This Week in The Journal

● Cellular/Molecular

The Battle of the LTDs in the Cerebellum

Wolfgang Mittmann and Michael Häusser

(see pages 5559–5570)

Purkinje cells provide the sole output of cerebellar cortex, thus serving as the final common pathway for cerebellar synaptic integration and plasticity. The cellular plasticity associated with cerebellar motor learning is thought to arise from long-term depression (LTD) of excitatory parallel fibers (PFs) triggered by simultaneous climbing fiber (CF) activity. Mittmann and Häusser show this week that it's not quite so simple: plasticity at feedforward inhibitory synapses is also important. The authors recorded from spontaneously spiking Purkinje cells in rat cerebellar slices. PF EPSPs increased Purkinje cell firing, whereas interneuron inhibitory PSPs reduced spiking. When CF inputs were paired with PF EPSPs or with interneuron IPSPs, LTD occurred in both inputs, but with opposite effects on Purkinje cell spiking. The net effect of this battle of the LTDs varied with inhibitory/excitatory input ratios. Plasticity produced a reduction in Purkinje cell spike output when there was only a small inhibitory component.

▲ Development/Plasticity/Repair

Dynein, LIS1, and Growth Cones

Peter W. Grabham, Garrett E. Seale, Malika Bennecib, Daniel J. Goldberg, and Richard B. Vallee

(see pages 5823–5834)

The molecular motor dynein and its regulatory factors dynactin and LIS1 associate with microtubules to promote cellular migration and axonal growth. This week, Grabham et al. examined the role of these molecules in growth cone dynamics. The authors treated embryonic chick dorsal root ganglion (DRG) neurons with laminin, which caused rapid reorganization of microtubules in growth cones as well as dynein staining that was concentrated at the leading edge. Dynactin and LIS1 were colocalized with dynein. A similar staining pattern was observed in growth cones of rat hippocampal neurons. Knockdown of LIS1 by RNA interference delayed polarization of hippocampal neurons and decreased axonal lengths. Dynein and LIS1 function-blocking antibodies reduced laminin-induced axon growth in chick DRG neurons. In neurons transfected with the microtubule plus end-tracking protein EB3, dynein antibodies caused retrograde movement of microtubule ends, reflecting retrograde actin flow and microtubule retreat from the growth cone periphery.

■ Behavioral/Systems/Cognitive

Reducing Cannabis Rewards

Marcello Solinas, Maria Scherma, Liana Fattore, Jessica Stroik, Carrie Wertheim, Gianluigi Tanda, Walter Fratta, and Steven R. Goldberg

(see pages 5615–5620)

This week, Solinas et al. focused on α_7 nicotinic receptors as a potential target for treatment of cannabis abuse. Homomeric α_7 receptors are coexpressed with the cannabinoid receptor CB1 in hippocampus and the mesolimbic dopamine system. The authors trained rats to discriminate between vehicle and delta-9-tetrahydrocannabinol (THC), the active ingredient in cannabis. The α_7 receptor-selective antagonist methyllycaconitine (MLA) diminished the ability of the rats to make this discrimination, whereas the non-α_7 receptor antagonist dihydrobetaerythroidine (DHBE) did not. Similarly, MLA, but not DHBE, reduced self-administration of the synthetic CB1 agonist WIN55,212-2, although at a slightly higher dose. MLA also blocked THC-induced elevations of dopamine in the shell of the nucleus accumbens, a molecular indicator of the rewarding effects of THC. Of relevance to potential clinical use, the doses used in rats did not cause depressant or toxic side effects.

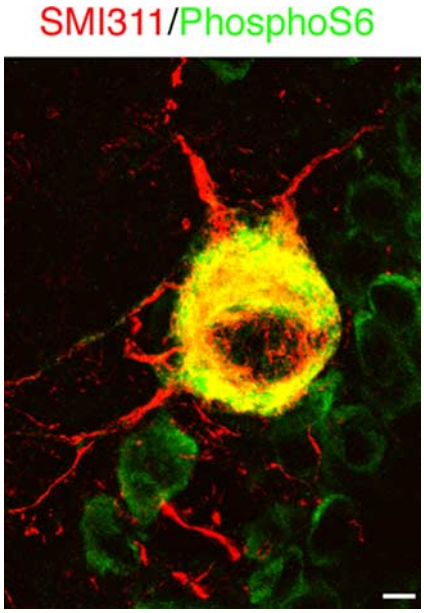
♦ Neurobiology of Disease

A Mouse Model of Tuberous Sclerosis

Lynsey Meikle, Delia M. Talos, Hiroaki Onda, Kristen Pollizzi, Alexander Rotenberg, Mustafa Sahin, Frances E. Jensen, and David J. Kwiatkowski

(see pages 5546–5558)

Tuberous sclerosis (TSC) arises from mutations in *TSC1* and *TSC2*, genes that encode tumor suppressor proteins. Cortical tubers in the brain parenchyma, a pathological hallmark of the disease, contain enlarged, dysplastic neurons, accompanied by neurological symptoms including seizures and developmental delay. In this week's *Journal*, Meikle et al. describe a new mouse model of TSC based on conditional deletion of Tsc1 in neurons. Neurons ceased to express *TSC1* around embryonic day 13. Developmental delays were apparent by postnatal day 5 and, unlike other TSC mouse models, the mice developed spontaneous seizures. Pathological features of TSC, such as enlarged, aberrant neurons in the cortex and hippocampus, and hypomyelination were also evident. The hypomyelination presumably resulted from axonal dysfunction. The mice had a wasting syndrome and died at 3–5 weeks of age. These observations support loss of neuronal *TSC1* as an important aspect of the clinical phenotype.



The image shows high-power view of typical enlarged dysplastic SMI311+/pS6+ neurons in the dentate granule cell layer. See the article by Meikle et al. for details.