This Week in The Journal

● Cellular/Molecular

Dephosphorylation of Connexin Reduces Coupling

W. Wade Kothmann, Stephen C. Massey, and John O'Brien

(see pages 14903–14911)

Rod bipolar cells transmit information to retinal ganglion cells only via AII amacrine cells, which are electrically coupled to each other and to cone bipolar cells. Coupling between AII cells varies with light levels to optimize detection and acuity. Dopamine, which is released in bright light, binds to D_1 receptors on AII cells, thereby activating adenylyl cyclase, increasing cAMP levels, and activating protein kinase A (PKA). Because PKA can phosphorylate the gap junction protein connexin 36, uncoupling of AII cells was expected to result from such phosphorylation. But Kothmann et al. show that in rabbit retina, D_1 agonist decreased phosphorylation of connexin, whereas antagonist increased connexin phosphorylation and AII cell coupling. Inhibiting PKA blocked the effect of agonist, as shown previously, but the effects were also blocked by inhibiting protein phosphatase 2A (PP2A). Activating PKA decreased connexin phosphorylation, and inhibiting PP2A prevented this effect, suggesting that PKA phosphorylates PP2A, leading to dephosphorylation of connexin.

▲ Development/Plasticity/Repair

Chondroitinase Modestly Accelerates Functional Recovery

Veronica J. Tom, Harra R. Sandrow-Feinberg, Kassi Miller, Lauren Santi, Theresa Connors, et al.

(see pages 14881–14890)

Researchers have had some success developing treatments that minimize damage and maximize recovery when administered immediately after spinal cord injury. But at chronic stages, when axons have further degenerated and lost more intrinsic growth capacity and the inhibitory glial scar is well established, the barriers to recovery seem insurmountable. Tom et al. investigated whether a combination of strategies that showed promise in treating acute injury would work if attempted 2 months after injury in rats. A segment of peripheral nerve infused with glial-cell-line-derived neurotrophic factor to stimulate axon growth was grafted into the lesion site, and the nerve end was treated with chondroitinase to digest the glial scar. As usual, rats showed significant spontaneous recovery of function before the graft was inserted. Insertion of the graft caused some loss of this function, but function recovered, and chondroitinase sped recovery. Nonetheless, rats did not appear to recover function beyond the level reached spontaneously.

■ Behavioral/Systems/Cognitive

Dopamine Acts Directly on Retinal Ganglion Cells

Yuki Hayashida, Carolina Varela Rodríguez, Genki Ogata, Gloria J. Partida, Hanako Oi, et al.

(see pages 15001–15016)

In addition to uncoupling AII amacrine cells, dopamine reduces spiking of retinal ganglion cells (RGCs), which is hypothesized to prevent saturation of responses in bright light. This effect has generally been thought to be indirect, resulting from dopaminergic actions on other retinal cells and subsequent alteration of input to RGCs. But Hayashida et al. show that D_{1a} dopamine receptors are present in rat RGCs, which were definitively identified by backfilling via the optic nerve. In dissociated cultures of RGCs, dopamine D_1 agonist decreased the number of spikes elicited by current injection, increased spike width, and decreased spike amplitude. Contrary to previous results, dopamine's effects persisted when the hyperpolarization-activated cation current I_h was inhibited. Instead, dopamine appeared to reduce spiking by decreasing the voltage-activated sodium current. Under control conditions, successive current injections produced similar spike trains, with little variability in spike timing. Interestingly, dopamine appeared to reduce the number of spikes without altering the timing of the remaining spikes.

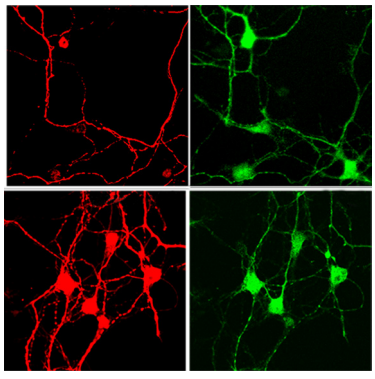
♦ Neurobiology of Disease

Pin1 and Phosphatase Regulate Neurofilament Phosphorylation

Parvathi Rudrabhatla, Wayne Albers, and Harish C. Pant

(see pages 14869–14880)

Many proteins are regulated by conformational changes brought about by phosphorylation and dephosphorylation by kinases and phosphatases. In some proteins that are regulated by phosphorylation of serine or threonine residues that precede a proline (i.e., proline-directed phosphorylation), an additional level of regulation is mediated by Pin1, which catalyzes the isomerization of proline when the motif is phosphorylated. Depending on the protein, Pin1 can promote phosphorylation or dephosphorylation, as well as regulating downstream processing such as protein cleavage or degradation. Abnormal proline-directed phosphorylation of cytoskeletal proteins is associated with several neurodegenerative diseases. Although many studies have explored the roles of kinases in this process, accumulating evidence suggests phosphatases and Pin1 may be critical. Rudrabhatla et al. found that inhibition of protein phosphatase 2A (PP2A) caused abnormal phosphorylation of neurofilament proteins in somata of cultured neurons, reduced transport of neurofilaments into axons, and ultimately led to apoptosis. Reducing Pin1 activity prevented the effects of the inhibitors.



Phosphorylated neurofilaments (red) are present only in axons, whereas PP2A (green) is expressed at high levels in the somata of cultured neurons in control conditions (top). Inhibition of PP2A (bottom) caused an increase in phosphorylated neurofilaments in somata. See the article by Rudrabhatla et al. for details.