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Stimulation of α-synuclein amyloid formation by phosphatidylglycerol micellar tubules

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Abstract

α-Synuclein (α-Syn) is a presynaptic protein that is accumulated in its amyloid form in the brains of Parkinson's patients. Although its biological function remains unclear, α-syn has been suggested to bind to synaptic vesicles and facilitate neurotransmitter release. Recently, studies have found that α-syn induces membrane tubulation, highlighting a potential mechanism for α-syn to stabilize highly curved membrane structures which could have both functional and dysfunctional consequences. To understand how membrane remodeling by α-syn affects amyloid formation, we have studied the α-syn aggregation process in the presence of phosphatidylglycerol (PG) micellar tubules, which were the first reported example of membrane tubulation by α-syn. Aggregation kinetics, β-sheet content, and macroscopic protein-lipid structures were observed by Thioflavin T fluorescence, circular dichroism spectroscopy and transmission electron microscopy, respectively. Collectively, the presence of PG micellar tubules formed at a stochiometric (L/P =1) ratio was found to stimulate α-syn fibril formation. Moreover, transmission electron microscopy and solid-state nuclear magnetic resonance spectroscopy revealed the co-assembly of PG and α-syn into fibril structures. However, isolated micellar tubules do not form fibrils by themselves, suggesting an important role of free α-syn monomers during amyloid formation. In contrast, fibrils did not form in the presence of excess PG lipids (≥ L/P = 50), where most of the α-syn molecules are in a membrane-bound α-helical form. Our results provide new mechanistic insights into how membrane tubules modulate α-syn amyloid formation and support a pivotal role of protein–lipid interaction in the dysfunction of α-syn.

Keywords: membrane remodeling, protein-lipid interaction, Parkinson's disease, transmission electron microscopy, Thioflavin T, circular dichroism

Abbreviation: α-Syn (α-Synuclein); Parkinson's disease (PD); L/P (lipid-to-protein); POPG (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol)); POPA (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphate); POPS (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phospho-L-serine); POPG-d31 (1-palmitoyl(D31)-2-oleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol)); ThT (Thioflavin T); GuHCl; (guanidinium hydrochloride); MOPS (3-(*N*-morpholino) propanesulfonic acid); Tris (tris(hydroxymethyl)aminomethane); TEM (transmission electron microscopy); CD (circular dichroism); MLV (multilamellar vesicle); SUV (small unilamellar vesicle).