This Week in The Journal

● Cellular/Molecular

Adenylyl Cyclase Is Required for Long-Term Fear

Qiang Shan, Guy C.-K. Chan, and Daniel R. Storm

(see pages 12864–12867)

The hippocampus is required for memory formation, but once formed, long-term memory retention requires the cortex. In mice, contextual fear memory no longer requires hippocampal activity after a few weeks, and instead relies on anterior cingulate cortex. Shan et al. examined the role of a calcium–calmodulin-dependent type 1 adenylyl cyclase (AC1) in long-term (remote) fear memory by examining mice lacking or overexpressing this protein. Contextual fear was induced by delivering a foot shock to mice in a specific chamber. When returned to the chamber, all mice spent a significant amount of time freezing, suggesting that contextual fear learning was not impaired. No difference in freezing between wild-type and mutant mice was measured during the first 5 weeks, but at 11 weeks, mice lacking AC1 froze significantly less often than controls. At 22 weeks, freezing was reduced in wild-type mice, but was significantly more frequent in mice overexpressing AC1, suggesting that AC1 activity enhances remote fear retention.

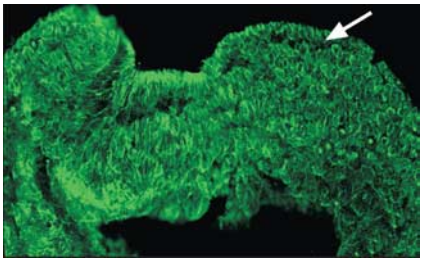
▲ Development/Plasticity/Repair

Neogenin Helps Form Neural Tube

Nigel Kee, Nicole Wilson, Melissa De Vries, DanaKai Bradford, Brian Key, and Helen M. Cooper

(see pages 12643–12653)

Development of the nervous system begins when cells on the dorsal surface of the embryo form the neural plate. Next, deep layer cells in the lateral regions of the plate elongate toward the dorsal surface and intercalate with superficial cells, forming neural folds. The neural folds elevate, eventually bending toward the midline and fusing to form the neural tube. Defects in neural tube closure occur in 1:1000 human pregnancies, causing anencephaly or spina bifida. Kee et al. now report that the receptor protein neogenin is essential in neural fold elevation. In *Xenopus*, knockdown of neogenin, which was expressed laterally in the neural plate, prevented elongation and intercalation of deep cells with superficial cells, likely by disrupting microtubule organization. Although the neural tube eventually formed, loss of neogenin disrupted intracellular interactions. Neuroepithelia cells did not adhere to each other or to the apical or basal surfaces, and therefore were highly disordered.



Knockdown of neogenin on one side of the *Xenopus* embryo (right) disrupted neural fold elevation (arrow). See the article by Kee et al. for details.

■ Behavioral/Systems/Cognitive

Neuropeptide Y Enhances Fear Extinction

Alisa R. Gutman,Yong Yang, Kerry J. Ressler, and Michael Davis

(see pages 12682–12690)

Neuropeptide Y (NPY) is widely expressed in the brain and is thought to moderate animals' response to stress. Reduced levels of NPY have been tied to alcoholism, anxiety, and post-traumatic stress disorder. Experiments reported this week by Gutman et al. suggest that NPY may promote resilience to stress in part by enhancing retention of fear extinction. Sudden acoustic stimuli produce startle responses in rats, and responses are increased when the sound is presented with a conditioned stimulus tied to foot shock. If the conditioned stimulus is repeatedly presented without foot shock, the fear is extinguished, and the conditioned stimulus no longer potentiates acoustic startle responses. Gutman et al. found that infusion of NPY into the basolateral amygdala reduced fear potentiation of startle and accelerated fear extinction. Moreover, NPY enhanced retention of extinction memory across sessions, whereas an NPY receptor antagonist reduced extinction retention, suggesting that NPY is involved in fear extinction learning.

♦ Neurobiology of Disease

Synapse Loss May Be Neuroprotective in HIV Dementia

Hee Jung Kim, Kirill A. Martemyanov, and Stanley A. Thayer

(see pages 12604–12613)

The HIV transcriptional activator Tat is secreted by infected macrophages and glia and causes neurodegeneration and cognitive decline. In the previous issue, we learned that Tat interacts with the NMDA receptor, possibly causing persistent channel activation that results in excitotoxic cell death. Neurons exposed to Tat lose synapses before they die, and because cognitive decline in HIV-associated dementia closely parallels synaptic loss, some treatment strategies have targeted this symptom. But now Kim et al. present evidence that the pathways underlying Tat-mediated synaptic loss diverge from those leading to neurodegeneration, and the former may represent neuronal attempts to limit excitotoxicity. In rat hippocampal cultures, inhibiting nitric oxide synthase prevented cell death, but did not decrease synapse loss. In contrast, preventing proteasomal degradation of the scaffolding protein PSD95 prevented synapse loss but made neurons more susceptible to Tat-induced degeneration. These results indicate that treatments for HIV-associated dementia should target molecules upstream of the pathway divergence.