This Week in The Journal

● Cellular/Molecular

Cholinergic Activation Switches LTP to LTD

Yanjun Zhao and Thanos Tzounopoulos

(see pages 3158 –3168)

At many synapses, both long-term potentiation (LTP) and depression (LTD) require NMDA receptor activation and calcium influx, but the intracellular signaling pathways underlying potentiation and depression subsequently diverge. The two pathways can be activated simultaneously, and the more robustly activated pathway then determines whether net potentiation or depression occurs. Often, the outcome is determined by the relative timing of presynaptic and postsynaptic spikes: if presynaptic firing precedes postsynaptic firing, LTP is produced, whereas the opposite pattern produces LTD. Neuromodulators can also alter the relative strength of LTP and LTD. Zhao and Tzounopoulos report that although pairing afferent stimulation with subsequent postsynaptic spikes normally produced LTP in mouse dorsal cochlear nucleus neurons, the same stimulation produced LTD when muscarinic acetylcholine receptors (mAChRs) were activated. This likely resulted from mAChR-induced activation of phospholipase C, which increases production of endocannabinoids, which in turn diffuse retrogradely and reduce presynaptic release probability. Blocking cannabinoid receptors unmasked LTP in the presence of mAChR agonists.

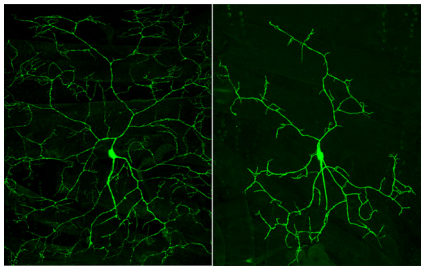
▲ Development/Plasticity/Repair

Dar1 Inhibition of Spastin Promotes Dendrite Growth

Bing Ye, Jung Hwan Kim, Limin Yang, Ian McLachlan, Susan Younger, et al.

(see pages 3309 –3319)

The functional specialization of axons and dendrites depends in part on their unique structural features: whereas dendrites are relatively wide at the base and taper toward the tip, axons are uniformly narrow throughout. These differences arise during development through selective targeting of proteins that regulate the actin and microtubule cytoskeleton. Differential growth of axons and dendrites is achieved in part by temporal segregation of their development (axons often are established before dendrites), but their growth is also controlled by different transcription factors. Ye et al. found that the *Drosophila* transcription factor *Dar1* is required for growth of dendrites, but not axons, in peripheral neurons. *Dar1*-deficient embryos had shorter, less branched dendrites than wild-type embryos, and overexpression of Dar1 increased dendritic length and branching. These effects likely resulted from Dar1-dependent inhibition of transcription of spastin, a microtubule-severing protein. Spastin transcript levels were increased in Dar1 mutants, and overexpression of spastin reduced dendritic growth and branching.



Loss of Dar1 (right) greatly reduces dendritic branching in *Drosophila* peripheral neurons. See Ye et al. for details.

■ Behavioral/Systems/Cognitive

Transcranial Magnetic Stimulation Adds Noise

Dietrich Samuel Schwarzkopf, Juha Silvanto, and Geraint Rees

(see pages 3143–3147)

Transcranial magnetic stimulation (TMS) induces current flow that alters neuronal activity in the brain. Exactly how TMS affects neuronal activity is debated, however. TMS is often used to inactivate small areas of cortex during performance of a task, suggesting that TMS suppresses neural communication. But under some circumstances, TMS facilitates performance, leading to the hypothesis that it introduces noise into the neural system. Although excessive noise obscures signals and impairs performance, when signals are just below the detection threshold, a small amount of noise can push those signals above threshold, thus improving detection. This is called stochastic resonance. To test whether TMS produces effects consistent with noise addition, Schwarzkopf et al. delivered different intensities of TMS while subjects performed a motion discrimination task. When discriminability was high, it was reduced by strong TMS. In contrast, when discriminability was low, it was improved by low-intensity TMS, supporting the hypothesis that TMS works by adding noise.

♦ Neurobiology of Disease

Attention Is Impaired in Mouse Model of Alzheimer's Disease

Carola Romberg, Mark P. Mattson, Mohamed R. Mughal, Timothy J. Bussey, and Lisa M. Saksida

(see pages 3500 –3507)

Memory loss is the most striking cognitive feature of Alzheimer's disease (AD), and spatial learning and memory are routinely tested in animal models of AD. Attention is also impaired in AD, however, and attention deficits can impair performance on memory tests. Human attention is often measured with serial reaction time tasks (SRTTs) in which subjects rapidly touch cues as they appear on a screen. Romberg et al. used a similar touchscreen test to study attention in mice. Transgenic mice in which AD-associated proteins were mutated learned to perform the SRTT as well as controls, but when attentional demand was increased by reducing stimulus duration, mutant mice made more errors. Error rate increased over many trials, suggesting that sustained attention was impaired. Attention deficits in AD likely result from disruption of cholinergic pathways, because enhancing cholinergic transmission reduces deficits. Likewise, a cholinesterase inhibitor reduced SRTT errors in mice, indicating that the deficit resulted from decreased cholinergic function.