The presence of an abnormally expanded polyglutamine (polyGln) sequence in huntingtin protein ultimately results in beta-sheet-rich fibrillar aggregates, a hallmark of Huntington's disease. Current challenges are to map out the polyGln aggregation pathway by identifying the various precursor structures and establish their pathological roles. We are using time-resolved small-angle neutron scattering (SANS) to probe the aggregates formed by peptides having the protein context of huntingtin exon 1 (HD protein) and with varying polyGln lengths. SANS is a particularly useful technique for following structural changes on the nanometer length-scale in solution. From the time-resolved scattering data, we obtain snapshots of the polyGln structures as the kinetics reaction ensues, which yields quantitative information on the size and shape of precursors and the internal structure of the resulting fibrils. Measured changes in the radius of gyration and mass per length illustrate multiple growth regimes with a transition from early aggregates to fibril elongation and association. Our SANS results on mature polyGln fibrils are consistent with the Perutz beta-helix structural model. This research is providing new insights into the pathway of polyGln aggregation and should later assist in determining the role that precursors play in neuronal toxicity.

1130-Plat
Solid State NMR Studies Of Structural And Motional Complexity In Amyloid-Like Fibrils Of The Peptide GNNQQNY
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Solid state NMR allows the site-specific characterization of structure and dynamics in a variety of immobilized biomolecules, and thus allows a unique structural view on amyloid fibrils. These fibrils are common to various human disorders and appear to share a number of characteristic features, both in terms of their structure and formation. In the hope of delineating the biophysical details of the fibrillization process and the fibrils themselves, various groups have focused on the experimental and theoretical study of small peptide fragments of amyloid-forming proteins. One prominent system is the $GNNQQNY_{7\text{-}13}$ fragment of the yeast prion protein Sup35p, since it was found to form not just amyloid-like fibrils, but also seemingly amyloid-like microcrystals. X-ray diffraction based structures from the latter have inspired numerous theoretical analyses and generalizations regarding the biophysics and structures of amyloid fibrils.
We have instead applied biological solid state NMR methods to characterize the GNNQQNY fibrillar aggregates. Magic angle spinning (MAS) solid state NMR was used for various structural measurements, aimed at both the intramolecular as well as intermolecular structural motifs of the fibrils (as well as the crystalline aggregates). Our studies have revealed a remarkable complexity in these fibrils, despite the relatively small size of the peptide building blocks. This is in marked contrast with the rigid and homogeneous nature of the crystalline structures, as revealed by X-ray crystallography and solid state NMR. These observations provide further insights into the structure of the fibrils of this peptide model system and should also be of importance as input to numerous theoretical studies that rely on the crystal structure data.

1131-Plat
Computational Study of Assembly and Toxicity Inhibition of Amyloid Beta-Protein and Its Arctic Mutant
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Amyloid b-protein (Ab) exists in two main alloforms, Ab40 and Ab42, of which Ab42 is linked particularly strongly to Alzheimer's disease (AD). Prior computational work demonstrated that the ab initio discrete molecular dynamics approach with an intermediate-resolution protein model captures biologically relevant differences between Ab40 and Ab42 folding and oligomerization. In the present work we apply the same approach to explore the relationship between the structure and toxicity. Assuming that Ab42 oligomers are more toxic than oligomers formed by Ab40, our structural analysis indicates that the solvent accessible surface area (SASA) in the N-terminal region of Ab42 oligomers is significantly higher than that of Ab40 oligomers. We then investigate effects of the C-terminal fragment (CTF), which was shown to attenuate Ab42 oligomer toxicity in a cell culture, on Ab42 oligomerization. Our results indicate that CTFs associate with Ab42 to form heterooligomers, consistent with quasielastic light scattering data. We show that the presence of CTFs significantly reduces SASA in the N- terminal region of Ab42 compared to the same region in Ab42 oligomers formed in the absence of CTFs.
We further explore folding and oligomer formation of the Arctic mutants, [E22G]Ab40 and [E22G]Ab42, associated with a familial form of AD. Our results demonstrate that the substitution E22G disrupts the folding structure and oligomerization pathways of both Arctic mutants and results in increased SASA at the N-terminus of the Arctic Ab40 mutant. These findings suggest that Ab oligomer neurotoxicity might be directly or indirectly associated with the degree of solvent exposure of the N-terminal region of Ab.

1132-Plat
Discrete Molecular Dynamics simulations on hexameric amyloid-β (1-40) and (1-42) models
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Aggregation of amyloid-β peptides (Aβ) may play a pivotal role in neurotoxicity of Alzheimer's disease. Two major alloforms of Aβ are the 40-residue long Aβ40 and the 42-residue long Aβ42. Though Aβ42 has only two more residues at the end of C-terminus, Aβ40 and Aβ42 show different characteristics in early aggregation: Aβ40 aggregates to exist from monomers up to tetramers while Aβ42 exists from monomers to hexamers, dodecamers, or even octadecamers. However, the molecular mechanism of the different aggregation between Aβ40 and Aβ42 is not clearly understood since their oligomeric structures are not available from experiments due to their meta-stable characteristics. Here, we simulated nine hexameric Aβ40 and nine hexameric Aβ42 models with Discrete Molecular Dynamics (Discrete MD). The hydrophobic core of these models is a six-stranded β-barrel formed by residues 30-40 that has three-fold symmetry about its axis. This core is shielded from water by residues 1-28. The models differ by the relative positions of the core β strands, and whether the other segments surrounding the core contain α helices or β-strands. The potential energy of Aβ40 measured by Miyazawa-Jernigan interaction matrix were considerably lower than the potential energy of Aβ42 in all of 18 models tested, probably because more hydrophobic residues are exposed to water in theAβ42 models. In two of nine models of Aβ42, dangling hydrophobic β-strands emerged on the surface. This implies that the association of these hexamers may be possible, which could lead to the formation of larger assemblies.

Platform X: Exploring the Unfolded State of Peptide & Proteins

1133-Plat
Concentration Dependent Instability of ß-sheet aggregates of Ac-(AAKA) 4NH2 in solution
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The amphiphatic polyalanine peptide, Ac-(AAKA)4-NH2, has recently been shown to aggregate into a hydrogel at high chloride concentration or alkaline pH. It forms soluble ß-sheet type aggregates at neutral pH and centimolar concentrations. In order to further characterize the transition from the monomeric to the aggregated state, we measured the far UV-ECD spectrum at different concentrations between 35 - 700 μM. At very low concentration (i.e. 0.05 mg/mL or 35 μM) the observed spectrum is indicative of a stable mixture of right handed α-helical and ß-strand (sheet) conformations. At higher concentrations (> 1 mM) we observed a spectrum reflecting a very stable ß-sheet aggregate. However, at concentrations between 70 - 700 μM the peptide shows a very strange, and totally unexpected, behavior. Upon dissolving it in solution, a statistical coil-like mixture comprising polyproline II (PPII), α-helical and ß-sheet-like conformations is formed. Subsequently, most of the ß-sheet fraction decays into a conformation which exhibits a PPII-type ECD spectrum on a time scale of 104-105 s. The kinetics of the process follows a power law at low concentrations and becomes mono-exponential at higher concentration. Generally, the relaxation slows down with increasing peptide concentration until the ß-sheet becomes stable on the time scale of our experiments (<105 s). We hypothesize that aggregation involves multiple steps with the formation of a rather unstable ß-sheet as the first step. The second step involves the formation of stable fibers. This step competes with the formation of collagen like coil-coil state, rather, which is known to exhibit a PPII-like ECD spectrum.

1134-Plat
Characterization of the Disordered Regulatory Domain from Calcineurin
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Calcineurin (CaN) is a highly-conserved, ubiquitous Ser/Thr phosphotase that plays vital roles in memory development and retention, cardiac growth, and