This Week in The Journal

Cellular/Molecular

Loss of FMRP Delays Shift in Cl^- Reversal Potential

Qionger He, Toshihiro Nomura, Jian Xu, and Anis Contractor

(see pages 446 – 450)

Neuronal resting Cl^- concentration is determined by two chloride transporters: NKCC1, which transports Cl^- into the cell, and KCC2, which extrudes Cl^-. In newborn neurons, expression of NKCC1—and thus the intracellular Cl^- concentration—is relatively high, and consequently, activation of $GABA_A$ receptors causes Cl^- efflux and depolarization. As neurons mature, NKCC1 expression decreases, KCC2 expression increases, intracellular Cl^- concentration and Cl^- reversal potential drop, and GABA becomes hyperpolarizing. The early depolarizing action of GABA is thought to be critical for synaptogenesis and incorporating neurons into circuits. Intriguingly, He et al. report that the developmental switch in Cl^- transporter expression is delayed in mice lacking fragile X mental retardation protein (FMRP). Whereas NKKCl levels had decreased and GABA was hyperpolarizing in normal 10-day-old mice, levels remained high and GABA was depolarizing in FMRP-null mice until postnatal day 14. Such a delay may contribute to the developmental delays seen in humans with fragile X syndrome, which is caused by loss of FMRP.

Systems/Circuits

Simple Instructions Allow Neurons to Form Functional Circuits

Alan Roberts, Deborah Conte, Mike Hull, Robert Merrison-Hort, Abul Kalam al Azad, et al.

(see pages 608 – 621)

During development, molecular gradients drive differentiation of cells into specific neuron types and—together with substrate-bound cues and physical barriers—guide the axons of these neurons toward their targets. But how neurons identify appropriate postsynaptic cells to create functional networks is unclear. In fact, work in *Xenopus* tadpoles has suggested that spinal neurons choose targets probabilistically, not specifically. Using data describing soma position, dendritic extent, and axon length and branching patterns for seven types of spinal and hindbrain neurons, Roberts et al. created a computational model of ~1400 neurons in which axonal growth cones were steered by dorsal–ventral and rostral–caudal gradients of guidance cues, growth was restricted by the floor plate and rows of neuronal somata, and axons probabilistically established synapses with any dendrites they encountered. After connections were established and experimentally derived physiological properties were added, simulated sensory input evoked realistic fictive swimming motor patterns with alternating left–right bursts, indicating that the simple growth model allowed development of functional circuits.

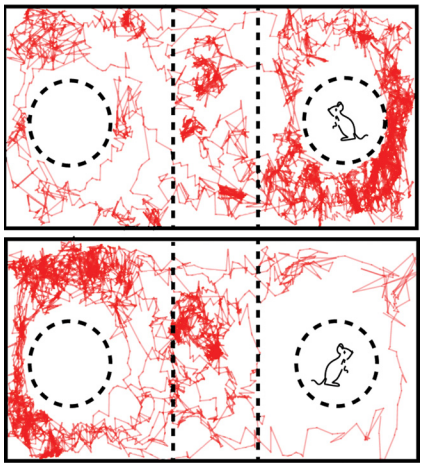
Behavioral/Cognitive

Amygdalar Inputs to Hippocampus Reduce Social Interaction

Ada C. Felix-Ortiz and Kay M. Tye

(see pages 586 –595)

The desire to interact with others varies over time and across individuals. Lesion and pharmacological studies have implicated both the basolateral amygdala (BLA) and the ventral hippocampus in social behaviors. Although these two areas are reciprocally connected, how they may interact during social behaviors had not been investigated. Therefore, Felix-Ortiz and Tye virally expressed channelrhodopsin or halorhodopsin in mouse BLA pyramidal neurons, allowing optical excitation or inhibition of the neurons' projections to the ventral hippocampus *in vivo*. When BLA inputs were inhibited, mice spent more time investigating a juvenile intruder mouse and less time exploring the cage. Conversely, when BLA inputs were excited, mice spent less time with the intruder and more time grooming themselves. The latter effects required activation of glutamate receptors in the hippocampus. The results indicate that BLA projections to the ventral hippocampus regulate social interaction behaviors and suggest that inhibition of this pathway could be a useful target for treating people who are socially impaired.



Mouse tracks before (top) and after (bottom) optogenetic activation of BLA projections to the hippocampus show that activation decreases the time spent near another mouse in a three-chamber sociability test. See the article by Felix-Ortiz and Tye for details.

Neurobiology of Disease

Increasing LRRK2 Expression Increases Cell Death Risk

Gaia Skibinski, Ken Nakamura, Mark R. Cookson, and Steven Finkbeiner

(see pages 418 – 433)

Mutations in leucine-rich-repeat kinase 2 (LRRK2) are the most common cause of hereditary Parkinson's disease. Why these mutations cause dopaminergic neurons to die is unknown, but possible mechanisms include increased kinase activity and misfolding that overloads protein quality control mechanisms and leads to accumulation of misfolded proteins in inclusion bodies. These mechanisms are difficult to disentangle because inhibiting LRRK2 kinase activity reduces LRRK2 stability and thus its accumulation, and reducing LRRK2 levels reduces cell-wide kinase activity. To resolve these issues, Skibinski et al. tracked hundreds of cultured rat neurons expressing mutant LRRK2 and used Cox proportional hazard analysis to determine which factors most strongly predicted cell death. Neurons with inclusion bodies were no more likely to die than neurons with similar LRRK2 levels but no inclusions, and neurons with similar LRRK2 levels were equally likely to die whether or not kinase activity was blocked. These data suggest that elevated LRRK2 increases neuronal death independently of inclusion formation and increased kinase activity.