Structural and functional analysis of molecular interactions in neuronal membrane uptake and their malfunctions in neurodegenerative diseases

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Sweden

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Structural and functional analysis of molecular interactions in neuronal membrane uptake and their malfunctions in neurodegenerative diseases

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Research Abstract

The goal of the proposed research is to elucidate molecular links between the mechanisms regulating membrane trafficking and in particular endocytosis in the nerve terminal and the onset and spread of Parkinson´s disease (PD)-related pathology. The early stages of PD are

characterized by a loss of dopaminergic nerve terminals in the striatum accompanied by the accumulation of alpha-synuclein-containing protein aggregates, Lewy bodies, in nigrostriatal synapses as well as other synapses in the brain. We will clarify the role of synuclein that interacts with synaptic vesicles (SVs) and curved membranes via ALPS (Amphipathic Lipid Packing Sensor)-motif in intact synapses, and propose to investigate the functional relationship between synuclein and other lipid-binding proteins, that transiently associate with SV membrane and curved membranes during SV recycling, such as BAR (Bin-amphiphysin-RVS)-domain endocytic proteins and other ALPS-motif containing presynaptic proteins. We hypothesize that malfunctions in the ability of these molecules to interact with the SV membrane may interfere with the synuclein function and lead to the formation of pathological aggregates and onset degeneration. We aim at clarifying how malfunctions in signaling mechanisms, such as posttranslational modifications of endocytic proteins, and functions of transcription factors, e.g., Lmx1a and Lmx1b that has been implicated in early degeneration of dopaminergic nerve terminals in striatum, become involved.

Further information available at:

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