This Week in The Journal

Sodium Enhances Synaptic Vesicle Endocytosis

Yun Zhu, Dainan Li, and Hai Huang

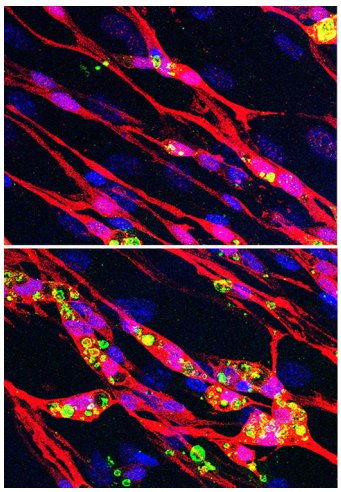
(see pages 6112–6120)

When axon terminals are depolarized, synaptic vesicles fuse to the plasma membrane, releasing neurotransmitter into the cleft. This inevitably reduces the number of vesicles available for subsequent signaling and inserts vesicular membrane and proteins into the active zone, increasing membrane capacitance and distorting synaptic structure. These effects would degrade synaptic communication if exocytosis were not tightly coupled to endocytosis, which quickly retrieves and recycles vesicle components. Depending on the cell type and firing rate, this may occur via slow, clathrin-dependent or fast, clathrin-independent endocytosis of single vesicles or through bulk endocytosis of larger membranous structures.

Although several proteins involved in synaptic vesicle recycling have been identified, the mechanisms coupling endocytosis and exocytosis remain unclear. Calcium, which triggers exocytosis, appears to facilitate endocytosis at some synapses, but endocytosis can occur without calcium elevation. Components of the vesicle fusion machinery and active-zone scaffold have also been proposed to play a role in exocytosis–endocytosis coupling, as have actin, membrane lipids, and sensors of membrane curvature. Zhu, Li, et al. now show that sodium promotes activity-dependent endocytosis at synapses.

A fluorescent sodium indicator showed that sodium levels increased with increasing spike frequency in the large presynaptic terminals of mouse calyx of Held synapses. As expected, membrane capacitance increased as vesicles fused during afferent nerve stimulation, and then returned to baseline at different rates—reflecting fast and/or slow endocytosis—depending on the stimulation protocol. When intracellular sodium concentrations were reduced in the terminal by using sodium-free solution in the recording pipette, the rates of both fast and slow endocytosis decreased. Conversely, when sodium levels increased, endocytosis rates increased. Moreover, after strong stimulation, capacitance sometimes decreased below baseline, indicating more membrane was retrieved than was exocytosed; the number of cells showing such an overshoot and the size of the overshoot increased with intracellular sodium concentration.

These experiments suggest that activity-dependent sodium influx couples exocytosis and endocytosis. Additional experiments showed that changes in sodium concentration did not affect calcium dynamics, and although sodium can affect glutamate uptake into vesicles, altering this uptake did not affect endocytosis. Changes in potassium or pH were also unlikely to be involved. Therefore, future work will need to determine how sodium promotes endocytosis.



After 7 days in culture, wild-type (top) mouse sciatic-nerve Schwann cells (red) had digested most of their myelin protein P0 (green). In contrast, much P0 remained in calcineurin-deficient Schwann cells (bottom). Blue is DAPI. See Reed et al for details.

Calcineurin Promotes Myelin Autophagy in Injured Nerves

Chelsey B. Reed, Luciana R. Frick, Adam Weaver, Mariapaola Sidoli, Elizabeth Schlant, et al.

(see pages 6165–6176)

Myelination of peripheral axons is mediated by Schwann cells derived from the neural crest. Early in development, unmyelinated peripheral axons are bundled together in nerves along with Schwann cell precursors. Survival of these precursors and their differentiation into immature Schwann cells are promoted by neuregulin-1, which is produced by the axons. Neuregulin-1 acts on ErbB2/3 receptors, which in turn activate several intracellular signaling pathways. One such pathway involves the calcium-dependent phosphatase calcineurin and downstream activation of the transcription factor NFAT. Notably, knockout of calcineurin in neural crest cells has been reported to reduce expression of myelin proteins and impair myelination of peripheral nerves (Cartwright et al., 2009, Science 323:649). But in that study, knockout occurred before Schwann cell precursors began to differentiate into immature Schwann cells, and mice died within 24 h of birth, when myelination had just begun. To avoid these confounds, Reed et al. knocked out calcineurin selectively in Schwann cells.

Surprisingly, Schwann cell-specific knockout of calcineurin had minimal effects on myelination of peripheral nerves. Although fewer axons were myelinated in mutant mice than in wild type at all ages tested (up to 6 months after birth), myelin thickness and the expression of myelin-specific proteins were similar in mutant and wild-type sciatic nerves. Schwann cell proliferation was also unaffected.

Loss of calcineurin altered Schwann cell responses to nerve injury, however. When wild-type peripheral nerves are crushed, myelinating Schwann cells dedifferentiate, degrade their myelin through autophagy, and assume a repair phenotype that promotes axon regeneration. Schwann cell-specific knockout of calcineurin slowed the clearance of distal myelin and axon fragments after nerve crush. This defect was attributable to impaired autophagy in Schwann cells, resulting from reduced activation of the transcription factor TFEB. TFEB activation recovered within a few days, however, and subsequent nerve regeneration and remyelination were comparable to those in controls.

These results suggest that calcineurin does not have an essential role in postnatal myelination or in remyelination after injury. Moreover, although calcineurin triggers myelin autophagy after nerve injury, autophagy can eventually be initiated through other pathways. Therefore, calcineurin appears to be one of several redundant pathways regulating Schwann cell function.

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