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Computational study on effects of lipids on α-synuclein

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Abstract: Parkinson's disease is a progressive degenerative disorder of central nervous system with several motor and non-motor symptoms. The pathological hallmark of this disorder is the presence of insoluble deposits in brain known as Lewy bodies, mainly composed of filamentous aggregates of an intrinsically disordered protein called α-synuclein. Misfolding and aggregation of α-synuclein is ubiquitously associated with the pathology of Parkinson's disease. A significant fraction of α-synuclein is localized with membrane fractions, especially at the pre-synaptic terminals. Both the physiological and the pathological roles of α-synuclein involve interactions with neuronal membranes. The objective of the present work is to elucidate the structural, functional and toxic consequences of α-synuclein due to interactions with lipid membranes. To model the native environment of the protein, the compositions of the lipid membranes used in this study are chosen to mimic the synaptic vesicle membrane. Using extensive multiscale simulations, we have elucidated the membrane binding and insertion affinity of α-synuclein as well as its ability to perturb the membrane structure, as a function of change in lipid-protein interactions with the change in membrane lipid composition. We have employed enhanced sampling molecular dynamics simulations to characterize the stable conformational states of α-synuclein on the membrane surface. Our results suggest the important role of brain lipids in the early onset of Parkinson's disease which involves co-dependent lipid-protein interactions.