This Week in The Journal

● Cellular/Molecular

CaM Kinase Produces LTP or LTD Depending on Phosphorylation State

Hyun Jae Pi, Nikolai Otmakhov, David Lemelin, Paul De Koninck, and John Lisman

(see pages 8704 – 8709)

Calcium entering through NMDA receptors activates calcium/calmodulin-dependent kinase II (CaMKII). With sufficient activation, CaMKII subunits phosphorylate each other at residue Thr286, allowing the kinase to remain autonomously active after calmodulin dissociates. The resulting long-lasting CaMKII activity produces long-term potentiation (LTP). But autonomously active CaMKII also undergoes autophosphorylation at residues Thr305 and Thr306, which blocks binding to calmodulin and other proteins and thus prevents reactivation of the kinase, hinders LTP, and facilitates long-term depression (LTD). Although deletion of the domain containing Thr286 produces constitutively active CaMKII that quickly saturates potentiation, mutating Thr286 to mimic phosphorylation—which should render the kinase autonomously active—does not saturate LTP. In fact, Pi et al. found that expressing of T286D CaMKII in rat hippocampal neurons depressed EPSCs. Whether T286D produced depression or potentiation depended on the phosphorylation state of Thr305/Thr306: when paired with Thr305/Thr306 mutations that prevented phosphorylation, T286D CaMKII potentiated synapses, whereas when paired with pseudophosphorylation of Thr305/Thr306, T286D CaMKII depressed synapses.

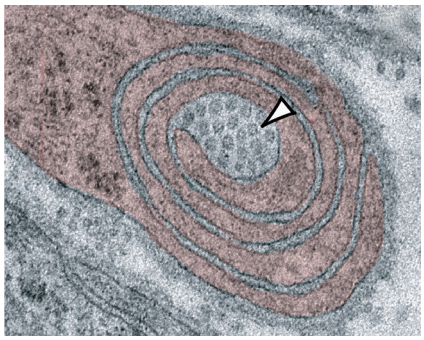
▲ Development/Plasticity/Repair

PTEN Regulates Myelination in PNS and CNS

Sandra Goebbels, Jan H. Oltrogge, Robert Kemper, Ingo Heilmann, Ingo Bormuth, et al.

(see pages 8953– 8964)

Many extracellular signaling molecules promote cell proliferation, differentiation, and survival by activating phosphoinositide 3-kinase (PI3K), which converts phosphatidylinositol 4,5-bisphosphate (PIP2) to the signaling molecule PIP3. Excessive growth and proliferation are prevented by the phosphatase and tensin homolog PTEN, which dephosphorylates PIP3. Goebbels et al. demonstrate the importance of these pathways in myelination. Conditional knockout of PTEN in mouse myelinating glia increased PIP3 levels, reduced PIP2 levels, and caused hypermyelination of axons in both PNS and CNS. In the CNS, oligodendrocyte processes excessively wrapped axons, producing thickened myelin sheaths without affecting the number of oligodendrocytes. In contrast, increased myelination in the PNS resulted in part from increases in the number of Schwann cells, some of which enwrapped collagen fibrils and small-diameter axons that are normally unmyelinated. Similar changes occurred after knock-out of PTEN in adult mice, suggesting that targeting PIP3 pathways might effectively treat demyelinating diseases.



Electron micrograph showing abnormal wrapping of collagen fibrils (arrowhead) by PTEN-null Remak Schwann cells (pseudocolored in red). See the article by Goebbels et al. for details.

■ Behavioral/Systems/Cognitive

Dopamine Levels Affect Temporal Discounting Rate

Alex Pine, Tamara Shiner, Ben Seymour, and Raymond J. Dolan

(see pages 8888 – 8896)

Although people generally prefer larger rewards to smaller ones, if forced to choose between an immediate small reward and a future large reward, they sometimes choose the smaller reward. Such "intertemporal choices" are influenced by the difference in the size of the rewards and how long one has to wait to receive the future reward. Weighting of these variables varies across individuals. Because people with altered dopamine function are more prone to choose smaller, immediate rewards, Pine et al. asked whether dopamine alters the influence of relative reward size (marginal utility) or delay (temporal discounting). All subjects chose smaller, sooner options more often after taking L-dopa than after taking placebo, and this effect was paralleled by larger decreases in activity in several brain areas as rewards became more delayed. A mathematical model based on the data suggested that L-dopa increased the rate of temporal discounting without affecting the rate of diminishing marginal utility.

♦ Neurobiology of Disease

Cortical Spreading Depression Activates Meningeal Nociceptors

XiChun Zhang, Dan Levy, Rodrigo Noseda, Vanessa Kainz, Moshe Jakubowski, et al.

(see pages 8807– 8814)

Many migraine sufferers experience visual disturbances (auras) that spread across the visual field ~20 min before headache onset. Cortical spreading depression (CSD)—a wave of neuronal activity followed by temporary silence—seems the most likely cause of migraine aura: CSD-like waves propagate in visual cortex of patients experiencing auras, and the propagation rate of CSD and auras are similar. Although the link between cortical depolarization and sensory auras is readily apparent, the relationship between CSD and headache is less clear. One hypothesis is that increased extracellular levels of potassium and glutamate produced by CSD activate meningeal nociceptors. Zhang et al. bolster this hypothesis, showing that stimulation of rat visual cortex to elicit CSD often resulted in long-lasting increases in firing rate of nociceptors recorded in the trigeminal nucleus. Increases in firing sometimes occurred immediately after cortical stimulation, but were sometimes delayed until ~15 min after the cessation of the CSD wave—approximately the same interval as between aura and headache onset.