This Week in The Journal

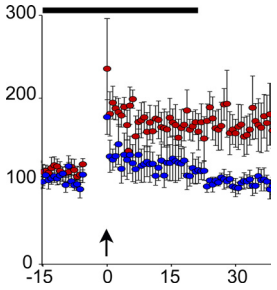
Development/Plasticity/Repair

Loss of Testosterone Increases Hippocampal Excitability

Vanessa A. Skucas, Aine M. Duffy, Lauren Harte-Hargrove, Alejandra Magagna-Poveda, Thomas Radman, et al.

(see pages 2338–2355)

Testosterone receptors are expressed at high levels in the hippocampus, suggesting testosterone influences hippocampal-dependent learning and memory. Testosterone levels decline with cognitive function as men age, and testosterone levels are particularly low in men with Alzheimer's disease. But studies exploring causal links between testosterone and cognitive performance have produced conflicting results, possibly because different tasks were used. To more directly assess the effects of testosterone on hippocampal function, Skucas et al. examined CA3 responses to mossy fiber stimulation in hippocampal slices from adult male rats that had undergone gonadectomy (Gdx) after puberty. The amplitude of field EPSPs and population spikes were greater, and more spikes were produced per stimulus in Gdx rats than in controls. Furthermore, stimulation that was unable to induce long-term potentiation in control rats did so in Gdx rats. These effects likely resulted from the increased expression of brain-derived neurotrophic factor (BDNF) in Gdx rats, because they were reversed by application of a BDNF receptor antagonist.



Stimulation of mossy fibers with two 25 Hz, 1 s trains, 10 s apart (at time indicated with arrow) induced LTP in hippocampal slices from Gdx rats (red). LTP was prevented by incubation of slices with dihydrotestosterone (blue) during time indicated by bar. See the article by Skucas et al. for details.

Systems/Circuits

Evolution of Serotonergic Responses May Allow Slugs to Swim

Joshua L. Lillvis and Paul S. Katz

(see pages 2709–2717)

The sea slug *Tritonia diomedea* exhibits escape swimming when electrically shocked. This behavior is produced by a central pattern generator that includes serotonergic dorsal swim interneurons (DSIs) and cerebral interneuron C2. DSI-mediated serotonergic modulation of C2 increases the amplitude of C2-evoked EPSPs in pedal ganglion neurons, and this modulation is necessary and sufficient to induce swimming. Although DSI and C2 homologs occur in all examined Nudipleura species, few species swim. Lillvis and Katz now suggest that parallel evolution of DSI–C2 neuromodulation led to independent evolution of swimming in distantly related Nudipleura species. As in *Tritonia*, stimulating DSI in *Pleurobranchaea* increased the amplitude of C2-evoked EPSPs in pedal interneurons. Likewise, bath application of serotonin enhanced C2-evoked EPSPs in both species. Interestingly, not all *Pleurobranchaea* could be induced to swim *in vivo*, and DSI modulated C2-evoked responses only in individuals that swam. Furthermore, neither DSI stimulation nor exogenous serotonin application increased C2-evoked EPSPs in *Hermissenda*, a closer relative of *Tritonia* that never swims.

Behavioral/Cognitive

Reduced CHT Expression Impairs Attention

Vinay Parikh, Megan St. Peters, Randy D. Blakely, and Martin Sarter

(see pages 2326–2337)

Cholinergic projections from the basal forebrain to the prefrontal cortex enhance attention. Neurons must import extracellular choline via the choline transporter (CHT) to produce acetylcholine (ACh), and allelic variations in CHT that reduce choline import are linked to attention-deficit/hyperactivity disorder. To investigate this link, Parikh et al. examined mice in which CHT expression was reduced by heterozygous deletion. In wild-type neurons, most CHT is localized to synaptic vesicles during rest and is transferred to the plasma membrane during synaptic activity. The resting distribution of CHT was shifted in CHT$^{+/-}$ mice: normal levels of CHT were present in the plasma membrane while levels in synaptic vesicles were much lower. Therefore, CHT$^{+/-}$ mice exhibited normal baseline extracellular choline concentrations, clearance of exogenous choline, and release of ACh. But stimulation that mimicked forebrain activity during attention tasks produced a smaller-than-normal increase in plasma-membrane CHT, and thus a smaller increase in ACh release. This may explain the poor performance of CHT$^{+/-}$ mice on a sustained attention task.

Neurobiology of Disease

Persistent Activity of mGluR1 May Underlie Epileptic State

Steven R. Young, Shih-Chieh Chuang, Wangfa Zhao, Robert K. S. Wong, and Riccardo Bianchi

(see pages 2526–2540)

Sustained stimulation of group 1 metabotropic glutamate receptors (mGluRs) in rodent hippocampal slices produces periods of prolonged, synchronous neuronal firing similar to ictal discharges occurring in epilepsy, and these continue to occur long after the inducing stimulus has been removed. Similar activation of mGluRs has been proposed to underlie epileptogenesis in fragile X syndrome. mGluR-induced epileptiform activity results from activation of a depolarizing voltage-dependent cation current, $I_{mGluR(V)}$, and suppression of the spike afterhyperpolarization (AHP) and leak conductance, making CA3 pyramidal neurons hyperexcitable. Synchronous discharges occurring after cessation of stimulation can be reversibly blocked by mGluR antagonists, suggesting that mGluRs remain active. Young et al. show that persistent changes in electrophysiological properties were unlikely to stem from residual agonist or self-sustained endogenous glutamate release. In addition, specific antagonists of mGluR1 and mGluR5 synergistically reduced hyperexcitability, but mGluR1 antagonists were more potent. The authors propose that sustained mGluR activity transforms the receptors into a persistently active state that does not require ligand binding.