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Biophysical Analysis of Dopac-induced Alterations in Alpha-synuclein and E46k Membrane Binding Dynamics

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α-Synuclein (Syn) is an intrinsically disordered protein involved in synaptic plasticity, adopting an α-helical conformation upon membrane binding. The E46K mutation, linked to early-onset Parkinson's disease (PD), promotes a more compact protein state and increases membrane affinity.

Here, we investigated the effects of DOPAC, a catechol derivative, on Syn and E46K interactions with lipid membranes using small unilamellar vesicles (SUVs) and an array of biophysical techniques, including far-UV circular dichroism (CD), surface plasmon resonance (SPR), and hydrogen-deuterium exchange mass spectrometry (HDX-MS).

Both proteins exhibit similar membrane affinity, but E46K undergoes faster lipid-induced folding and slower interaction kinetics. When pre-incubated with DOPAC, Syn shows increased deuterium exchange in the 55–70 region, whereas E46K remains unaffected. However, under membrane-bound conditions, DOPAC enhances solvent exposure in E46K, leading to its partial displacement, while no direct interaction with Syn is observed.

These findings suggest that DOPAC modulates Syn-membrane interactions while preferentially affecting the membrane-bound E46K species, enhancing their structural dynamics. By influencing Syn aggregation and membrane interactions, DOPAC may play a role in neurodegenerative processes, offering insights into potential therapeutic strategies for PD.