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What Structures Do Amyloid Beta Peptides Form in The Presence of Lipid Membranes?

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Alzheimer's disease is tightly associated with the misfolding of amyloid-β (Aβ) peptides towards β-sheet-rich fibrils. Increasing evidence suggests that early-stage Aβ oligomers formed along the misfolding trajectory exert neurodegenerative effects by interfering with neuronal membranes eventually leading to cellular dysfunction. But the mechanism and factors influencing these early events are debated. We analyze if the incorporation of Aβ into the membranes influences the (mis)folding process. Using the enhanced plasmonic detection of surface-enhanced infrared absorption (SEIRA) spectroscopy, we monitor the early phase of Aβ (mis)folding at tethered bilayer lipid membranes (tBLMs) systems that either permit or prevent transmembrane incorporation. Focusing on Aβ's amide bands, we track the secondary structural changes when interacting with membranes and quantify Aβ's orientation by comparison to computed spectra from density functional theory (DFT). We find that the incorporation of Aβ into membranes promotes the transition from antiparallel to parallel β-sheets, which are formed suddenly after a lag period indicating a cooperative process. The latter appears to be accelerated by negatively charged lipids, which are often discussed as misfolding catalysts. Our results strengthen the proposals that misfolding involves the formation of ion channel/pore-like oligomeric structures.