Misfolded alpha-synuclein: Assessment of Lactulose and Melibiose for Parkinson’s Disease

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Parkinson’s disease (PD) is a chronic central nervous system degenerative disease associated with resting tremor, bradykinesia, rigidity, and progressive degeneration of dopaminergic neurons. Characteristic pathological features of PD include proteinaceous alpha-synuclein positive inclusions called Lewy bodies in dopaminergic neurons. Although there are treatments including levodopa and other drug therapies, and physical therapy for PD, there is no cure at present. In this study, we established bimolecular fluorescence complementation (BiFC) and protein folding reporter assays to screen chemical chaperones assisting alpha-synuclein folding. BiFC assay is based on the reassembly of Venus from its two split nonfluorescent fragments, facilitated by the interaction between two alpha-synuclein proteins fused to each fragment. Protein folding reporter assay utilizes GFP fluorescence to reflect the folding status of E35K, E46K and E61K-mutated alpha-synuclein as the latter misfolded rapidly to decrease GFP fluorescence. Trehalose, a known disaccharide interfering with alpha-synuclein’s aggregation, reduced complementary fluorescence in a dose-dependent manner. As a chemical chaperone, trehalose also significantly increased green fluorescent intensity in E. coli cells expressing mutated alpha-synuclein-GFP fusion protein. The chemical chaperone activity of trehalose was confirmed using thioflavin T fluorescence assay. As trehalose is digested into glucose by trehalase and which reduced its efficacy in the disease target tissues, two trehalase-indigestible trehalose analogs, lactulose and melibiose, were assessed using the above assays. In addition, the neuroprotective effects of lactulose and melibiose on motor activity in MPTP-induced mouse model of PD were investigated.

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