Alpha-synuclein Fibrils Triggered by Pressure and the Seeding Mechanism in Parkinson Disease

de Oliveira, G.A.[1], Marques, M.A.[1], Cordeiro, Y.[2], Freitas, M.S.[1] and Silva, J.L.[1]

[1]Programa de Biologia Estrutural, Instituto de Bioquímica Médica Leopoldo de Meis, Instituto Nacional de Biologia Estrutural e Bioimagem, Centro Nacional de Ressonância Magnética Nuclear Jiri Jonas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.
[2] Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

Parkinson Disease (PD) is a devastating neurological disease in which aggregated forms of the alpha-synuclein (αS) protein believed to participate in regulatory pathways of synaptic vesicle release and trafficking, are found in the substantia nigra pars compacta. There is a direct and well-accepted link between αS oligomerization and fibrillation and the citopathological and neuropathological features of PD brains. High hydrostatic pressure (HHP) is a powerful physicochemical strategy to understand protein folding, ligand interaction and the assembly of supramolecular structures like amyloids. In this study, we asked whether we were able to contribute for the understanding of the molecular mechanisms of αS fibril disassembly and remodeling upon HHP challenge. We demonstrate by using different HHP techniques including circular dichroism, Fourier transformed infrared spectroscopy and solution and solid-state nuclear magnetic resonance that the major species released from HHP-disturbed fibrils are structurally modified monomers in which conformational exchange motions in the μs-ms timescale are present at the non-amyloid β component (NAC) and acidic C-terminal region of the protein. In addition, we show at atomic level the remodeling of HHP-disturbed fibril core and how these species contribute to seed αS aggregation. Our findings explain the key role that HHP can achieve in populating invisible αS species and fibril remodeling and the association of this physicochemical approach to help future therapeutics focused on the blockage of *de novo* aggregation and seeding that may represent an effective strategy to ameliorate PD progression.

Keywords: amyloid fibrils | high pressure spectroscopy | alpha-synuclein | Parkinson disease | solid-state spectroscopy

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