# Nerve cells borrow a trick from their synapses to dispose of garbage

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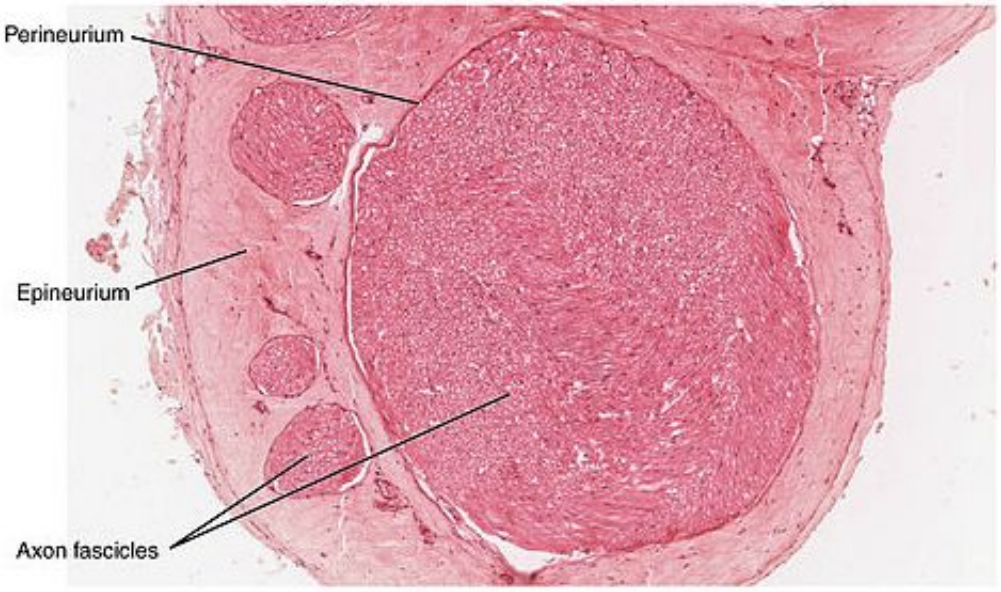


Cross-section of a nerve. Credit: OpenStax College/Wikipedia

Genetic defects affecting tiny channels in human nerve cells lead to several neurological diseases that result from aberrant nerve transmission, such as episodic ataxia, absence epilepsy, and migraines. These disorders have also been associated with neurodegeneration, but it has been less clear why this should be.

The transmission of nerve impulses requires the perfect orchestration of a series of complex cellular events in a matter of fractions of a second.

The membrane that surrounds a nerve cell is normally electrically polarized, but a nerve impulse triggers a Mexican wave of depolarization to travel along the nerve cell. When it hits the synapse at the end of the nerve, the depolarization causes the opening of voltage-gated calcium channels (VGCCs) that traverse the membrane, allowing calcium ions to flood into the neuron. This sudden pulse of calcium ions in turn triggers the release of neurotransmitters - chemicals that pass the nerve impulse onto the next cell- by causing neurotransmitter vesicles to fuse with the synaptic membrane.

Scientists at Zhejiang University in China and their collaborators at Baylor College of Medicine in the USA have now discovered an unexpected additional role of VGCCs in neurons of the fruit fly. In a paper publishing March 26th in the Open Access journal *PLOS Biology*, Drs. Chao Tong, Hugo Bellen and members of their research groups have shown that these VGCCs are not only present on the synaptic membrane of cells, but also in the membranes of cellular bodies called lysosomes, where they play a critical role in the cellular "garbage disposal" processes of lysosomal fusion and autophagy. The work potentially provides a new angle on our understanding of the neurogenerative pathology of VGCC-related diseases in humans.

Lysosomes are specialized vesicles within cells that contain proteins that can digest cellular waste and release processed waste for feeding the cell, acting as "recycling" centers. Cellular waste is first captured by a double membrane structure called the autophagosome and delivered into the lysosome through membrane fusion. Malfunction of the lysosome is highly problematic for the neuron because lysosomes are long lived and cannot renew their contents. As a result, the cellular waste accumulates inside until it kills the neuron.

While the fusion process between autophagosome and lysosomes is known to be tightly regulated, the detailed underlying mechanisms are

still unclear. "The neuronal terminals in the mutant fly eyes contain numerous autophagosomes, which have been rarely studied", said Dr. Tong, "and we were very surprised when we found out that the gene encoding the calcium channel, named cacophony, is affected in these mutants", she added.

Cacophony is a well-studied gene in fruitflies that encodes the key subunit in VGCCs already known to be needed for calcium influx in synapses and the release of neurotransmitters. "We went ahead to test whether the defects in neurotransmitter release cause autophagosome accumulation. But this is not the case", said Xuejun Tian, one of the lead authors of the paper. "Some data suggested that the fusion defects between lysosomes and autophagosomes might be the reason", added Upasana Gala, another lead author of the paper.

To test whether the VGCC also plays similar roles in mammals, the Tong and Bellen groups examined two mutant mice strains that carry mutant forms of the VGCC subunits CACNA1A and CACN2D2 in their genomes. "These mutant mice show very similar defects to the ones observed in mice that have mutations inautophagy-related genes", said Xuejun.

The authors then discovered that the VGCC subunit CACNA1A is present on the lysosomes and that its channel activity is required for the fusion between lysosomes and autophagosomes - in a similar fashion to its known role in the fusion of neurotransmitter vesicles with the synaptic membrane. Lysosomes have a high calcium content and are electrically excitable by a sodium channel that may induce membrane depolarization akin to that seen during nerve impulses.

"The reason for the requirement of a lysosomal membrane depolarization in this process has remained a mystery so far", Dr. Tong explained. "We now believe this depolarization activates the lysosomal

VGCC and allows calcium flow into the lysosomes triggering the fusion with autophagosomes. Our work suggests that the fusion events required in autophagy are not fundamentally different from those observed at neuronal terminals for neurotransmitter release", Dr. Tong concludes. Although this is a significant step forward, more work is required to tease out the detailed mechanisms and provide more insights into how the VGCC-related neurodegeneration is triggered.

**More information:** Tian X, Gala U, Zhang Y, Shang W, Nagarkar Jaiswal S, di Ronza A, et al. (2015) Voltage-Gated Calcium Channel Regulates Lysosomal Fusion with Endosomes and Autophagosomes and Is Required for Neuronal Homeostasis. *PLoS Biol* 13(3): e1002103. DOI: 10.1371/journal.pbio.1002103