescued learning. Overall, the data suggest that FMRP, mGluRs, and cAMP participate in a regulatory loop in which cAMP-mediated signaling promotes *dfmr1* transcription, FMRP reduces mGluR-mediated signaling by repressing mGluRA translation, and mGluRs inhibit cAMP production. Therefore, increased mGluR activity reduces FMRP-mediated translational repression of mGluRA.

▲ Development/Plasticity/Repair

Astrocytic Thrombospondin Enables Presynaptic Silencing

Devon C. Crawford, Xiaoping Jiang, Amanda Taylor, and Steven Mennerick

(see pages 13100–13110)

Structurally mature synapses can be silenced presynaptically or postsynaptically by eliminating vesicle release or by removing synaptic neurotransmitter receptors, respectively. Presynaptically silent synapses occur under normal conditions, but their number increases after prolonged presynaptic depolarization. The mechanisms linking depolarization and silencing are poorly understood, but are thought to involve activation of $G_{i/o}$-coupled receptors and downstream reduction of cAMP-dependent protein kinase (PKA) signaling. Crawford et al. present evidence that an additional link involves thrombospondin, a protein secreted from astrocytes that binds to the $\alpha2\delta$-1 subunit of neuronal voltage-gated Ca^{2+} channels. Unlike rat hippocampal neurons growing on living astrocytes, those growing on fixed astrocytes did not exhibit presynaptic silencing (i.e., EPSC depression) after prolonged depolarization, activation of $G_{i/o}$-coupled receptors, or inhibition of PKA. Pre-incubation with astrocyte-conditioned medium or thrombospondin restored silencing competence to neurons growing on fixed astrocytes. In contrast, preventing binding of thrombospondin to $\alpha2\delta$-1 reduced depolarization-induced silencing in neurons growing on living astrocytes.

■ Behavioral/Systems/Cognitive

Disinhibition of Superior Colliculus Causes Cervical Dystonia

Angela L. Holmes, Patrick A. Forcelli, Jacqueline T. DesJardin, Ashley L. Decker, Menna Teferra, et al.

(see pages 13326–13332)

The basal ganglia are essential for generating voluntary movements. Inhibitory projections from the two output nuclei—the substantia nigra pars reticulata (SNr) and the globus pallidus internal segment (GPi)—to the thalamus, superior colliculus (SC), and pedunculopontine nucleus are thought to tonically inhibit unwanted movements. Pauses in output-neuron spiking disinhibit these targets, allowing movement to occur. Dysregulation of basal ganglia circuits can cause dystonia—involuntary muscle contractions that produce repetitive movements and abnormal postures. Cervical dystonia (CD), in which the head tilts toward one shoulder, is sometimes caused by increased striatal inhibition of SNr and disinhibition of SNr targets. Because CD can be produced in monkeys by injecting $GABA_A$ agonist into SNr, but not into GPi, Holmes et al. reasoned that CD must be produced by disinhibition of the one target unique to SNr: the SC. Indeed, infusing $GABA_A$ agonist into the SC attenuated CD produced by inhibition of SNr.

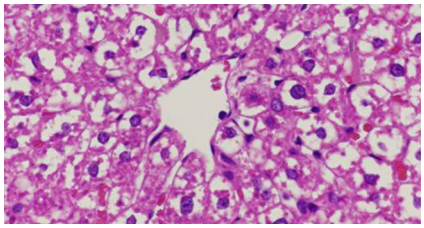
♦ Neurobiology of Disease

Ammonia Exacerbates Methamphetamine-Induced Neuropathology

Laura E. Halpin and Bryan K. Yamamoto

(see pages 13155–13163)

Methamphetamine increases cytosolic dopamine levels in synaptic terminals by activating tyrosine hydroxylase and inhibiting monoamine oxidase and the vesicular monoamine transporter 2. This, together with direct actions on the dopamine transporter, reverse the normal direction of dopamine transport, resulting in nonvesicular dopamine release. Chronic methamphetamine use depletes dopamine and leads to degeneration of dopaminergic terminals. Many of the pathological effects of methamphetamine stem from its sympathomimetic effects on the cardiovascular system, which eventually damage heart muscles and blood vessels, ultimately affecting all major organ systems. As demonstrated by Halpin and Yamamoto, such systemic effects can exacerbate neuropathological effects. Methamphetamine caused liver damage in rats, thus impairing ammonia metabolism and increasing ammonia levels in serum and brain. Direct infusion of ammonia along with methamphetamine into the striatum significantly increased dopamine depletion, whereas enhancing systemic ammonia clearance reduced depletion induced by methamphetamine. These results suggest that ammonia is a major contributor to methamphetamine-related neuropathology.



Methamphetamine causes disappearance of cytoplasm in rat liver cells. The subsequent increase in systemic ammonia levels contributes to neuropathology. See the article by Halpin and Yamamoto for details.