This Week in The Journal

● Cellular/Molecular

Ethanol Increases Spike-Induced Ca^{2+} Release in Dopamine Neurons

Brian E. Bernier, Leslie R. Whitaker, and Hitoshi Morikawa

(see pages 5205–5212)

Dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens enhance synaptic plasticity related to reward learning. Although alcohol suppresses plasticity in VTA targets, it enhances AMPA receptor currents in VTA neurons, and this might contribute to the development of addiction. Activation of NMDA receptors (NMDARs) is required to induce reward-related dopamine release, and long-term potentiation (LTP) of NMDAR currents occurs when sustained stimulation of inputs to dopamine neurons is paired with intracellular current steps to elicit action potentials. This LTP requires activation of metabotropic glutamate receptors (mGluRs) and subsequent production of inositol 1,4,5-trisphosphate, which in turn increases calcium-induced Ca^{2+} release from intracellular stores following action potentials, and thus increases Ca^{2+}-sensitive potassium currents ($I_{K(Ca)}$) after spikes. Bernier et al. show that repeated ethanol treatment increased mGluR-mediated facilitation of $I_{K(Ca)}$ and proportionally increased potentiation of NMDAR currents. This effect, which was sustained for weeks after ethanol cessation, might strengthen alcohol-related reward learning.

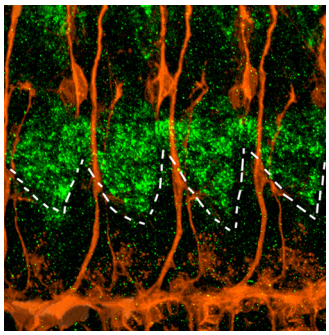
▲ Development/Plasticity/Repair

Mmp2 Substrate Frac Helps Promote Axon Fasciculation

Crystal M. Miller, Nan Liu, Andrea Page-McCaw, and Heather T. Broihier

(see pages 5335–5347)

Matrix metalloproteinases (MMPs) cleave growth factors, cell surface receptors, and extracellular matrix proteins, thus regulating diverse cellular processes, including migration, axon growth, and plasticity. In *Drosophila*, Mmp2 is expressed in exit glia, which guide motor axons as they leave the CNS, and it promotes axon fasciculation.



Frac (green) is expressed adjacent to the border of the ventral nerve cord (dashed line), near the exit points through which axons (red) extend. See the article by Miller et al. for details.

To identify Mmp2 substrates that might mediate this effect, Miller et al. performed a yeast two-hybrid screen. They identified a single protein, which they named *faulty attraction* (*frac*), that was expressed in the mesoderm adjacent to Mmp2-expressing glia during the period of motor axon outgrowth. As in Mmp2-null mutants, motor axons defasciculated and entered inappropriate nerve bundles in *frac*-null embryos. Surprisingly, *frac* overexpression also caused defasciculation, suggesting that *frac* does not promote fasciculation by itself, but rather requires a cofactor. *Frac* is structurally related to vertebrate fibrillins, extracellular structural proteins that regulate signaling via bone morphogenic proteins (BMPs). Correspondingly, overexpression of a BMP receptor suppressed both *Frac*-null and overexpression phenotypes.

■ Behavioral/Systems/Cognitive

COMT Genotype Influences Effects of Estradiol

Emily Jacobs and Mark D'Esposito

(see pages 5286–5293)

Working memory is associated with activity in the prefrontal cortex (PFC), and this activity is modulated by dopamine. A polymorphism in the human catechol-*O*-methyltransferase (COMT) gene, which affects COMT activity and thus dopamine turnover, alters baseline dopamine levels. People homozygous for the methionine allele (*met/met*) have lower COMT activity, higher baseline dopamine, and better working memory than those homozygous for the valine allele (*val/val*). Estradiol also regulates dopamine levels, by stimulating synthesis, release, and turnover. But studies of estradiol effects on working memory have yielded inconsistent results. Because both too much and too little dopamine impairs PFC function, Jacobs and D'Esposito hypothesized that past inconsistency stemmed from unrecognized differences in baseline dopamine levels resulting from COMT genotype. They found that female *val/val* subjects performed better on a working memory task when their endogenous estradiol levels were high, whereas *met/met* subjects performed better when their estradiols levels were low, demonstrating genotypic influences on individuals' responses to neuromodulators.

♦ Neurobiology of Disease

Heat Shock Protein 70 Stimulates β-Amyloid Clearance

Tatsuya Hoshino, Naoya Murao, Takushi Namba, Masaya Takehara, Hiroaki Adachi, et al.

(see pages 5225–5234)

Accumulation of β-amyloid (Aβ) likely contributes to synaptic dysfunction, neuronal degeneration, and cognitive decline in Alzheimer's disease (AD). In other neurodegenerative diseases characterized by protein deposits, overexpression of heat shock proteins (HSPs)—which help refold or degrade misfolded proteins—reduces abnormal protein accumulation and improves the associated symptoms. HSP70 was previously shown to reduce Aβ toxicity and stimulate Aβ phagocytosis *in vitro*, and now Hoshino et al. show that HSP70 overexpression reduced Aβ accumulation and AD-like symptoms *in vivo*. Spatial learning, which was impaired in a mouse model of AD, was rescued by HSP70 overexpression. Furthermore, HSP70 overexpression reduced Aβ levels, plaque formation, and neuronal and synaptic loss. Levels of amyloid precursor protein (APP) and activity of APP-processing proteins were unaltered by HSP70, suggesting that Aβ production was unchanged. In contrast, expression of an Aβ-degrading enzyme, a growth factor that activates phagocytosis by microglia, and a marker of microglial activation were increased, suggesting that HSP70 promotes Aβ clearance.