Cytosolic calcium disturbance in Parkinson's disease and their relevance for neuronal dysfunction

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Intraneuronal aggregation of the presynaptic protein alpha-synuclein (a-syn) is a key feature of Parkinson's disease and the larger group of neurodegenerative synucleinopathies. How the conversion of native a-syn into soluble oligomers and insoluble fibrils negatively impact neuronal function, survival and disease progression is the subject for several hypotheses and to a large extend unclear.

We will present data on two novel functions of a-syn.

First, we will extend our published data on the gain a novel function of a-syn aggregates that become an agonist for SERCA that reduces cytosolic calcium levels. The activation is prodegenerative because counteracting it by the SERCA inhibitor CPA protects neurons in vitro and a-syn transgenic c. elegans in vivo. We will provide novel in vivo data on how experimental strategies to increase cytosolic calcium slow disease progression in an a-syn transgenic mouse model of lethal prion-like spreading of a-syn aggregate pathology. Second, we will provide novel data on how native a-syn is an activator of PMCA and thereby may contribute to calcium homeostasis in the small presynaptic compartment wherein a-syn is present in very high concentrations. Hypothetically, presynaptic a-syn aggregation will change the flux of cytosolic calcium from being extruded to the extracellular environment via PMCA into the ER lumen via SERCA whereby it triggers neurodegenerative pathways.