This Week in The Journal

Development/Plasticity/Repair

GABAergic Signaling Promotes Neurogenesis via NFATc4

Giorgia Quadrato, Mohamed Y. Elnaggar, Ceren Duman, Andrea Sabino, Kirsi Forsberg, et al.

(see pages 8630–8645)

Effective antidepressant treatments stimulate neurogenesis in the adult hippocampus at least partly by increasing levels of brain-derived neurotrophic factor (BDNF), which stimulates GABAergic signaling. Anti-anxiety medications, which also enhance GABAergic signaling, may work by stimulating neurogenesis as well. Hippocampal neural precursor cells (NPCs) express the $GABA_A$ receptor subunits $\alpha 2$ (GABRA2) and $\alpha 4$ (GABRA4), and GABAergic signaling, which depolarizes NPCs, stimulates differentiation and incorporation of new neurons into neural circuits. Quadrato et al. report that the $GABA_A$ receptor agonist muscimol caused activation of the activity-dependent transcription factor NFATc4 in mouse NPCs. Moreover, knocking out NFATc4 prevented both muscimol-induced enhancement of neuronal differentiation and muscimol-induced reductions in anxiety-like behaviors measured with the elevated plus maze. Depleting newborn neurons also reduced the anxiolytic effects of muscimol, further linking neurogenesis to reduced anxiety. Interestingly, NFATc4 promoted expression of GABRA2 and GABRA4 expression in these cells, suggesting the presence of a positive feedback loop between GABAergic signaling and NFATc4 activity.

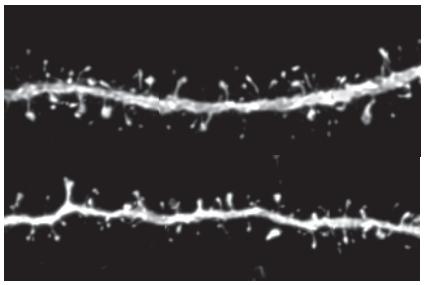
Systems/Circuits

High Corticosterone Levels May Exacerbate Cognitive Decline

Rachel M. Anderson, Andrew K. Birnie, Norah K. Koblesky, Sara A. Romig-Martin, and Jason J. Radley

(see pages 8387–8397)

Cognitive functions mediated by the prefrontal cortex (PFC) decline with age. This decline is associated with a loss of dendritic spines, particularly thin spines that are thought to be important for learning. The extent of cognitive decline during aging varies greatly across individuals, and this variability might stem partly from differences in stress experience throughout life. Indeed, subjecting young rats to chronic stress causes cognitive impairment and changes in dendritic structures similar to those that occur with aging. Anderson et al. extend these results by showing that high levels of the stress hormone corticosterone in the absence of deliberate stress exposure were associated with impaired cognitive function in old rats. Although corticosterone level in individual rats was not correlated with performance on a PFC-dependent task, old rats were worse on average than young rats, and old rats with high corticosterone levels were particularly impaired. Furthermore, old rats with high corticosterone levels had a lower density of thin spines in PFC than rats in other groups.



The density of thin spines in layer 2/3 of the prelimbic medial PFC in old rats with low corticosterone levels (top) was higher than in old rats with high corticosterone levels (bottom). See the article by Anderson et al. for details.

Behavioral/Cognitive

Near-Threshold Stimuli Reduce Training Generalization

Shao-Chin Hung and Aaron R. Seitz

(see pages 8423–8431)

Training on a perceptual task, such as judging whether two line segments are collinear, rapidly improves performance. Although such training could conceivably aid rehabilitation after injury, most studies have found that improved performance is limited to the specific task and, in the case of visual perceptual training, the retinal location where training stimuli are presented. Some recent studies, however, have found that training generalizes to an untrained region under some circumstances, for example when a different perceptual task (e.g., orientation discrimination) is trained in the other region. Hung and Seitz have found a simple explanation for differences in the generalization of perceptual training in different studies: the studies use different training procedures. Specifically, they found that the extent to which improvement transferred to a different region depended on how many near-threshold stimuli were presented during training. For multiple stimulus types, increasing the number of near-threshold stimuli reduced generalization. The data suggest that different types of training improve performance via different neural mechanisms.

Neurobiology of Disease

Sulfatide Inhibits Proliferation of Th17 Cells

Marcin P. Mycko, Beata Sliwinska, Maria Cichalewska, Hanna Cwiklinska, Cedric S. Raine, et al.

(see pages 8646–8658)

Multiple sclerosis (MS) is an autoimmune disease in which helper T (Th) cells that recognize myelin antigens enter the brain and cause inflammation, demyelination, and eventual axonal degeneration. In addition to protein antigens, Th cells can recognize glycolipids, particularly sulfatides, a major constituent of myelin. Although healthy people have Th cells that recognize myelin antigens, these cells are normally kept in a nonreactive state by peripheral regulatory immune cells. Defects in this regulation are thought to allow myelin-reactive Th cells to become activated. Subsequent entry of Th17-type cells into the brain leads to breakdown of the blood–brain barrier, which allows entry of additional immune cells, thus promoting inflammation and demyelination. Interestingly, sulfatide immunization has been shown to protect mice from experimental autoimmune encephalitis (EAE), a model of MS, by inhibiting the function of Th cells that recognize myelin proteins. Mycko et al. have discovered that sulfatide also protects against EAE by selectively suppressing differentiation of Th17 cells in response to myelin protein antigens.