

Commentary: Alpha-Synuclein Aggregates Cause Calcium Dysregulation by Activating Calcium Pump SERCA

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We have recently reported that alpha-synuclein aggregates induce calcium dysregulation by activating the calcium pump, SERCA in the endoplasmic reticulum¹. The dysregulation presents as a biphasic change in cytosolic calcium with an initial phase with 20% decreased calcium followed by final phase with increased calcium. These findings are novel with respect to; 1) demonstrating activation of SERCA as a gain-of-function acquired by aggregated alpha-synuclein; 2) demonstrating an initial phase with reduced cytosolic calcium in neurons that experience a build-up of alpha-synuclein aggregates. The initial phase occurs when cells appear morphologically unaffected and precedes the well-known later phase with increased cytosolic calcium and subsequent cell death. Although the reduction in cytosolic calcium of 20% may appear modest are its short and long-term consequences largely unknown because this phase not previously has been described. However, both the early and late phase of the calcium dysregulation can be antagonized pharmacologically by inhibiting SERCA and this treatment restored the survival of the cells to the level of the control cells not being subject to alpha-synuclein aggregate stress. The interaction between aggregated synuclein and SERCA could be demonstrated in neurons in brain tissue affected by dementia with Lewy bodies supporting that the initial phase with reduced cytosolic calcium is relevant for human pathology. We hypothesize the alpha-synuclein aggregate induced stimulation of SERCA and the early-phase with reduced cytosolic calcium will compromise neurons ability to support their role in normal circuitries, integrated brain functions and ultimately cause symptoms. This phase may exist for prolonged periods before the neurons enters the late-phase with increased cytosolic calcium that has been studied according to the original "calcium hypothesis"^{2,3}. Understanding the mechanisms whereby the abnormal activation of SERCA and its down-stream dysregulation of calcium contributes to neuronal dysfunction and eventual cell death holds potential for new symptomatic and disease modifying strategies for synucleinopathies.

Calcium Disturbances and Parkinson's Disease

The so-called "calcium hypothesis" has for 3 decades been used as a basis to understand the vulnerability of the aging brain by mechanisms that also may apply to late onset neurodegenerative diseases^{2,3}. Central to this hypothesis is that abnormal increases in cytosolic calcium plays a pivotal and detrimental role. The calcium hypothesis has received special attention in Parkinson's disease where the motor symptoms are associated to loss of the dopaminergic neurons in substantia nigra pars compacta. These dopaminergic neurons have a large terminal field and

display autonomous pace-making firing, which lead to a large influx of calcium ions via L-type voltage gated calcium channels (CaV). Maintaining the low normal cytosolic calcium level requires active transport processes and a large mitochondrial ATP production, which carry an inherent risk of oxidative stress⁴⁻⁶. The risk of developing Parkinson's disease is reduced in patients treated for hypertension with L-type calcium channel blockers targeting the CaV channels⁷⁻⁹. However, the treatment did not reduce the risk of developing dementia and the length of previous use of the calcium channel blockers prior to diagnosis was not associated with reduced risk of PD⁹. This led the authors suggest the treatment was associated with symptomatic relief rather than preventing disease development⁹ and may represent a modulation of the late phase of our hypothesis with increased calcium. The expression of L-type calcium channels is changed in brains affected by Parkinson's disease and the changes could be observed in early stage patients and in areas not expected to carry alpha-synuclein aggregate pathology¹⁰. These changes in CaV channel expression can hypothetically represent compensatory responses to alpha-synuclein aggregates stimulating SERCA and decreasing cytosolic calcium.

Calcium Dysregulation - Too High or Too Low?

The calcium hypothesis describes calcium dysregulation as increased cytosolic calcium, but our finding illustrates that cytosolic calcium can also be too low in order for neurons to maintain their functionality. There are other reports suggesting that elevation of cytosolic calcium actually protects peripheral neurons and spinal ganglion¹¹⁻¹³. Furthermore, stimulation of synaptic NMDA stimulated calcium channels induces an increase in nuclear transients with increased calcium levels that activates transcription of so-called neuroprotective "neuronal shield" genes¹⁴⁻²⁰. A reduction in the cytosolic calcium will likely reduce the efficacy of this protective calcium-dependent synapse-to-nucleus mechanism because the fenestrated nuclear membrane will allow diffusion of calcium into the cytosol thereby yielding a reduced nuclear calcium level. Moreover, stimulation of SERCA by aggregated alpha-synuclein overloads the endoplasmic reticulum with calcium, which can trigger a host of fundamental responses, including unfolded protein response, mitochondrial calcium filling, store-operated calcium entry²¹, dysregulation of presynaptic neurotransmitter release²² and activity of specialized overload calcium channels such as TMC01²³.

SERCA Activation, Presenilins and Calcium in the Endoplasmic Reticulum: Similarities between Synucleinopathies and Alzheimer's Disease

Some familial forms of Alzheimer's disease are linked to mutations in presenilins. Presenilins 1 and 2 are transmembrane proteins in the endoplasmic reticulum that

regulate the production of amyloidogenic A β peptides²⁴. Presenilins functions as low conductance calcium leak channels, that reduce the calcium load in the endoplasmic reticulum²⁵ and this effect is balanced by their function as physiological activators of SERCA, which pumps calcium back into the endoplasmic reticulum³⁰. This balance is destroyed in cells from families carrying Alzheimer's disease-causing mutations in their presenilins that block their calcium leak channel properties, which will tend to lower their neuronal cytosolic calcium. Such Alzheimer's disease patients may share pathophysiological signaling mechanisms with Parkinson's disease patients that also exhibit a phase with reduced cytosolic calcium in affected neurons and may comprise dysfunctions in store-operated calcium entry, expression of ryanodine receptors, and inositol trisphosphate receptors²⁶⁻²⁹.

Further studies into our "Calcium hypothesis, version 2" centered around mechanisms initiated by reduced cytosolic calcium and calcium overload in the endoplasmic reticulum hold potential for generating novel therapeutic strategies for both symptomatic relief and true disease modification in Parkinson's disease and subgroups of Alzheimer's disease.

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