were performed on αS in the absence and presence of SDS micelles to probe which specific protein-protein and protein-lipid interactions are involved as SDS denatures αS determining the structure and dynamics. In the absence of SDS, individual αS molecules rapidly fold to form globular structures in which the acidic C-terminus interacts strongly with the more basic N-terminus. Simulating these structures in the presence of SDS micelles shows an initial electrostatic interaction between the protein and lipid, but the tertiary structure remains compact over short time scales, instead of forming the extended structures obtained by others via NMR measurements. However, as the simulations progress, the electrostatic interactions between the protein and lipid become less favorable because the sulfate groups of the micelles compete with the acidic residues of the C-terminus. Meanwhile the interaction between hydrophobic residues and the lipid acyl chains increases with time. These results suggest that monomeric and soluble αS requires the presence of lipids to overcome the strong attraction between the N- and C-terminus prior to aggregation, or that soluble multimeric forms of αS are the primary agents of aggregation.

2346-Pos Board B316

A Molecular Dynamics Study on the Binding and Interaction of the Amyloid-Beta (1-42) Peptide with Phospholipid Bilayers

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The Amyloid-Beta (A-Beta) peptide is a key aggregate species in Alzheimer's disease. While aspects of the A-Beta peptide aggregation pathway have previously been elucidated, the initial conversion of monomer peptides into an oligomer during aggregation is not clearly understood. One potential mediator of these early stages of aggregation is interactions of A-Beta with cell membranes, particularly anionic cell membranes. We use unconstrained and umbrella sampling molecular dynamics simulations to investigate interactions between the 42-amino acid A-Beta peptide and model bilayers consisting of zwitterionic dipalmitoylphophatidylcholine (DPPC) lipids and anionic dioleoylphosphatidylserine (DOPS) lipids. From this work, we determine that A-Beta binds to the surface of DPPC and DOPS bilayers over the small length scales used in simulations. Our results also support the hypothesis that the charge on the bilayer surface and on the peptide affects both the free energy of peptide-membrane binding and the distribution of the peptide on the bilayer surface. Finally, no significant secondary structure change is observed in the peptide during the timescales used in these simulations. This result may indicate all-atom simulation times are too short to observe secondary structure changes in this system or that structure change during the oligomerization process requires peptide-peptide interactions. Our work demonstrates that interactions between the A-Beta peptide and lipid bilayers promote a peptide distribution on the bilayer surface that is prone to peptide-peptide interactions, which can influence the propensity of A-Beta to aggregate into higher order structures.

2347-Pos Board B317

Use of Transmembrane Peptides to Investigate Arginine Interactions with Lipid Bilayers

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With a pK $>$ 12, the guanidinium side chain of arginine (Arg; R) is positively charged over a very wide pH range. There has been much recent discussion concerning the energetics of Arg inserting into a lipid bilayer, or Arg crossing a lipid bilayer. The topic holds significant intrinsic intellectual interest and also is important for understanding the gating mechanism of voltage-dependent transmembrane channels. We address this problem by direct experimental observation using a designed transmembrane peptide that has interfacial tryptophan (Trp; W) anchors. Within membrane-spanning, alpha-helical GWALP23, acetyl-GGALW^{5}LALALAL^{12}ALALALW^{19}LAGA-amide (Vostrikov, *et al.* 2008. *J Am Chem Soc* **130**, 12584), we have substituted either R^{12} or R^{14} near the putative helix midpoint. Models suggest that the W^{5} and W^{19} side chains project from essentially the same side of the GWALP23 alpha-helix, with R^{14} projecting from the *opposite* face and R^{12} from the *same* face as the W^{5} and W^{19} anchors. The R^{12} side chain in effect is situated *between* the W anchors. Based upon solid-state NMR spectra from oriented lipid/peptide samples, specifically the deuterium quadrupolar splittings from several ^{2}H-labeled alanines in each Arg-containing peptide, the properties of these sequence isomers depend heavily upon the location of the Arg. We find that GWALP23-R14 adopts a transmembrane orientation with a tilt of about 17° in DOPC (compared to a tilt of about 6° for GWALP23 itself). By contrast, GWALP23-R12 seems to assume several different orientations with respect to a hydrated bilayer of DOPC; one or more of these orientations may represent surface-bound peptide.

2348-Pos Board B318

Influence of Proline upon the Folding and Geometry of the WALP19 Transmembrane Peptide

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The orientations, geometries and lipid interactions of designed, specifically anchored, transmembrane (TM) peptides have attracted significant experimental and theoretical interest. Because Pro will introduce a known discontinuity into an alpha-helix, we have sought to measure the extent of helix kinking caused by a single proline within an isolated TM helical domain, and to address the question: To what extent do the individual N-terminal and C-terminal segments adjust their tilts with respect to the bilayer normal in response to the proline? For this purpose, we synthesized WALP19-P10, acetyl-GWWLALALAP^{10}ALALALWWA-ethanolamide, and included pairs of deuterated alanines by using 60-100% fmoc-d_4-Ala at selected sequence positions. Remarkably, solid-state ^{2}H NMR spectra from oriented, hydrated samples (1/40, peptide/lipid; using DOPC, DMPC or DLPC) reveal signals from many of the Ala Cα deuterons as well as the Ala Cβ methyls; whereas signals from backbone Cα deuterons had not been observed for WALP19 without Pro. For example the magnitudes of the ^{2}H quadrupolar splittings are 70 and 10.7 kHz for the Ala^{11} Cα-D and side-chain methyl groups, respectively. We are considering possible reasons for the apparent ''unmasking'' of the backbone resonances in the presence of the proline. At the same time, the observed backbone resonances provide valuable additional data points for evaluating the segmental tilt angles of the N- and C-terminal segments. In order to make available still more data points for the Geometric Analysis of Labeled Alanines (GALA), we also are substituting selected leucines with d_4-Ala. Together the results suggest that the central proline influences not only the geometry but also the dynamics of WALP19.

2349-Pos Board B319

Comparison of Mechanical and Magnetic Alignment of WALP-like Peptides for Solid-State NMR

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Oriented lipid/protein and lipid/peptide samples for solid-state NMR spectroscopy can be prepared by using either hydrated lipid bilayers that are mechanically aligned on glass plates or mixed lipid bicelles (''bilayered micelles'') that are magnetically aligned in solution. The bicelles consist of a combination of long- and short-chain lipids that form lipid bilayer discs in which a planar portion is formed by the longer lipids while the sides are capped by the shorter lipids. In this study we compare the solid-state ^{2}H and ^{31}P NMR spectra from bilayer and bicelle samples containing deuterated peptides. Example peptides having deuterated alanines include WALP19 (a-GWW(LA)$_6$LWWA-e), WALP23 (a-GWW(LA)$_8$LWWA-e) and GWALP23 (a-GGALW(LA)$_6$LWLAGA-e) in which ''a'' is acetyl and ''e'' is ethanolamide. Using bicelles having two orientations, as well as mechanically aligned bilayers, we compare the measured ^{2}H quadrupolar splittings and the deduced average peptide tilt. Additional variables include the lipid composition, peptide-to-lipid ratio and temperature.

2350-Pos Board B320

Half-Anchored WALP Peptides: Effect Of Anchor Position On Peptide Orientation

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Peptides of the ''WALP'' family, acetyl-GWW(LA)$_n$LWWA-[ethanol]amide, provide an opportune model for investigating protein/lipid interactions. Because the motional behavior of the N- and C-terminal tryptophan (W) residues is different (van der Wel [2007] *Biochemistry*, 46:7514), it is of interest to investigate how the positions of the anchoring tryptophans will influence the average peptide orientation. To address this question, we synthesized ''half-anchored'' WALP peptides having only one pair of anchoring tryptophans at either the amino or carboxy terminus. These peptides are acetyl-GGWW(LA)$_8$-ethanolamide and acetyl-(AL)$_8$WWG-ethanolamide, which we designate as ''N-anchored'' and ''C-anchored'', respectively. The hydrophobic lengths of these peptides are similar to that of WALP23, but unlike WALP23 they are anchored to the lipid bilayer membrane on only one side. We find that the half-anchored WALP peptides incorporate into lipid bilayers and assume defined orientations. Unlike shorter half-anchored analogs that contain only three or four Leu-Ala pairs, these longer peptides with eight Leu-Ala pairs show no signs of aggregation and therefore allow further investigation of the peptide/lipid interactions. Circular dichroism spectra indicate that the N-anchored