This Week in The Journal

● Cellular/Molecular

P2X2 Receptor Expression Differs in Primates and Rodents

Alexandre Serrano, Gary Mo, Rebecca Grant, Michel Paré, Dajan O'Donnell, et al.

(see pages 11890–11896)

ATP released by distension of the bladder, gut, and other visceral tissues activates homomeric P2X3 and heteromeric P2X2/3 receptors on mechanosensory and nociceptive neurons. ATP is also released in the spinal cord, where it acts on glia and neurons involved in pain pathways. All this is true in rodents, at least; Serrano et al. now suggest that primates are somewhat different. Although expression of P2X3 was similar in dorsal root ganglion (DRG) of rats, monkeys, and humans, the P2X2 subunit was expressed at very low levels in primates. Furthermore, monkey DRG neurons did not exhibit slowly desensitizing responses—characteristic of P2X2/3 currents—to agonist *in vitro*. More importantly, the potency of P2X2 and P2X2/3 antagonists was greatly reduced in monkey DRG neurons, as well as in HEK cells expressing human P2X3. These results suggest that antagonists of these receptors, which reduce hyperalgesia in rodent models of chronic pain, may be less effective in humans.

▲ Development/Plasticity/Repair

Continuous Estrogen Treatment Does Not Affect Spine Density

Daniel T. Ohm, Erik B. Bloss, William G. Janssen, Karen C. Dietz, Shannon Wadsworth, et al.

(see pages 11700–11705)

Women's cognitive abilities fluctuate during the menstrual cycle. When estrogen levels are high, performance on verbal working memory increases; when levels are low, spatial ability improves. Working memory also declines after menopause, but whether hormone replacement therapy reverses this effect is controversial. Inconsistent results have been obtained partly because progesterone—which opposes estrogen actions in the brain—is usually prescribed along with estrogen. Nonetheless, an influential study found that unopposed estrogen treatment worsened cognitive performance and increased risk of dementia in postmenopausal women. Estrogen appeared to improve cognition in women who began treatment at younger ages, however. Another factor that may affect cognitive benefits of estrogen is treatment schedule (continuous vs. cyclic). Although studies in ovariectomized monkeys have found that cyclic estrogen treatment improves cognition and increases dendritic spine density in the dorsolateral prefrontal cortex, Ohm et al. report that neither continuous estrogen treatment nor cyclic estrogen combined with progesterone affected spine density.

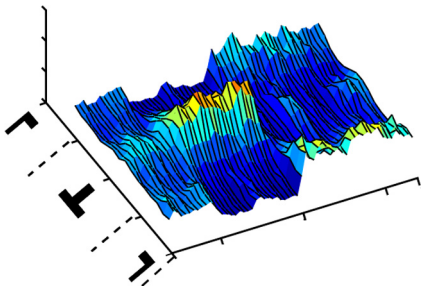
■ Behavioral/Systems/Cognitive

Two GABAergic Neurons Mediate Reversal Learning in Flies

Qingzhong Ren, Hao Li, Yanying Wu, Jing Ren, and Aike Guo

(see pages 11524–11538)

Animals must learn how to secure rewards and avoid punishment while remaining flexible enough to change their behavior when contingencies change. This flexibility is studied using reversal learning tasks: two cues are presented, one of which is associated with reward or punishment; after the association is learned, the reward or punishment is instead paired with the formerly neutral cue. To investigate the neural bases of such learning in *Drosophila*, Ren et al. used a visual discrimination task in which orientation toward one cue resulted in punishment. Normal flies quickly learned both the initial and the reversed association, but reversal learning was blocked by knocking down either $GABA_A$ receptors in the mushroom bodies or GABA synthesis in a single pair of giant GABAergic neurons that innervate the mushroom bodies. Remarkably, these treatments were specific for reversal learning: initial learning, extinction, and learning to discriminate between two novel stimuli remained intact.



The percentage of time (*y*-axis) normal flies spent orienting toward different visual targets (*z*-axis) across trials (*x*-axis). After 6 baseline trials, punishment was associated with orientation toward an upright T for 10 trials. Punishment was then associated with the inverted T. Flies avoided the punished direction before and after reversal. See the article by Ren et al. for details.

♦ Neurobiology of Disease

NF-κB Impairs Ciliogenesis, Causing Hydrocephalus

Michael Lattke, Alexander Magnutzki, Paul Walther, Thomas Wirth, and Bernd Baumann

(see pages 11511–11523)

Hydrocephalus is an accumulation of CSF that enlarges the cerebral ventricles and can impair development and function of adjacent brain regions. It typically results from increased CSF production, reduced absorption, or obstruction of CSF circulation. Although hydrocephalus often develops in association with neuroinflammation, the link between these phenomena is poorly understood. Lattke et al. examined this relationship in mice that conditionally expressed a constitutively active form of the IκB kinase complex (IKK2) in astrocytes and some ependymal cells. IKK2 activates nuclear factor κB (NF-κB), a transcription factor that triggers neuroinflammation. Early postnatal transgene expression activated NF-κB and caused upregulation of NF-κB target genes. This led to massive infiltration of macrophages into the ventricles, hydrocephalus formation, and abnormal hippocampal development. Neither obstruction of CSF flow nor fibrosis that could impair CSF resorption was detected; instead, poor development of cilia on ependymal cells that line the ventricles and promote CSF movement was the apparent cause of hydrocephalus.