

Calcium channels play a role in neuronal homeostasis and elimination of toxic buildup of proteins

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Taking out the garbage is a crucial step in housecleaning. Similarly, autophagy is the body's first-line of defense against the buildup up of toxic substances, degrading old organelles and proteins to provide new substrates and building blocks. In this way, autophagy prevents the buildup of "garbage" that can result in destruction of neurons and cause neurologic diseases.

A forward genetic screen in *Drosophila melanogaster* (fruit flies) identified mutant copies, or alleles, of a gene called cacophony associated with defects in [autophagy](#) and cellular homeostasis. In a report that appears in *PLOS Biology*, Dr. Hugo Bellen and his colleagues at Baylor College of Medicine and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and BCM, and Dr. Chao Tong, at the Life Sciences Institute and Innovation Center for Cell Biology, Zhejiang University in Hangzhou, China, find that mutations of human homologs (genes that carry out similar functions) of cacophony and its partner straightjacket (Cacna1a and Cacna2d2 respectively) cause defects in autophagy in neurons. The human homologues of these genes are associated with severe [neurologic diseases](#) such as episodic ataxia 2, familial hemiplegic migraine, absence epilepsy, progressive ataxic and spinocerebellar ataxia 6, but the molecular mechanisms by which mutations in these genes cause these diseases are poorly understood so far.

In both flies and mice, loss of autophagy-related genes leads to progressive neurodegeneration, the researchers wrote. This study found that when cacophony and its related gene straitjacket are mutated, they cause similar degenerative phenotypes in the mutant neurons as autophagy mutants. Proteins hang around, literally gumming up the works and preventing neurons from doing their job.

Voltage-gated calcium channels cannot form properly when cacophony is mutated, preventing fusion of the synaptic vesicle with the plasma membrane and neurotransmitter release.

"We were surprised to find that mutations in this gene also affect fusion of autophagic organelles," said Upasana Gala, a graduate student in the Program in Developmental Biology at BCM in Bellen's laboratory.

The authors show that the voltage gated calcium channels are present on the lysosomes that dispose of proteins. In this study, "we argue that when the acidified lysosome is depolarized by a sodium channel, it results in calcium efflux from lysosomes via the calcium channel encoded by the cacophony gene," they wrote. The calcium efflux results in higher local calcium concentration than the rest of the cell, promoting the fusion of the lysosome with endosomes.

In summary, the authors wrote, "We present a model in which [calcium channels](#) play a role in autophagy by regulating the fusion of autophagic vesicles with lysosomes and hence functions in maintaining neuronal homeostasis."

Provided by Baylor College of Medicine

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