This Week in The Journal

● Cellular/Molecular

GSK3β Is Involved in Axonal Pruning

Mark Chen, Janice A. Maloney, Dara Y. Kallop, Jasvinder K. Atwal, Stephen J. Tam, et al.

(see pages 13439–13453)

Glycogen synthase kinase 3 (GSK3), a constitutively active protein, phosphorylates various transcription factors and microtubule-associated proteins, inactivating them and promoting their degradation. Growth factors induce phosphorylation and thus inactivation of GSK3, and this inactivation is required for neurogenesis, migration, and axon growth to occur. In contrast, excessive GSK3 activity is implicated in autism, schizophrenia, and neurodegeneration. Chen et al. show that activity of the GSK3 β isoform is also involved in axonal pruning during development. Knockdown of GSK3β in mouse retinal ganglion cells reduced axonal pruning in the superior colliculus *in vivo*. Furthermore, axon degeneration induced by removal of nerve growth factor (NGF) in dorsal root ganglion explants was accompanied by dephosphorylation (and thus activation) of GSK3β. Degeneration was reduced by inhibiting GSK3β, but only if inhibitors reached the soma, suggesting that GSK3β activation promotes degeneration via transcriptional, rather than cytoskeletal, effects. These transcriptional effects likely include upregulation of the transcription factors dleu2 and tbx6.

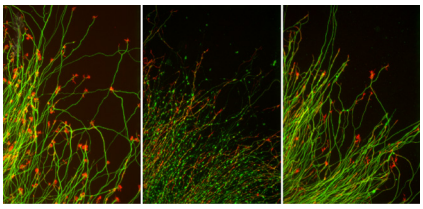
▲ Development/Plasticity/Repair

Endocannabinoids Regulate Spontaneous Activity

Carlos Gonzalez-Islas, Miguel Angel Garcia-Bereguiain, and Peter Wenner

(see pages 13597–13607)

Spontaneous activity in the developing nervous system guides axon growth and refines synaptic connections. In embryonic chicken spinal cord, episodes of spontaneous network activity (SNA) are initiated by quantal release of GABA and glutamate (both of which are excitatory at this time), which



Labeling of microtubules (green) and actin (red) reveals axons growing in the presence of NGF (left) and degenerating after NGF withdrawal (middle). GSK3β inhibitors reduced degeneration after NGF withdrawal (right). See the article by Chen et al. for details.

causes motor neurons to spike. SNA episodes are followed by periods during which spontaneous and evoked glutamatergic activity is suppressed. In the mature nervous system, endocannabinoid synthesis and release are triggered by postsynaptic depolarization, and endocannabinoids inhibit evoked presynaptic release. Gonzalez-Islas et al. hypothesized that a similar phenomenon occurs during embryonic SNA. Contrary to this hypothesis, neither blocking endocannabinoid receptors nor increasing endocannabinoid levels affected evoked glutamate release or suppression of glutamatergic activity after an SNA episode. Nonetheless, increasing or decreasing endocannabinoid signaling decreased or increased miniature EPSC (mEPSC) frequency, respectively, suggesting that endocannabinoids tonically inhibit quantal release. In this way, endocannabinoid signaling regulated the frequency of SNA episodes.

■ Behavioral/Systems/Cognitive

Adaptation and Perceptual Learning Interact

David P. McGovern, Neil W. Roach, and Ben S. Webb

(see pages 13621–13629)

Prolonged viewing of a stimulus produces adaptation, which reduces neural responses to that stimulus. This can aid or hinder discrimination of similar stimuli. For example, visual adaptation to vertically moving dots improves people's ability to discriminate movement in near-vertical directions, whereas adaptation to dots moving 20° from vertical impairs discrimination of near-vertical motion. Practicing perceptual discrimination often improves performance, but little is known about whether and how perceptual learning and adaptation interact. To address this, McGovern et al. asked people to practice discriminating near-vertical motion while adapted to 20° motion, then tested subjects' ability to discriminate such motion while adapted to 0°, 20°, and 50° motion. Practice improved performance for discrimination while adapted to 20° motion so much that adapted performance surpassed unadapted performance. But the same training worsened performance while adapted to 0° motion, making performance worse than in the unadapted state. The neural bases for these interactions remain unknown.

♦ Neurobiology of Disease

MeCP2 Has a Role in Homeostatic Plasticity

Melissa P. Blackman, Biljana Djukic, Sacha B. Nelson, and Gina G. Turrigiano

(see pages 13529–13536)

Methyl-CpG binding protein 2 (MeCP2) binds to methylated CpG dinucleotides in DNA, causing chromatin compaction and making nearby genes inaccessible for transcription. Mutations in MECP2 cause several disorders, including mild mental retardation, autism, and Rett syndrome (RTT). MeCP2 expression increases as neurons mature, and loss of MeCP2 reduces the number of glutamatergic synapses in mouse cortex and hippocampus, resulting in decreased excitatory drive. Results from Blackman et al. suggest that MeCP2 is required not only for maintenance of glutamatergic synapses, but also for homeostatic regulation of glutamatergic synaptic strength. Consistent with previous results, knockdown of MeCP2 in a subset of cultured rat cortical pyramidal neurons reduced the number of glutamatergic synapses. Additionally, neither tetrodotoxin nor AMPA receptor antagonist produced homeostatic increases in miniature EPSC amplitude in MeCP2-deficient neurons. Similarly, visual deprivation did not increase miniature EPSC amplitude in visual cortical neurons in MeCP2-null mice, as it does in wild-type mice.