Neuronatin-mediated aberrant calcium signaling and endoplasmic reticulum stress underlie neuropathology in Lafora disease.

Sharma J, Mukherjee D, Rao SN, Iyengar S, Shankar SK, Satishchandra P, Jana NR.
Cellular and Molecular Neuroscience, National Brain Research Centre, Manesar, Gurgaon 122 050, India.

Abstract

Lafora disease (LD) is a teenage-onset inherited progressive myoclonus epilepsy characterized by the accumulations of intracellular inclusions called Lafora bodies and caused by mutations in protein phosphatase laforin or ubiquitin ligase malin. But how the loss of function of either laforin or malin causes disease pathogenesis is poorly understood. Recently, neuronatin was identified as a novel substrate of malin that regulates glycogen synthesis. Here we demonstrate that the level of neuronatin is significantly up-regulated in the skin biopsy sample of LD patients having mutations in both malin and laforin. Neuronatin is highly expressed in human fetal brain with gradual decrease in expression in developing and adult brain. However, in adult brain, neuronatin is predominantly expressed in parvalbumin-positive GABAergic interneurons and localized in their processes. The level of neuronatin is increased and accumulated as insoluble aggregates in the cortical area of LD brain biopsy samples, and there is also a dramatic loss of parvalbumin-positive GABAergic interneurons. Ectopic expression of neuronatin in cultured neuronal cells results in increased intracellular Ca(2+), endoplasmic reticulum stress, proteasomal dysfunction, and cell death that can be partially rescued by malin. These findings suggest that the neuronatin-induced aberrant Ca(2+) signaling and endoplasmic reticulum stress might underlie LD pathogenesis.