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nEUROsyn: Molecular mechanisms underlying synaptic dysfunction in prototypic neurodegenerative diseases related to protein misfolding

Project Description

A novel concept has recently emerged in neurodegenerative disorders: synaptic dysfunction may precede neuronal death by several years and can underlie many important but still reversible symptoms. The aim of this project is to investigate the mechanisms that lead to synaptic impairment and eventual demise of neurons in two prototypic neurodegenerative conditions related to protein misfolding, i.e. Alzheimer disease (AD) and Huntington disease (HD). Both disorders involve production and deposition of abnormal protein fragments which harm neurons. The rationale of the study is that AD and HD share critical cellular changes such as the dysregulation of Ca2+ homeostasis and mitochondrial function. The resulting Ca2+ imbalance initially results in a “synaptopathy” and eventually progresses to neuronal death. In a series of five complementary and interactive sub-projects based on cellular and animal models, we will monitor alterations of synaptic and dendritic spine remodelling, investigate changes in receptor trafficking at the synapse, explore disturbances in trafficking of different cellular components and study the role of exosomes in neurodegeneration. We will pay special attention to the Permeability Transition Pore, which is another important target of Ca2+/mitochondrial dysregulation that may be affected in AD and HD. The study will provide important information for the identification of novel therapeutic targets for treatment strategies in early stages of the pathology.

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