properties. In the first 0.15 microseconds of TVREX simulations, β-sheet and α-helical aggregates form both at the interface and in the hydrophobic core of the lipid bilayer. We quantify the extent to which these aggregates compromise the integrity of the lipid bilayer. This analysis indicates that fragments of human prion peptides and of Alzheimer's-related apolipoprotein, which form β-sheet amyloid fibrils *in vivo*, are capable of forming β-sheet aggregates that disrupt lipid bilayers. Taken together, our results reveal, in atomistic detail, a variety of modes by which amyloidogenic peptides may disrupt lipid bilayers, providing mechanistic insights into the molecular basis of toxicity in this important class of human diseases.

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1221-Plat

A Coarse Grained Molecular Dynamics Study of Amyloid Beta Transmembrane Pores

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Amyloid-beta protein has been implicated in the pathogenesis of Alzheimer's disease for many decades now. However, the exact molecular mechanism by which it effects neurodegeneration is not yet understood. One promising disease model is based on the discovery that amyloid-beta forms large pores across lipid bilayers. These pores cause an uncontrolled flux of ions as well as larger molecules and can potentially disrupt cell homeostasis. AFM images of amyloid-beta pores provide an estimate of the size and symmetry of the pores, but the secondary and tertiary structure of amyloid-beta within the membrane is unknown. This study tests the stability of a hypothetical pore structure and will predict the number of monomers within amyloid-beta pores using coarse-grained molecular dynamics simulations. The change in stability of the pore structure with changes in membrane composition will also be investigated, since membrane composition is known to vary with age - the greatest risk factor for Alzheimer's disease.

Platform: Protein Aggregates

1222-Plat

Oxidative Footprinting of Fibrillar and Prefibrillar Oligomer Forms of Amyloid Beta

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The mechanism by which amyloid-β (Aβ) plaque accumulation contributes to neurodegeneration in Alzheimer's disease (AD) remains poorly understood. With biophysical, thermodynamic and kinetic characterization of the various Aβ structures involved in plaque development, we aim to identify connections between polymerization cascade events and AD pathogenesis. Herein, we present oxidative footprinting with mass spectrometry to probe the solvent accessibility of specific amino acid side chains in Aβ40 fibrils and oligomeric forms of Aβ40. These accessibilities are compared to those of a fully exposed reference state using hydroxyl radicals (*OH) generated either by water radiolysis or by Fe(II)-EDTA reaction with peroxide. Using this information we distinguish topological relationships within the fibril to allow selection of the relevant tertiary structural model of fibrillar Aβ from those suggested by NMR and those by cryogenic electron microscopy. This work provides important steps towards correlating structure and morphology in Aβ fibrils – essential for understanding the molecular pathogenesis of AD.

1223-Plat

Tracking Conformational Changes during Amyloidogenesis in Real-Time at Atomic-Resolution by NMR

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Understanding the structural transitions that amyloid proteins undergo during amyloidogenesis would greatly enhance our understanding of this process. However, our knowledge has been currently largely limited to global conformational changes, with high-resolution structural information only available for the monomeric proteins and for a few structures of the final amyloid product. In particular, high-resolution structures of intermediate states have been notoriously absent with few exceptions. We show here that high-resolution structures of intermediates can be obtained by using SOFAST-HMQC, CPMG, NOESY, magic-angle-spinning, and other experiments in real-time to track the aggregation pathway at atomic-level detail and at a time-resolution of minutes. As examples, we show the aggregation pathways of Aβ and IAPP, two initially unstructured peptides implicated in Alzheimer's and type II Diabetes, respectively.

While previous studies commonly show the $A\beta_{1\text{-}40}$ is largely unstructured in solution before the formation of β-sheet oligomers, we show that $A\beta_{1\text{-}40}$ gradually adopts a compact, partially folded helical structure over a period of several days. In this structure, the central hydrophobic region of the peptide forms a 3_{10} helix from H13 to D23 and the N- and C-termini collapse against the helix due to the clustering of hydrophobic residues (pdb:2LFM). The formation of the helical intermediate is concentration dependent and can be partially reversed by dilution of the peptide. Helical intermediates have been predicted to be crucial on-pathway intermediates in amyloid fibrillogenesis, and the structure presented here presents a new target for structure-based intervention, shown here by the interaction of the helical intermediate with polyphenols. By contrast, the more amyloidogenic IAPP peptide shows only a gradual transition to the fiber form after an initial pH dependent formation of a micelle-like aggregate, with distinct β-sheet small oligomers forming only a small fraction of the observable population.

1224-Plat

Beta Sheets, Mutations, and Orthomolecular Inhibitors, Oh My: A Comparison of Beta-Sheet Production Across Mutants and the Effects of B17 on Inhibition of Fibril Formation

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Beta-sheet fibril deposits are a crucial hallmark of Alzheimer's disease. Characterized by accumulations of highly toxic beta-sheet structures, fibril tangles disrupt synaptic function causing impaired memory. Amassing toxicity results in neuronal degradation and ultimately complete brain death. Beta-amyloid research focuses on one region of the 40-42 amino acid length beta-amyloid known as ''KLVFFA''; this region, from residues 16-21, is believed to be the single, shortest, and most important contributor to beta-sheet formation. However, these theories overlook the crucial portion of the peptide, at residues 23-28, containing an ionic interaction inducing a hair pin turn. This potential rate limiting step in the folding of beta-amyloid provides new insight into the pathogenesis of Alzheimer's disease. Cleavage at residues 22 and 35 excludes the effect of ''KLVFFA'' and limits secondary folding interactions of the N-terminus after 35. Spectral analysis of the Wild Type WT Aβ22-35 lays ground work for various single point mutations within the shorter fragment. Aβ-E22G and Aβ-D23N, also known as the Arctic mutation and Iowa mutation respectively, are characterized by faster accumulation of amyloid fibrils. Beta-sheet production occurs rapidly, but can be observed by the implementation of ATR-IR spectroscopy focusing on signature chemical shifts in the amide one and amide two regions within the peptide. Second, pentamaric binding of multiple secondary beta structures to Congo-Red dye solution confirms the production of beta-sheets via UV/Vis. Moreover, time dependant TEM imaging of the WT revealed the presence of fibrils, demonstrating the importance of studying this shorter fragment. Suppression of fibril formation by the addition of concentrated orthomolecular compounds could yield therapeutic techniques or possibly even a cure for Alzheimer's disease.

1225-Plat

Simulation of Amyloid Nucleation with Bias-Exchange Metadynamics

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Starting from a disordered aggregate, we have simulated the formation of ordered amyloid-like beta structures in a system formed by 18 poly-valine chains in explicit solvent, by employing molecular dynamics accelerated by bias-exchange metadynamics. We exploited 8 different collective variables to compute the free energy of hundreds of putative aggregate structures, with variable content of parallel and anti-parallel beta-sheets and different packing among the sheets. This allowed characterizing in detail a possible nucleation pathway for the formation of amyloid fibrils: first the system forms a relatively large ordered nucleus of anti-parallel beta-sheets, then a few parallel sheets start appearing. The relevant nucleation process culminates at this point: when a sufficient number of parallel sheets is formed, the free energy starts to decrease towards a new minimum in which this structure is predominant. The complex nucleation pathway we found cannot be described within classical nucleation theory, namely employing a unique simple reaction coordinate like the total content of beta-sheets.