This Week in The Journal

● Cellular/Molecular

Phosphatase 2cα and Calcium Channels

Dongjun Li, Fushun Wang, Meizan Lai, Yuan Chen, and Ji-fang Zhang
(see pages 1914–1923)

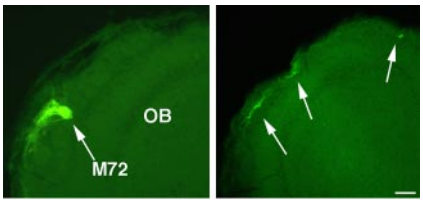
The identification of protein complexes, including kinases, phosphatases, and effectors such as channels and receptors, has become a growth industry. The idea that "scaffold" and adaptor proteins place signaling proteins in close proximity to their effectors is now an accepted view. This week Li et al. went looking for proteins that interact with the intracellular C-termini of N- and P/Q-type calcium channels using a yeast two-hybrid screen. Among other proteins, they identified protein phosphatase 2cα (PP2cα). They confirmed that PP2cα associated directly with neuronal calcium channels and that it was the most effective phosphatase in dephosphorylating channels that had been phosphorylated by PKC. Expression of a dominant-negative PP2cα enhanced PKC-dependent modulation of calcium channels in cultured hippocampal neurons. Because PP2cα is constitutively active, tethering it to calcium channels may regulate such PKC-dependent processes as the association of G-proteins and SNARE complexes with intracellular loops of calcium channel subunits.

▲ Development/Plasticity/Repair

Cell-Surface Carbohydrates in Olfactory Axon Pathfinding

Timothy R. Henion, Denitza Raitcheva, Robert Grosholz, Franziska Biellmann, William C. Skarnes, Thierry Hennet, and Gerald A. Schwarting
(see pages 1894–1903)

The axons of olfactory receptor neurons must find their way through the cribiform plate to the olfactory bulb, and if that isn't enough, they then must converge on glomeruli in an odorant-specific manner. A number of molecules, including the odorant receptors themselves, have been implicated in this tour de force of pathfinding. This week, Henion et al. examine the importance of cell-surface carbohydrates in this process. The authors analyzed mice deficient in β1,3-*N*-acetylglucosaminyltransferase 1 (β3GnT1), a glycosyltransferase important for synthesis of a glycan, lactosamine, which is expressed in olfactory sensory nerve terminals. In postnatal null mice, mature sensory neurons were greatly reduced, and formation of glomeruli was disrupted. By the second postnatal week, a presumed compensatory increase in lactosamine biosynthesis resulted in reinnervation, making a "necessary and sufficient" case for surface carbohydrates in the pathfinding of olfactory sensory neurons. Lactosamine may play a similar role in nociceptive dorsal root ganglion neurons, first noted to express lactosamine by Dodd and Jessell (1985).



The M72-internal ribosomal entry site (IRES)-tau-green fluorescent protein (GFP) reporter line was crossed to β 3GnT1 $^{+/-}$ and β 3GnT1 $^{-/-}$ mice to track the formation of M72-specific glomeruli. M72 axons converged on a glomerulus on the dorsomedial surface in β 3GnT1 $^{+/-}$ mice (left), but in β 3GnT1 null mice, M72 axons primarily remain in the nerve layer (right). Scale bar, 50 μm. See the article by Henion et al. for details.

■ Behavioral/Systems/Cognitive

Antagonizing the Effects of Cocaine

Rajeev I. Desai, Theresa A. Kopajtic, Mikhail Koffarnus, Amy Hauck Newman, and Jonathan L. Katz
(see pages 1889–1893)

Treatment of addictions such as cocaine surely would be a lot easier with the right magic bullets, "pure" antagonists that block without having their own behavioral effects. Although many compounds bind to the dopamine transporter (DAT), a prime target for cocaine, such drugs also induce cocaine-like effects. In this week's *Journal*, Desai et al. report on a promising cocaine antagonist, the benztropine analog JHW007. Like cocaine, JHW007 crossed the blood–brain barrier and bound to DAT with high affinity, but with a 10-fold slower apparent association *in vivo*. JHW007 did not evoke the locomotor and stimulant effects of cocaine. Most importantly, pretreatment prevented the behavioral effects of subsequent cocaine delivery in mice, suggesting that the rate of DAT occupancy may determine the behavioral effects of cocaine. Although JHW007 can bind to sites other than the DAT, this compound may be useful in examining pharmacological approaches to cocaine addiction.

♦ Neurobiology of Disease

A Model of Tardive Dyskinesia in RGS9 Knock-Out Mice

Abraham Kovoor, Petra Seyffarth, Jana Ebert, Sami Barghshoon, Ching-Kang Chen, Sigrid Schwarz, Jeffrey D. Axelrod, Benjamin N. R. Cheyette, Melvin I. Simon, Henry A. Lester, and Johannes Schwarz
(see pages 2157–2165)

The dopamine receptor antagonists used as antipsychotics and the dopamine agonists used in Parkinson's disease can cause abnormal involuntary movements, dyskinesias, side effects that limit effective treatment. Dyskinesias appear to result from activation of striatal D_2-like dopamine receptors. Such G-protein-coupled receptor signaling is time-limited by GTPase activity intrinsic to the Gα subunit and can be shortened by regulator of G-protein signaling (RGS) proteins that increase GTPase activity. This week, Kovoor et al. look for a link between RGS9-2, which is expressed exclusively in the striatum, and D_2 receptors. Mice deficient in RGS9 developed dyskinesia-like movements when D_2 receptors were activated after dopamine depletion. D_2 receptors and RGS9 colocalized in Chinese hamster ovary cells, an interaction that the authors report is attributable to the N-terminal DEP (Disheveled, EGL-10, Pleckstrin homology) domain of RGS9-2. The authors postulate that alterations in termination of D_2 signaling, perhaps by alterations in RGS9-2, could contribute to tardive dyskinesias and L-DOPA induced dyskinesias.