

# This Week in The Journal

## ● Cellular/Molecular

### *Calcium-Dependent Vesicle Release Can Occur Without SNAREs*

Ferenc Deák, Xinran Liu, Mikhail Khvotchev, Gang Li, Ege T. Kavalali, et al.

(see pages 8639–8648)

Synaptic vesicle release is triggered by depolarization-induced calcium influx, which allows docked vesicles to fuse with the plasma membrane. Docking and fusion depend on a complex of proteins that includes SNAREs, MUNCs, and others. The black-widow-spider neurotoxin  $\alpha$ -latrotoxin also triggers vesicle release, by both calcium-dependent and calcium-independent mechanisms.  $\alpha$ -Latrotoxin forms ionophores in the plasma membrane that allow calcium entry, and thus could induce physiological release via the SNARE complex. Remarkably, however, Deák et al. report that only calcium-independent release by  $\alpha$ -latrotoxin requires the SNARE complex—calcium-dependent release does not. Mouse neurons lacking SNAREs or Munc13-1 did not respond to  $\alpha$ -latrotoxin when calcium was absent, but the toxin induced vesicle release when calcium was present. Similarly, another calcium ionophore induced vesicle release from knock-out neurons in the presence, but not in the absence of calcium. The data suggest a previously unrecognized, SNARE-independent release mechanism is activated at synapses when excessive calcium enters.



Black-widow-spider venom contains the neurotoxin  $\alpha$ -latrotoxin, which evokes vesicle release from presynaptic terminals via both calcium-dependent/SNARE-independent and calcium-independent/SNARE-dependent mechanisms. See the article by Deák et al. for details. Photo courtesy of the U.S. Fish and Wildlife Service.

## ▲ Development/Plasticity/Repair

### *Nogo Knock-Out Does Not Improve Regeneration*

Jae K. Lee, Andrea F. Chan, Sen M. Luu, Yuhong Zhu, Carole Ho, et al.

(see pages 8649–8654)

Myelin-associated inhibitory molecules impede regeneration of CNS axons, and blocking these inhibitors has been a focus of therapy development. Early studies suggested Nogo was a promising target, because an antibody that recognizes Nogo increased axonal regeneration in rats. Subsequent studies using genetic manipulation of Nogo led to mixed results, however: some found robust regeneration, but others showed none. These studies were confounded by labeling artifacts (in the study that found extensive regeneration) and the presence of other Nogo isoforms (in most other studies). Therefore, Lee et al. have re-examined the role of Nogo, both in the mutant line that originally showed regeneration and in a newly developed line that lacks all three Nogo isoforms. Being careful to avoid labeling artifacts, they found no significant difference in regeneration or functional recovery after dorsal spinal cord hemisection in mutant mice compared to wild type. Thus, exclusively targeting Nogo seems unlikely to improve regeneration.

## ■ Behavioral/Systems/Cognitive

### *Stress Affects LTD Differently in Dorsal and Ventral Hippocampus*

Nicola Maggio and Menahem Segal

(see pages 8633–8638)

Dorsal and ventral hippocampus differ in anatomical connections, electrophysiology, and protein expression, resulting in different functional properties. Dorsal hippocampus participates in working and spatial memory via connections with neocortex, whereas ventral hippocampus is primarily involved in emotional memory and anxiety, via connections to amygdala and hypothalamus. Long-term potentiation (LTP) is more readily evoked in dorsal than in ventral hippocampus, and forced-swim-

induced stress suppresses LTP in dorsal, but enhances LTP in ventral hippocampus. Maggio and Segal report that low-frequency stimulation produced comparable long-term depression (LTD) in dorsal and ventral hippocampus. After stress, however, the same stimulus produced enhanced LTD in dorsal, but produced LTP in ventral hippocampus. These differences likely resulted from differential expression of corticosterone receptors. Specific agonists of glucocorticosterone receptors enhanced LTD in both dorsal and ventral regions, whereas mineralocorticosterone receptor agonists converted LTD to LTP in both. Moreover, antagonizing the principal corticosteroid receptor in dorsal or ventral hippocampus equalized the effects of stress.

## ◆ Neurobiology of Disease

### *Dlg1 Interactions Might Regulate Myelination*

Annalisa Bolis, Silvia Coviello, Ilaria Visigalli, Carla Taveggia, Angela Bachi, et al.

(see pages 8858–8870)

To produce myelin of appropriate thickness, Schwann cells and oligodendrocytes must regulate the amount of membrane inserted into their myelinating processes. Excess membrane creates myelin outfoldings, as happens in Charcot-Marie-Tooth disease type 4B1, caused by loss of the phospholipid phosphatase myotubularin-related protein 2 (MTMR2), which associates with the scaffolding protein Discs large 1 (Dlg1). Targeted membrane insertion depends on several proteins, including transport proteins, e.g., kinesin 13B (kif13B), and a targeting and tethering complex called the exocyst. Bolis et al. found that Dlg1 interacts with kif13B and the exocyst protein Sec8, as well as with MTMR2. In cocultures of dorsal root ganglion neurons and myelinating Schwann cells that lack MTMR2, myelin outfoldings were produced, but were rescued by titrated knockdown of Sec8. Knockdown of Dlg1, kif13B, or Sec8 decreased myelination by wild-type Schwann cells. The authors propose that Dlg1 interactions with kif13B/Sec8 or MTMR2 promote or inhibit membrane addition, respectively.