This Week in The Journal

Cellular/Molecular

Forebrain NAD$^+$ Knockout Causes Atrophy and Gliosis

Liana Roberts Stein, David F. Wozniak, Joshua T. Dearborn, Shunsuke Kubota, Rajendra S. Apte, et al.

(see pages 5800–5815)

Nicotinamide adenine dinucleotide (NAD$^+$) is well known for its role as a coenzyme in redox reactions, particularly glycolysis and oxidative phosphorylation. But NAD$^+$ has many other important roles, such as being a substrate for situins, which help cells adapt to low energy states and thereby slow aging. Because NAD$^+$ is rapidly consumed, it must be continuously replenished to maintain cell viability. Most NAD$^+$ is synthesized in adipose and liver cells, where its chief biosynthetic enzyme, nicotinamide phosphoribosyltransferase (Nampt) is abundant. Nampt levels are low in most of the brain, but it is expressed at relatively high levels in hippocampal, and some cortical, pyramidal neurons. Therefore, cell-autonomous NAD$^+$ production may be important in these neurons. In support of this hypothesis, Stein et al. found that knocking out Nampt selectively in postnatal forebrain excitatory neurons caused brain atrophy, astrogliosis, and microgliosis, as well as abnormal dendritic morphology in the hippocampus. These anatomical changes were accompanied by abnormal behavior, particularly increases in locomotion and exploration.

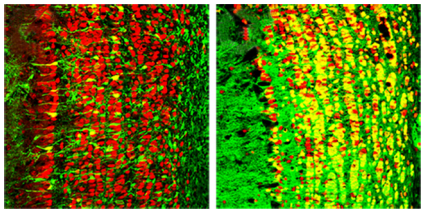
Development/Plasticity/Repair

Adult-Born Neurons Are Needed for Flexible Odor Learning

Masayuki Sakamoto, Nao Ieki, Goichi Miyoshi, Daisuke Mochimaru, Hitoshi Miyachi, et al.

(see pages 5788–5799)

Throughout postnatal life, the subventricular zone generates new neurons that migrate to the olfactory bulb (OB) and differentiate into inhibitory interneurons. The extent to which these neurons integrate into existing olfactory circuits and the role, if any, they play in olfactory learning remain unclear, however. To address these questions, Sakamoto et al. first selectively labeled postnatally generated SVZ neurons in mice and then suppressed transmitter release selectively in these neurons. Postnatally generated neurons differentiated into several subclasses of OB interneurons. Initially, newborn neurons increased the total number of OB neurons, but after postnatal day 35, the number of neurons stabilized and newborn neurons began to replace embryonically generated neurons. Inhibiting neurotransmitter release selectively in postnatally generated OB interneurons did not obviously affect animals' ability to discriminate two similar odors or to associate one of the odors with a sugar reward. But the animals were impaired when the reward pairing was reversed, indicating that postnatally born neurons contribute to making flexible associations.



In the granule cell layer of the olfactory bulb, the proportion of neurons (red) that were generated postnatally (green) greatly increases between postnatal days 7 (left) and 90 (right). See the article by Sakamoto et al. for details.

Behavioral/Cognitive

Midbrain Area Is Hyperactive in Generalized Anxiety Disorder

Jiook Cha, Joshua M. Carlson, Daniel J. DeDora, Tsafrir Greenberg, Greg H. Proudfit, et al.

(see pages 5855–5860)

To thrive in the world, we must distinguish cues that indicate potential threats from similar, unthreatening stimuli. This ability appears to be impaired in people with generalized anxiety disorder (GAD). Because the midbrain ventral tegmental area (VTA) is thought to have a role in identifying aversive stimuli, Cha et al. asked whether VTA is hyperactive in people with GAD. Volunteers were told that a midsize conditioned stimulus (CS) would sometimes be followed by an electric shock, but no shock would occur after larger or smaller stimuli (GS). Functional magnetic resonance imaging revealed that VTA activity increased during CS presentation both in women diagnosed with GAD and in controls. With GS presentation, VTA activity in controls scaled with the similarity between GS and CS, and VTA–hippocampus coupling increased. In people with GAD, however, VTA activity increased uniformly for all stimuli, and GS increased VTA–prefrontal–cortical coupling. These results suggest that mesocorticolimbic circuits involved in threat detection are dysfunctional in people with GAD.

Neurobiology of Disease

GluK1 Is Unnecessary for Seizure Induction

Brita Fritsch, Janine Reis, Maciej Gasior, Rafal M. Kaminski, and Michael A. Rogawski

(see pages 5765–5775)

Maintaining a proper balance between excitation and inhibition is essential for normal brain function. Loss of this balance contributes to several neurological conditions, including epilepsy. Kainate receptors are upregulated in human epileptic brain, and repeated kainate injections induce recurrent seizures in rodents, in part by activating receptors containing the GluK2 subunit. The role of GluK1-containing receptors is unclear, but some studies have suggested they protect against seizures by activating inhibitory neurons. In support of this hypothesis, Fritsch et al. found that higher doses of kainate were required to induce seizures in GluK2-null than in wild-type mice, but the seizure threshold was reduced in GluK1-null mice. In contrast, the threshold for seizure induction by the convulsant drug PTZ, AMPA, corneal electroshock, or olfactory bulb kindling was similar in wild-type and GluK1-null mice. Moreover, although high doses of a GluK1 agonist induced seizures in wild-type mice, the same dose induced seizures in GluK1-null mice. Thus, GluK1 appears unnecessary for seizure induction, and may sometimes be protective.