

Calcium signaling in the CNS in health and neurodegenerative disease

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Abstract:

Statement of the Problem: A shared aspect among many neurodegenerative disorders is a limited understanding of cellular disease mechanisms. In our research, we have found that dysregulated calcium channels play a central and early role in driving diseases such as Alzheimer's, Huntington's and brain injury. Specifically, defects in intracellular calcium stores within the endoplasmic reticulum (ER) and their resident release channels such as the ryanodine receptor (RyR) are upstream of the major disease features such as protein aggregates and synaptic deficits. By focusing upon the proximal calcium channelopathy, rather than later-stage features, significant advances in understanding disease etiology may be made.

Methodology & Theoretical Orientation: Whole cell patch clamp electrophysiology combined with 2-photon calcium imaging are used to record signaling from hippocampal neurons in acute brain slices from mouse models of Alzheimer's disease (AD) and human neurons transformed from AD patients. Immunoassays and qRT PCR probe protein and transcript levels in mouse and human neurons.

Findings: In early stage AD mice, RyR-evoked calcium signals are significantly greater than non-transgenic controls, while calcium signaling through voltage-gated channels and NMDA receptors are not different. Similar observations were made in human neurons from AD patients. Additionally, RyR 2 message is increased in both the mouse and human AD neurons. Pharmacologically normalizing RyR-calcium release restores RyR2 levels in mice, as well as reduces many of the AD features including beta amyloid, hyperphosphorylated tau and synaptic loss.

Conclusion & Significance: Dysregulated ER calcium channel functioning is an early feature of AD in mouse models and human samples and likely initiates a pathogenic cascade in the proximal disease stages. Because of the multiple and essential roles of calcium signaling in neurons, alterations in RyR-channel properties can generate multiple downstream maladaptive effects such as those seen in neurodegenerative disorders.

Biography:

Grace E Stutzmann focuses on early mechanisms of neurodegenerative disorders. She received her PhD from New York University, Center for Neural Science and completed her Postdoctoral fellowships at Yale University and UC Irvine. She is currently an Associate Professor at Rosalind Franklin University/The Chicago Medical School and serves as the Director for the Center for Neurodegenerative Disease and Therapeutics. Her research investigates effects of calcium signaling dysregulations associated with AD on neuronal physiology, synaptic transmission, and histopathology. She uses transgenic mice expressing human mutations that cause familial AD and employs techniques such as in vitro electrophysiology and 2-photon calcium imaging to study activity in neurons, in addition to immuno-based assays, molecular biology and behavioral approaches. Her research has shown that specific calcium-mediated signaling pathways are dysregulated in AD and over time, facilitate amyloid plaques and tangles formation, interfere with memory encoding circuits, and eventually can kill the cell.