This Week in The Journal

● Cellular/Molecular

Regulation of Intracellular Chloride Concentration and $GABA_A$ Signaling

Audrey C. Brumback and Kevin J. Staley

(see pages 1301–1312)

Activating $GABA_A$ receptors opens an intrinsic chloride channel, which normally results in chloride influx and hyperpolarization. In some contexts, however (e.g., development, neuropathic pain, and epilepsy), the intracellular chloride concentration (Cl_i) is elevated; thus, $GABA_A$ receptor activation leads to chloride efflux and depolarization. New experiments by Brumback and Staley reveal that the elevated Cl_i during development in rats is maintained by the ion transporter NKCC1. They showed that the direction of Cl^- transport by NKCC1 depends solely on the electrochemical driving force of Na^+, K^+, and Cl^-. Because of this, Cl_i can be regulated by altering the intracellular Na^+ concentration (Na_i). The authors demonstrate this by triggering trains of action potentials in hippocampal neurons. The resulting Na^+/K^+-pump-dependent changes in Na_i led to Cl_i elevation by NKCC1. Thus, the synaptic signal provided by GABA may depend on whether a neuron has been recently active.

▲ Development/Plasticity/Repair

Acetylcholine-Induced, Activity-Independent Long-Term Potentiation

David Fernández de Sevilla, Angel Núñez, Michel Borde, Roberto Malinow, and Washington Buño

(see pages 1469–1478)

Activation of muscarinic acetylcholine receptors (mAChRs) can induce synaptic enhancement in the absence of correlated activity, as demonstrated this week by Fernández de Sevilla et al. Puffing ACh onto the apical dendrites of rat hippocampal pyramidal cells in slice cultures resulted in a long-lasting increase in the EPSC. Experiments using calcium imaging, receptor blockers, and uncaging of inositol trisphosphate (IP_3) revealed that this form of long-term potentiation (LTP) requires mAChR activation, IP_3 production, activation of IP_3 receptors, and subsequent release of calcium from internal stores. The authors therefore named this form of plasticity LTP_{IP3}. Tracking of fluorescently tagged glutamate receptors (GluR1 and GluR2) suggested that LTP_{IP3} may result from increased insertion of AMPA receptors in dendritic spines. LTP_{IP3} did not require NMDA receptor activation, occurred even when action potentials were blocked with tetrodotoxin, and, when paired with traditional LTP-inducing protocols, doubled the amount of potentiation.

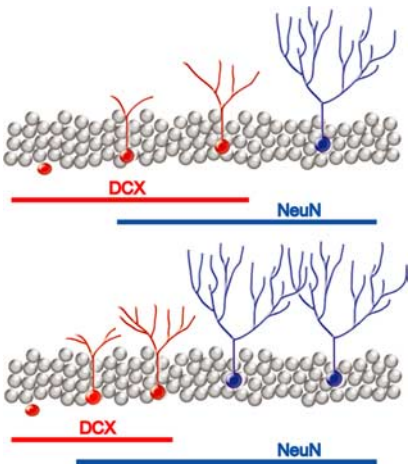
■ Behavioral/Systems/Cognitive

Fear Extinction in Developing Rats

Jee Hyun Kim and Rick Richardson

(see pages 1282–1290)

Conditioned responses (CRs) to fear can be extinguished by repeatedly presenting the conditioned stimulus (CS) without the unconditioned stimulus (US). In adult rats, extinction is thought to be produced primarily by inhibiting the CR, rather than by eliminating the conditioned memory, because the CR often reappears without reconditioning. Developing rats, however, don't show spontaneous recovery of the CR after extinction, suggesting that a different mechanism is involved. This week, Kim and Richardson provide more evidence that this is the case. They inactivated the amygdala in young rats during extinction training, reconditioning, or reextinction and found that initial extinction was amygdala dependent at postnatal day 17 (P17) and P24. After subsequent reconditioning at P26, however, reextinction was amygdala dependent only in those rats initially extinguished at P17. Interestingly, the switch from amygdala dependence to independence parallels temporally the maturation of hippocampus and medial prefrontal cortex—structures thought to be involved in extinction in adults.



Schematic drawing illustrates accelerated development in fluoxetine-treated neurons. The immature doublecortin (DCX)-expressing period is shorter, NeuN expression starts sooner, and dendrites develop more quickly in fluoxetine-treated neurons (bottom) than in controls (top). See the article by Wang et al. for details.

♦ Neurobiology of Disease

Accelerated Neuronal Maturation with Antidepressant Treatment

Jing-Wen Wang, Denis J. David, James E. Monckton, Fortunato Battaglia, and René Hen

(see pages 1374–1384)

Selective serotonin reuptake inhibitors (SSRIs) speed maturation of neurons as well as increase neurogenesis, according to a report by Wang et al. in this issue. Like others, these authors found that chronic treatment with the SSRI fluoxetine (Prozac) increased the number of newborn neurons in adult rats, as indicated by immunostaining for bromodeoxyuridine (BrdU) and the neuronal-specific nuclear protein (NeuN). In addition, fluoxetine treatment decreased the proportion of BrdU- and NeuN-positive neurons that expressed doublecortin, a marker of young neurons, suggesting that more newborn neurons had fully matured. Furthermore, those neurons that did express doublecortin had more extensive dendritic arbors than neurons in controls. Killing new neurons with x-irradiation prevented the reduced latency to eat food in a novel environment and blocked the enhancement of a form of LTP that is normally observed in rats chronically treated with fluoxetine, indicating that neurogenesis is required for some physiological and behavioral effects of fluoxetine.