Central role of calcium signalling abnormalities in neurodegenerative disease

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Despite the increasing prevalence of neurodegenerative diseaseas and related dementias, there are no effective treatments that protect cognitive function and underlying pathogenic causes remain elusive. This in part may reflect an incomplete understanding of proximal disease mechanisms, particularly those that directly affect learning and memory encoding.

Here, we examine several neuronal signaling and protein handling cascades in neurodegenerative disease mouse models and transformed neurons from human patients to identify pathogenic cascades and validate novel therapeutic targets. We examine upstream intracellular Ca^{2+} pathways at various disease stages to examine their role in synaptic plasticity encoding, and in organelles important for protein handling and cellular metabolism. This is accomplished using live cell imaging, electrophysiological recordings of neurophysiological properties, and immunoassays of pathogenic protein species in the mouse and human neural networks.

We identified several key upstream pathogenic events in human AD neurons that are also present in AD mouse models. These include significantly increased ER-Ca^{2+} release, increased phospho-tau species, altered synaptic plasticity expression, and defects in lysosomal pH and clearance of aberrant proteins. Incubation in RyR-modulating compounds prevented excess Ca^{2+} release, and reversed related downstream pathology such as synaptic defects, amyloid and tau aggregation, lysosomal dysfunction, and other Ca^{2+}-regulated events that drive memory decline. Thus, aberrant calcium signaling presents as an early and upstream driver of many of the central features of AD, particularly those regulating memory encoding, and may be a novel target for disease-modifying therapeutic strategies. Furthermore, utilizing clinically-relevant models to investigate AD, such as human neurons derived from AD patients, can reveal critical and clinically relevant pathogenic mechanisms by which to validate novel targets.