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TO WHOM IT MAY CONCERN

This is to certify that the following activities were conducted under the Collaborative Research Activities signed between Government General Degree College, Mangalkote, Panchanantala, Khudrun Dighi, P.O: Majhigram, Block – Mangalkote, Dist: Purba Bardhaman (W.B.) INDIA, PIN-713132 and Dr. Nakul Chandra Maiti, Senior Principal Scientist, CSIR-IICB, Kolkata 700032, West Bengal, India for a period of five years with effect from 08/09/2022.

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Structure specific neuro-toxicity of α-synuclein oligomer

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ABSTRACT

Parkinson's disease (PD) is linked to α-synuclein (aS) aggregation and deposition of amyloid in the substantia nigra region of the brain tissues. In the current investigation we produced two distinct classes of aS oligomer of differed protein conformation, stability and compared their toxic nature to cultured neuronal cells. Lyophilized oligomer (LO) was produced in storage of aS at-20 °C for 7 days and it was enriched with loosely hold molten globule like structure with residues having preferences for α-helical conformational space. The size of the oligomer was 4–5.5 nm under AFM. This kind of oligomer exhibited potential toxicity towards neuronal cell lines and did not transform into compact β-sheet rich amyloid fiber even after incubation at 37 °C for several days. Formation of another type of oligomer was often observed in the lag phase of aS fibrillation that often occurred at an elevated temperature (37 °C). This kind of heat induced oligomer (IO) was more hydrophobic and relatively less toxic to neuronal cells compared to lyophilized oligomer (LO). Importantly, initiation of hydrophobic zipping of aS caused the transformation of IO into thermodynamically stable β-sheet rich amyloid fibril. On the other hand, the presence of molten globule like conformation in LO, rendered greater toxicity to cultured neuronal cells.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder and largely characterized by progressive movement disorder with symptoms of tremor, rigidity of limbs and impaired balance. [1] These bedevilled etiology arises due to the death of dopamine producing neuronal cells in the substantia nigra region of the brain. In PD and similar other neurodegenerative disorders a key finding is the engulfment of amyloid inclusions, known as 'lewy bodies' or 'lewyneurities' enriched with protein aggregates. The main component of these 'lewy bodies' is α-synuclein (aS) along with other proteins such as p62 and ubiquitin. [2–4] However, from different investigation it is established that aS is the key component in these inclusion bodies of patients suffering from PD. Several missense mutation, such as A53T, E46K, A30P are also found to be involved in the pathogenic amyloids found in PD. [5] However, the mechanistic details behind the cause are still a matter of dilemma.

aS is a member of the synuclein family that also includes β and γ-synuclein often found to localize at the nuclear envelope and at pre-synaptic nerve terminals. [6] However the real function or biological role of the protein is poorly understood. It has been suggested that aS may have role in synaptic neuro-transmission, and may regulate synaptic membrane biogenesis. [7] The native structure of the protein *in-vivo* is illusive and may remain associated with lipid molecules preferably with α-helical structure. [8–10] However, *in vitro* solution conditions the structure of the protein is highly fluctuating. It is highly dynamic and capable of adopting different conformation depending upon its surrounding environments. The solution state NMR and Raman spectroscopic analysis firmly established its disordered state without having a compact and stable globular fold. [5,11–14] In addition, under appropriate solution condition the protein transformed into β-sheet enriched fibrillar structure. During the formation of fibrillar aggregates of aS, several *in-situ* measurements observed various intermediate

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