This Week in The Journal

● Cellular/Molecular

Synapsin Tethers Resting Vesicles

Ayelet Orenbuch, Lee Shalev, Vincenzo Marra, Isaac Sinai, Yotam Lavy, et al.

(see pages 3969 –3980)

Synaptic vesicles are classified into groups based on their localization and dynamics. "Readily releasable" vesicles are docked at active zones and are quickly released upon stimulation; "recycling" vesicles diffuse within nerve terminals and are released upon moderate stimulation; and "resting" vesicles are tethered and released only upon strong stimulation. Vesicles can move between pools, and recycling vesicles have been hypothesized to enter the resting pool by associating with tethering proteins. Orenbuch et al. provide evidence that synapsin is the tether. Although a previous study reported that synapsin knock-out did not affect the mobility of FM1-43-labeled vesicles, this dye only labels recycling vesicles. Orenbuch et al. found that the average mobility of the total vesicle pool was less than that of FM1-43-labeled vesicles, reflecting the relative immobility of resting vesicles. Synapsin knock-out increased the average mobility of the total pool to that of the recycling pool, suggesting that synapsin immobilizes resting vesicles.

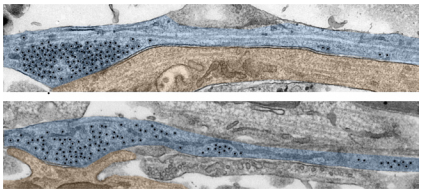
▲ Development/Plasticity/Repair

H1N1 Infection Alters Neuronal Structure and Function

Heidi A. Jurgens, Kaushik Amancherla, and Rodney W. Johnson

(see pages 3958 –3968)

Peripheral infections cause immune cells to secrete proinflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). These molecules activate sensory neurons that project to brainstem neurons, which in turn project to the amygdala and hypothalamus. Circulating cytokines also induce choroid plexus and circumventricular organ cells to release cytokines that enter the brain and activate



In the axons (blue) of wild-type neurons (top) vesicles (black dots) are clustered near synaptic terminals, whereas in synapsin-null neurons (bottom), vesicles are more mobile and disperse into the axon shaft. See the article by Orenbuch et al. for details.

microglia, which secrete more cytokines. Together, these effects lead to changes in behavior and cognition, including reduced appetite, fatigue, irritability, loss of interest in surroundings, and impaired attention and memory. Jurgens et al. found that infecting mice with H1N1 influenza virus increased the expression of IL-1β and TNF-α in the hippocampus. Subsequently, expression of brain-derived neurotrophic factor decreased in the hippocampus, and dendritic morphology of pyramidal neurons and granule cells was altered. In addition, performance on the reversal learning portion of the Morris water maze task was impaired, suggesting that infection-induced changes in hippocampus can cause cognitive deficits.

■ Behavioral/Systems/Cognitive

$BDNF_{Met}$ *Exacerbates Behavioral Effects of Stress in Mice*

Hui Yu, Dong-Dong Wang, Yue Wang, Ting Liu, Francis S. Lee, et al.

(see pages 4092– 4101)

Brain-derived neurotrophic factor (BDNF) regulates CNS development, adult neurogenesis, and plasticity, and increased BDNF expression likely mediates some effects of antidepressants. A common polymorphism in the human gene encoding BDNF causes substitution of methionine for valine. Carriers of the methionine allele ($BDNF_{Met}$) reportedly have smaller prefrontal cortical volumes and impaired episodic memory and fear extinction compared with people homozygous for $BDNF_{Val}$. In some studies, $BDNF_{Met}$ has been linked to susceptibility to depression and anxiety, particularly when combined with early-life stress. But other studies found no such link or found that the effect depended on variation in other genes. Supporting a role of $BDNF_{Met}$ in increased susceptibility to psychiatric effects of stress, Yu et al. report that heterozygous $BDNF_{Met}$ knock-in mice had greater stress-induced increases in plasma stress hormone levels and lower post-stress levels of BDNF in the prefrontal cortex than wild-type mice. Furthermore, stress-induced memory impairment and depression- and anxiety-like behaviors were greater in $BDNF^{+/Met}$ mice.

♦ Neurobiology of Disease

Prostaglandin E_2 Contributes to Responses to Repeated Stress

Kohei Tanaka, Tomoyuki Furuyashiki, Shiho Kitaoka, Yuta Senzai, Yuki Imoto, et al.

(see pages 4319 – 4329)

Being caged with a more aggressive male causes social defeat stress in male mice. After repeated encounters, defeated mice distance themselves from aggressor mice, even when direct contact is prevented. Other molecular and behavioral effects of such psychological stress overlap with those of illness. Because prostaglandin E_2 (PGE_2) receptors underlie behavioral responses—including social withdrawal—to sickness, Tanaka et al. hypothesized that PGE_2 also promotes behavioral responses to psychological stress. Indeed, brain levels of PGE_2 increased after repeated social defeat, and mice lacking the PGE_2 receptor EP1 or an enzyme involved in PGE_2 synthesis did not avoid aggressor mice after repeated exposure. This effect appeared to result from disinhibition of dopamine neurons. Although social defeat initially increased dopamine turnover in prefrontal cortex, turnover was attenuated after repeated exposure and was inversely correlated with the amount of social avoidance. Dopamine turnover remained elevated in EP1-deficient mice, but dopamine receptor antagonists restored social avoidance in these mice.