This Week in The Journal

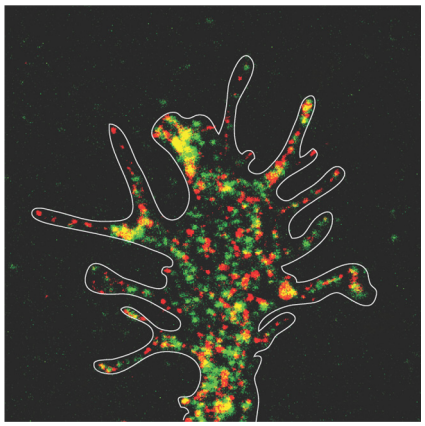
Development/Plasticity/Repair

Endocytosis of Frizzled3 Receptor Steers Growth Cones

Keisuke Onishi, Beth Shafer, Charles Lo, Fadel Tissir, Andre M. Goffinet, et al.

(see pages 19071–19085)

Growing axons make their way through the developing brain guided by a symphony of signaling molecules and their receptors, but how those signals are translated to "turn left" or "turn right" is not fully understood. After crossing the midline, spinal commissural axons follow planar cell polarity (PCP) signals and turn in an anterior direction to follow a gradient of Wnt proteins—major players in the orchestra. This week, Onishi et al. report that the Wnt receptor Frizzled3 is endocytosed from filopodia tips in response to Wnt5a binding, and this spurs elongation of filopodia. Dishevelled1 stabilizes Frizzled3 receptors at the membrane by hyperphosphorylating them, but Dishevelled2 blocks that modification. These opposing actions might provide feedback amplification of the Wnt signaling. The small GTPase Arf6, a key protein in Frizzled3 receptor recycling, was also required for Wnt-mediated filopodial growth, bolstering a role for Frizzled3 recycling in axon guidance directed by PCP proteins. Finally, the report demonstrated Wnt5a-mediated directional steering of growth cones.



In the presence of Wnt5a, Frizzled3 (green) colocalizes with the endocytic protein AP-2 (red) at the tips of filopodia. See the article by Onishi et al. for details.

Systems/Circuits

Neuroestrogen Rapidly Modulates Reproductive Hormone Release

Brian P. Kenealy, Amita Kapoor, Kathryn A. Guerriero, Kim L. Keen, James P. Garcia, et al.

(see pages 19051–19059)

Since the 1960s, scientists have sketched out a signaling loop key to regulation of reproductive behavior: neurons in the hypothalamus produce and release gonadotropin-releasing hormone (GnRH) to the pituitary gland, which in turn releases gonadotropin, stimulating estradiol release from the ovaries. Circulating peripheral estradiol feeds back to both positively and negatively influence GnRH release. Recent research has shown that estradiol is also produced by neurons and can have rapid signaling actions. Kenealy et al. now show that so-called neuroestrogen has direct excitatory actions on hypothalamic GnRH neurons *in vivo*. In ovarectomized rhesus monkeys, a direct infusion of an estradiol mimic to the stalk-median eminence at the base of the hypothalamus led to rapid release of GnRH there. Electrical stimulation of the hypothalamus led to GnRH and E2 release, which was prevented by infusion of an inhibitor of aromatase, the enzyme that converts androgen to estrogen. The findings support a new role for neuroestrogen as a neurotransmitter.

Behavioral/Cognitive

κ-Opioid Receptors May Cause Negative Aspects of Addiction

Joel E. Schlosburg, Timothy W. Whitfield Jr, Paula E. Park, Elena F. Crawford, Olivier George, et al.

(see pages 19384–19392)

Whereas activation of mu-type opioid receptors blocks pain and induces pleasant feelings, agonists at kappa opioid receptors (KORs) produce dysphoria. Schlosburg et al. hypothesized that the endogenous kappa opioid dynorphin plays a critical role in the negative-reinforcement aspects—that is, avoidance of withdrawal symptoms—that contribute mightily to establishment of addiction. Rats allowed to self-administer heroin for long periods (12 h) daily escalated their dosage over several weeks, but that escalation was blocked by a single dose of the long-acting KOR antagonist nor-BNI. Interestingly, nor-BNI also blocked withdrawal-associated anxiety behaviors but not hypersensitivity to pain, although this effect appeared to be separate from the motivational aspects. The researchers next investigated the neural substrate of these actions. Infusion of nor-BNI to the shell region of the nucleus accumbens, a basal ganglia structure involved in addiction, reduced long-access but not immediate heroin administration. In contrast, nor-BNI infused to the nucleus accumbens core had the opposite effects. The results implicate KOR in compulsivity associated with opiate addiction.

Neurobiology of Disease

Rho-Associated Kinase ROCK2 Emerges as Alzheimer's Target

Jeremy H. Herskowitz, Yangbo Feng, Alexa L. Mattheyses, Chadwick M. Hales, Lenora A. Higginbotham, et al.

(see pages 19086–19098)

Inhibition of the GTPase protein RhoA can decrease production of amyloid-beta (Aβ), the toxic protein in Alzheimer's disease (AD). But the signaling events that connect RhoA and Aβ have remained a mystery. Herskowitz et al. show that RhoA's effector kinases, ROCK1 and ROCK2, regulate Aβ production in opposite directions. In a human cell line, reducing ROCK2 using RNA interference decreased Aβ production significantly, whereas ROCK1 knockdown increased Aβ. An isoform-specific inhibitor of ROCK2 decreased Aβ production in cultured mouse neurons and in an AD mouse model. The researchers also showed that ROCK2 phosphorylated BACE1, the rate-limiting enzyme in Aβ generation, and amyloid precursor protein (APP) itself. Phosphorylation of APP at a specific threonine position was required for processing to Aβ, and could be prevented with ROCK2 inhibition. Moreover, brain tissue samples from people with early-stage AD, mild cognitive impairment, and full-blown AD all showed elevated levels of ROCK2. The findings suggest ROCK2 as a potential target for an AD therapeutic.