This Week in The Journal

● Cellular/Molecular

PDP1 Regulates CLOCK Expression

Xiangzhong Zheng, Kyunghee Koh, Mallory Sowcik, Corinne J. Smith, Dechun Chen, et al.

(see pages 10920–10927)

PAR domain protein 1 (PDP1) is a *Drosophila* transcription factor whose expression level fluctuates with the circadian rhythm. Its role in the circadian clock is uncertain: although initial studies suggested PDP1 regulates expression of the master clock protein CLOCK, subsequent studies produced conflicting results. Knockout of all *Pdp1* isoforms results in embryonic lethality and therefore cannot resolve the issue. Zheng et al. have identified flies harboring a null mutation that affects only PDP1ε, the predominant PDP1 isoform in clock neurons. Mutant flies were arrhythmic both in constant darkness (DD) and during light–dark (LD) cycling . Expression of CLOCK and its target proteins, including its reciprocal clock regulator PERIOD, were greatly reduced in clock neurons in DD and were somewhat reduced in LD. Overexpression of CLOCK restored PERIOD levels but did not restore behavioral rhythms, suggesting that PDP1 regulates the central clock oscillator by increasing CLOCK expression, but also regulates clock output by another mechanism.

▲ Development/Plasticity/Repair

Enriched Environment Increases Retinal IGF-1 and BDNF

Silvia Landi, Francesca Ciucci, Lamberto Maffei, Nicoletta Berardi, and Maria Cristina Cenni

(see pages 10809–10819)

Compared to standard laboratory housing, enriched environments (EEs) that provide rodents with opportunities to explore, exercise, and interact socially increase neurogenesis, gliogenesis, and synaptogenesis, and improve performance on memory tasks. Housing pregnant rats in EE accelerates brain development in the pups, including development of retinal circuitry and visual acuity. Landi et al. provide evidence that the effects of EE on retinal development are mediated by increases in insulin-like growth factor 1 (IGF-1), which increases expression of brain-derived growth factor (BDNF) and the number of dopaminergic amacrine cells. IGF-1 was elevated in retinas of pups born into EE, and intraocular injection of IGF-1 mimicked the effects of EE, whereas blocking IGF receptors prevented these effects. Blocking BDNF prevented accelerated visual development in rats injected with IGF-1. Finally, IGF-1 injections and EE increased the number of tyrosine-hydroxylase expressing cells in the retina, and blocking this expression prevented the accelerated development of acuity produced by EE.

■ Behavioral/Systems/Cognitive

Fear Extinction Does Not Require mPFC in Young Rats

Jee Hyun Kim, Adam S. Hamlin, and Rick Richardson

(see pages 10802–10808)

Extinction of conditioned fear responses by repeated exposure to a conditioned stimulus in the absence of negative reinforcement is commonly used to treat anxiety disorders. With this training, subjects learn to suppress inappropriate fear responses; but the conditioned association remains and responses may reappear over time. Accumulating evidence suggests that extinction in young animals differs from that in adults. For example, reinstatement of extinguished fear responses is unlikely to occur in young animals, suggesting that the original association is erased, rather than the response being suppressed. Kim et al. report that the medial prefrontal cortex (mPFC), which is essential for retention of extinction learning in adult animals, is not required in preweanling rats. Although postnatal day 24 (P24) and P17 rats both exhibited reduced freezing behavior during extinction training, blocking activity in the mPFC before extinction training resulted in subsequent resumption of freezing response to the conditioned stimulus only in P24 rats.

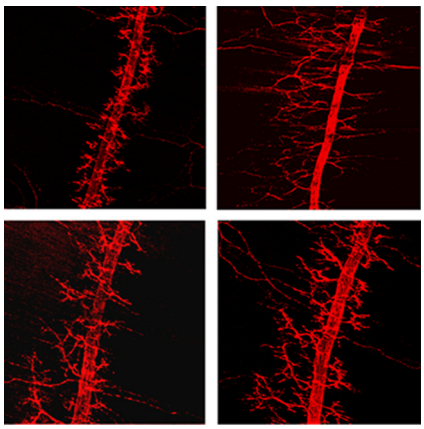
♦ Neurobiology of Disease

Pre- and Postsynaptic APP Promote Synapse Formation

Zilai Wang, Baiping Wang, Li Yang, Qinxi Guo, Nadia Aithmitti, et al.

(see pages 10788–10801)

Sequential cleavage of amyloid precursor protein (APP) produces β-amyloid, which forms plaques in Alzheimer's disease; but the normal physiological roles of APP and its cleavage products are unclear. APP is a transmembrane protein that is highly expressed in neurons but is also present in other tissues. Mice lacking APP and a related family member, APLP2, have abnormal synaptic structure and transmission at the neuromuscular junction (NMJ), resulting in part from deficient expression and activity of the high-affinity choline transporter, a crucial determinant of synaptic transmission in cholinergic neurons. Using muscle- or neuron-specific deletion of APP, Wang et al. show that both presynaptic and postsynaptic APP are required for normal synapse formation at the NMJ. Furthermore, cultured hippocampal neurons formed synaptic puncta on HEK293 cells that expressed APP. Such coculture experiments revealed that only the extracellular domain was required postsynaptically to induce synapse formation, whereas both the intracellular and extracellular domains were required presynaptically.



Restricted knockout of APP in neurons (bottom left) or muscle (bottom right) results in increases in nerve terminal sprouting (compared to controls, upper left) that is similar to sprouting in germline mutants (upper right). See the article by Wang et al. for details.