This Week in The Journal

Cellular/Molecular

Amygdalar Axo-Axonal Synapses Cover Spike-Initiating Zones

Judit M. Veres, Gergö Attila Nagy, Viktória Krisztina Vereczki, Tibor Andrási, and Norbert Hájos

(see pages 16194–16206)

GABAergic inhibition not only can suppress spiking of postsynaptic cells, it can also influence when spikes occur, thus contributing to synchronization. Axo-axonal cells (AACs), which primarily target axon initial segments (AISs), may have a particularly strong influence over principal cell firing. AACs in the basolateral amygdala fire in response to noxious stimuli and might play a role in fear conditioning. Because of their potential importance, Veres et al. delved deeper into the structure and function of amygdalar AAC synapses. Each AAC made 2–16 inhibitory synapses with the AIS of principal neurons, and the average number of inhibitory inputs to an AIS was 52, suggesting each principal neuron receives input from 4–10 AACs. Most synaptic boutons were located 20–40 μm from the soma, closely overlapping with the region of highest sodium channel density. As predicted, evoking spike bursts in AACs was sufficient to greatly reduce the probability of postsynaptic cell spiking and could delay spiking for up to 27 ms.

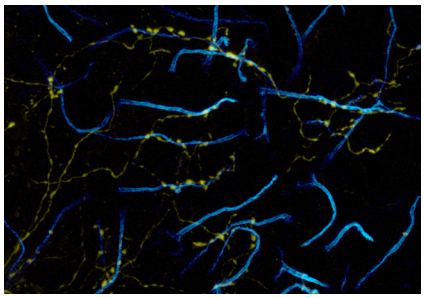
Systems/Circuits

Failure of Astrocytic Glutamate Uptake Might Cause Depression

Wanpeng Cui, Hiroaki Mizukami, Michiko Yanagisawa, Tomomi Aida, Masatoshi Nomura, et al.

(see pages 16273–16285)

Many antidepressant treatments target monoamine signaling, which is often disrupted in depressed people. This disruption may stem from hyperactivity in the lateral habenula (LHb), which regulates monoaminergic midbrain nuclei: increased habenular activity has been reported not only in patients with major depression, but also in animal models. What causes habenular hyperactivity is unknown, but reduced glutamate uptake by astrocytes might be a factor. Indeed, reduced expression of a glial glutamate transporter (SLC1A2) has been reported in patients with major depressive disorder and allelic variation in *SLC1A2* is associated with suicide attempts. Moreover, Cui et al. found that inhibiting the homolog of SLC1A2 (GLT-1) in mouse LHb increased firing rate of LHb neurons, increased activation in downstream GABAergic neurons, and reduced activation of those neurons' serotonergic and dopaminergic targets. In addition, inhibiting habenular GLT-1 produced depression-related behavior. Knocking out GLT-1 selectively in habenular astrocytes also increased spiking of LHb neurons and produced depression-like phenotypes that were reversed by an antidepressant serotonin-reuptake inhibitor.



Axon terminal cartridges of axo-axonic cells (yellow) form around axon initial segments (blue) of principal neurons in mouse basolateral amygdala. See the article by Veres et al. for details.

Behavioral/Cognitive

Social Interaction Improves Cognitive Performance in Mice

Ya-Hsin Hsiao, Hui-Chi Hung, Shun-Hua Chen, and Po-Wu Gean

(see pages 16207–16219)

Social isolation during aging increases the risk of dementia and Alzheimer's disease (AD); similarly, isolation reduces cognitive performance in AD-model mice. In contrast, Hsiao et al. found that housing 6-month-old AD-model mice with younger "helper" mice for 3 months improved contextual fear memory, and mice that performed better on the fear memory task also performed better on spatial learning, memory, and recognition tasks. These memory improvements were correlated with the amount of interaction between mice in a short-term interaction test: memory performance did not improve if helper mice showed minimal interaction with AD mice. The memory-enhancing effects of social interaction were attributable in part to increased expression of brain-derived neurotrophic factor (BDNF) and associated increases in neurogenesis during the co-housing period. Knocking down *Bdnf*, inhibiting stem cell proliferation, or selectively killing neurons generated during co-housing blocked improvements in memory performance. In contrast, overexpressing *Bdnf* increased neurogenesis and improved fear memory in AD mice co-housed with helpers that showed low levels of social interaction.

Neurobiology of Disease

Traumatic Brain Injury Disrupts the Glymphatic System

Jeffrey J. Iliff, Michael J. Chen, Benjamin A. Plog, Douglas M. Zeppenfeld, Melissa Soltero, et al.

(see pages 16180–16193)

Traumatic brain injury (TBI) increases the risk for developing dementia and causes intracellular accumulation of hyperphosphorylated tau—a feature of several neurodegenerative diseases. How TBI produces these effects is unclear, but disruption of the glymphatic system—a network of channels that lie between blood vessels and astrocytic endfeet—may be a factor. Analogous to the peripheral lymphatic system, the glymphatic system carries CSF through interstitial spaces and clears extracellular waste. Iliff et al. found that, in mice, TBI slowed the movement of CSF from the subarachnoid space into the brain parenchyma and slowed clearance of injected solutes for at least 4 weeks. Knocking out aquaporin-4, a channel protein that localizes to astrocytic endfeet and is important for glymphatic function, exacerbated the effects of TBI: it further reduced solute clearance, increased interstitial and intraneuronal accumulation of abnormally phosphorylated tau (which was cleared via the glymphatic system in healthy mice), increased axonal degeneration, and worsened performance on motor and cognitive tests.