This Week in The Journal

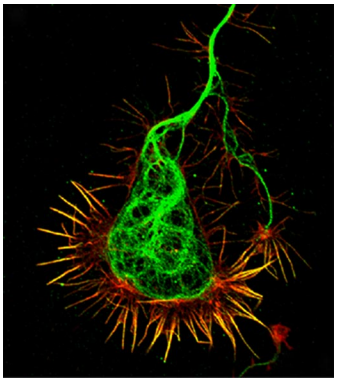
● Cellular/Molecular

Lfc Regulates RhoA to Prevent Excessive Axon Formation

Cecilia Conde, Cristina Arias, Maria Robin, Aiqun Li, Masaki Saito, et al.

(see pages 6793–6800)

As neurons develop, they extend several neurites, one of which acquires the molecular and structural characteristics of an axon, whereas the remainder become dendrites. The cellular processes that ensure formation of a single axon are not completely understood, but the small GTPases Rac and RhoA appear to have opposing roles: Rac is required to form any axon, whereas RhoA prevents formation of multiple axons. The activity of Rac and RhoA is regulated by specific guanine nucleotide exchange factors (GEFs). Conde et al. show that overexpression of the GEF Lfc in cultured rat hippocampal neurons reduced the number of neurites per cell and prevented axon formation, whereas Lfc knockdown promoted axonal growth and increased the number of neurons with multiple axons. These effects were reversed by inhibiting downstream mediators of RhoA signaling, and by expressing a constitutively active form of RhoA, respectively. Lfc activity was inhibited by Tetex-1, a dynein light chain that regulates the actin cytoskeleton.



Lfc (green) is present in growth cones of nascent axons, where it localizes with microtubules in the central region and with actin-rich filopodia (labeled with rhodamine–phalloidin, red) in the periphery. See the article by Conde et al. for details.

▲ Development/Plasticity/Repair

Kainate Receptors Regulate AHP Amplitude in Neonate Interneurons

Mikael Segerstråle, Juuso Juuri, Frédéric Lanore, Petteri Piepponen, Sari E. Lauri, et al.

(see pages 6507–6514)

In the developing brain, GABAergic synapses form before glutamatergic synapses, and the activity of GABAergic interneurons drives oscillatory activity that is thought to shape the development of neuronal networks. Until approximately postnatal day 14 (P14) in rodents, when expression of the K^+–Cl^{2-} cotransporter KCC2 increases, GABA depolarizes postsynaptic cells. Segerstråle et al. report that during this same period, the firing rate of hippocampal CA3 interneurons decreases. Moreover, they present evidence that the decreased spike rate results from an increase in the amplitude of the postspike afterhyperpolarization (AHP), which in turn results from decreased coupling between the GluK1 kainate receptor and the apamin-sensitive, calcium-dependent potassium current that underlies the AHP. In hippocampal slices from P3–P5 mice, blocking GluK1 activity increased the amplitude of the AHP and decreased spike rate in interneurons, but this effect was absent in P14–P16 mice. Likewise, a specific GluK1 agonist decreased AHP amplitude in neonates but not older mice.

■ Behavioral/Systems/Cognitive

Steroids Increase Spiking of Inhibitory Hypothalamic Neurons

Carlos A. A. Penatti, Matthew C. Davis, Donna M. Porter, and Leslie P. Henderson

(see pages 6497–6506)

Misuse of anabolic androgenic steroids (AASs) has become prevalent among professional and recreational athletes, and it has been reported in boys as young as 12. Long-term use of AASs has numerous detrimental effects in humans, including testicular atrophy, cardiovascular disease, and mood disorders. AASs delay puberty in male mice, but the effects of AASs on puberty onset in humans are unknown. Puberty is triggered by an increase in pulsatile release of gonadotropin-releasing hormone (GnRH) from hypothalamic neurons. This increase results in part from decreased GABAergic inhibition of GnRH-expressing neurons. Penatti et al. suggest that AASs delay puberty by increasing the activity of hypothalamic GABAergic neurons, which—unlike GnRH neurons—express high levels of androgen receptors. In prepubescent male mice, AASs increased spiking of non-GnRH neurons, increased the frequency of GABAergic PSCs in GnRH neurons, and decreased the spike frequency of GnRH neurons. GABA receptor antagonists restored spike frequency of GnRH neurons to control levels.

♦ Neurobiology of Disease

Alternatively Spliced FMRP Isoforms May Have Distinct Functions

Paromita Banerjee, Brian P. Schoenfeld, Aaron J. Bell, Catherine H. Choi, Michael P. Bradley, et al.

(see pages 6782–6792)

The fragile X mental retardation protein (FMRP) is an RNA-binding protein involved in trafficking mRNAs to neurites and regulating local translation at synapses. Human FMRP, encoded by *FMR1*, has 20 alternatively spliced isoforms, most of which vary in the C-terminal domain. The extent to which the isoforms serve distinct functions is unknown. Banerjee et al. approached this question in *Drosophila* by comparing wild-type and *dFMR1*-null flies to flies expressing a *dFMR1* allele in which a glutamine/asparagine (Q/N)-rich putative protein-interaction domain had been mutated. Expression of mutated dFMR1 rescued many, but not all of the defects present in *dfmr1*-null flies: hatch rates and axonal pathfinding phenotypes were completely rescued; rhythmic circadian locomotion and immediate recall of conditioned courtship behavior were partially rescued; and overabundance of neuromuscular junction boutons, reduced naïve courtship behaviors, and impairments in short-term memory were not rescued. These results suggest that splice variants that include or lack the Q/N domain have different roles.