INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Parkinson's disease is a movement disorder that happens due to the loss of neurons in the brain's nigral dopaminergic pathway. The accumulation of the protein α-synuclein (αS) in the nigrostriatal pathway has been held responsible for the loss of neurons in the substantia nigra pars compacta (SNpc). The disease's familial form is associated with gene duplication and six missense mutations in the αS gene that translate to the mutant proteins. In the disease's sporadic form, various environmental factors are linked to the development of neuronal inclusions and the formation of Lewy bodies.

In the current thesis, we compared the interfacial properties of the N-terminal acetylated αS (Ac-αS) with non-acetylated αS (NH2-αS) at the air-water interface. Both these protein forms display very high surface activity with the surface pressure reaching up to ~30 mN/m upon monolayer compression. The interfacial activity for both the protein forms was very similar. Compression/expansion cycles display large hysteresis, suggesting self-assembly upon compression. The Blodgett-deposited protein were investigated using CD and LD spectroscopy, and the AFM. The protein displayed a random coil to α-helical transition as the air-water interface, and the protein films get anisotropically deposited.

The study was further extended to explore the interfacial behaviour of the Parkinsonian variants of the αS protein (A30P-αS, E46K-αS, H50Q-αS, G51D-αS, A53E-αS, and A53T-αS) at the air-aqueous interface. We have demonstrated the structural transition of the unordered conformation in the aqueous solution into the α-helix-rich protein monolayer at the air-aqueous interface. The protein's LB film's anisotropic nature was established using linear dichroism spectroscopy. Binding of the αS's parkinsonian variants to the flat membranes was investigated using lipid monolayers. The αS's Parkinsonian variants have a higher affinity for the negatively charged lipid flat membranes than towards the zwitterionic membranes. The atomic force microscopy of the αS Parkinsonian variants LB films revealed vivid microstructure formation with minimal defects.

We subsequently investigated the role of polymyxin B, a circular lipopeptide that seem to improve the movement disorders in PD patients, on αS amyloid formation. Polymyxin B was found to have a strong effect on the αS aggregation. The lag phase in the presence of equimolar polymyxin B was reduced to ~40%. Using circular dichroism spectroscopy and transmission electron microscopic imaging, we show that the β-sheet rich fibril formation is complete in the presence of equimolar polymyxin B, whereas it does not even start in the polymyxin B's absence.

Overall, the insights gained from the interfacial assembly of αS and its Parkinsonian variants have led to a better understanding of the unstructured protein's behaviour when it interacts with interfaces. Such insights open opportunities to the design of therapeutics targeting the interfacial assembly of the protein.