compensated, at least in part, by interactions with the channel wall and by interactions with the lipid headgroups at the channel mouth. Consequently, differences in single channel permeability (pf) measured for gramicidin A channels embedded into different lipids were interpreted in terms of differences in water dehydration costs. However, recent atomistic molecular dynamics simulations identified lipid headgroup interactions with the channel entrance leading to transient blocking of the channel. This observation suggests that the lipid environment affects the channel not only by changing the water energetics but also by mechanically blocking the entrance. To test this hypothesis we measured ion and water fluxes through acylated gramicidin-A derivatives, which were reconstituted into solvent free diphytanoyl-phosphatidyl-choline membranes. Ion conductance of channels with C9 and C10 acyl-chain anchors differed only by about 20 % from wild type gramicidin-A conductance. Similarly, the anchor had only a minor effect on dimer stability as indicated by a decrease in channel lifetime from 2.3 s to 2 s or 1.6 s for the C9 and C10 derivatives, respectively. As the gramicidin channels most of the time do not contain ions, the acyl-chain anchor affects water transport more efficiently. Two C9 anchors increased pf by a factor 2 or 3 depending on their position. In contrast, derivates with only one C9 or C10 acyl anchor showed no increase in pf. Taken together with data about the lipid dependency of pf, these results indicate that the lipid headgroups affect single file transport by both changing the solvation energy and by blocking the channel entrance.

1464-Pos

Amyloid Oligomers Increase the Lifetime and Single Channel Conductance of Gramicidin Channels

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Our previous data suggest that Aβ does not itself contribute a new intrinsic conductance to the membrane but instead alters physical properties of the membrane specifically increasing the apparent dielectric constant of hydrocarbon region. This change could in turn affect the properties of membrane ion channels.

In order to test this notion we compared the effects of amyloid oligomers on the single channel conductance and mean open time of gramicidin in 2 M NaCl and CsCl using DOPC and a series brominated lipids that change the dielectric properties of lipid bilayer at different depths into the membrane (11,12-bromo-16:0, 10,9- bromo-16:0 and 7,6- bromo-16:0, PC). Amyloid oligomers always increase the single channel conductance and mean open time both in 2 M NaCl and CsCl regardless of the nature of lipid used. The single channel conductance of gramicidin in brominated lipid membranes is always lower than that in DOPC membranes.

In terms of a simple three-barrier two- site model such as that used by Barnett et al., 1986, this suggests that amyloid oligomers lower the energies of both Cs and Na ions in the gramicidin channel but at different critical locations relative to the barrier profile. For Na^+, amyloid oligomers lower the principal central barrier and thus increase the translocation rate of Na^+ at a given voltage. For Cs^+, amyloid oligomers act as if they lower the energy of the Cs ion in the channel, but in such a way as to increase the depth of one or both of the two wells in the barrier profile. Brominated lipids apparently increase the depth of the wells at the ends of the channel consistent with their X-ray locations.

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1465-Pos

Observation of Beta-Amyloid Formation Via Membrane Binding

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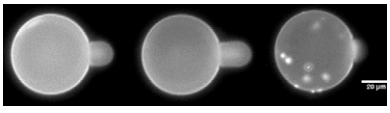
Alzheimer's Aβ-40 and penetratin exhibited the same conformation changes upon binding to membranes. Recently we have studied the thermodynamics of membrane-mediated β-aggregate formation in equilibrium experiments using penetratin-lipid mixtures. The results showed that penetratin bound to the membrane interface in the α-helical conformation at low peptide-to-lipid (P/L) ratios. As P/L exceeds a lipid dependent critical value P/L*, small β-aggregates were formed, which served as the nuclei for large β-aggregates. We tested this free energy description in a kinetic experiment using GUVs. A GUV made of 7:3 DOPC/DOPG and 0.2% lipid dye was aspirated by a micropipette and transferred to a solution of containing penetratin in various concentrations. As the peptides began to bind to the GUV, the membrane area initially expanded till it reached a maximum (this corresponds to P/L->P/L*). Then the area began to decrease from the maximum expanded value (corresponding to P/L exceeding P/L* where the membrane thinning decreases with increasing P/L). Concomitant with the area decrease, lipid aggregates began to appear on the surface of GUV and some of them came off the GUV surface.



1466-Pos

Membrane Mediated Peptide Conformation Change from Alpha-Monomers to Beta-Aggregates

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The major component of Alzheimer's disease amyloid plague, β-amyloid protein 1-40 and the peptide penetratin exhibited the same membrane mediated conformation changes. Both peptides are random coils in solution but change to α-helical or β-like conformations in the presence of negatively charged lipid membranes. Both peptides change from α to β conformations as the lipid charge increases or as the peptide concentration increases. Since the principle behind these phenomena might clarify the molecular mechanism of β-amyloid formation, we investigated the correlation between the peptide conformation of penetratin and its effect on the membrane thickness in four different lipids with varying degrees of chain unsaturation. The results revealed a new effect of membranes on penetratin , i.e., as the degree of chain saturation increased, the peptide changed from α-helical to β-like conformation. We found that penetratin in the helical conformation was bound to the interface and thinned the membrane. In contrast, penetratin in the β-conformation had little effect on the bilayer thickness, therefore it was most likely bound on the surface of lipid headgroups. From the systematic results we were able to deduce the molecular mechanism in terms of free energies that explains the effect of membrane binding on the secondary structure of penetratin. The mechanism could be the prototype for the membrane-mediated version of nucleation-dependent amyloid formation proposed by Jarrett and Lansbury. It might explain why membrane binding has been suspected as the catalyst for polymerization leading to amyloid formation.

1467-Pos

The Hydrophobic Surfactant Proteins Induce Cubic Phases Without Altering Spontaneous Curvature

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Prior evidence suggests that the hydrophobic surfactant proteins, SP-B and SP-C, promote adsorption of the surfactant lipids to the alveolar air/water interface by facilitating formation of a rate-limiting negatively curved stalk between the vesicular bilayer and the interface. In support of the proposed model, the physiological mixture of the surfactant proteins (SP), in amounts as low as 0.03% (w:w), induce 1-palmitoyl-2-oleoyl phosphatidylethanolamine (POPE) to form inverse bicontinuous cubic (Q_{II}) phases, in which each leaflet has the saddle-shaped net-negative curvature predicted for the hypothetical stalk. One mechanism by which the proteins might promote formation of the Q_{II} phases is by altering the spontaneous curvature of the lipid leaflets. If the lipid-protein mixtures form the inverse hexagonal (H_{II}) phase, then a shift in spontaneous curvature would change the dimensions of the unit cell. POPE forms H_{II} structures only above 71°C, and only for 0-0.03% SP. To obtain H_{II} structures with a wider range of protein contents, we substituted lipids that form H_{II} structures at lower temperatures. X-ray diffraction showed that 1,2-dioleoyl phosphatidylethanolamine and its stereoisomer 1,2-dielaidoyl phosphatidylethanolamine form Q_{II} phases with SP at or above 0.03%. During heating from 10 to 95°C, both lipids form H_{II} structures over the full range of protein concentrations from 0-3% SP. The dimensions of the H_{II} unit cell were unaffected by the content of protein. The lack of any effect of the surfactant proteins on the size of the H_{II} phase indicates that the proteins facilitate formation of the Q_{II} phases, and suggests that they promote adsorption, by a mechanism other than changing spontaneous curvature. (Studies conducted at the Stanford Synchrotron Radiation Lightsource).

1468-Pos

Modifications to Surfactant Protein B Structure and Lipid Interactions Under Ards Conditions: Consequences of Tryptophan Oxidation

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Oxidation of Surfactant Protein B (SP-B) is one of several mechanisms proposed to lead to inactivation of lung surfactant in patients with Acute Respiratory Distress Syndrome (ARDS). We have used solution NMR, circular dichroism and molecular dynamics simulation to explore the consequences of oxidation of the tryptophan residue in fragments of SP-B. These fragments include the N-terminal helix of SP-B, as well as Mini-B, a fragment that includes both the N-and C-terminal helices. The fragments were studied in a number of conditions including aqueous solution, organic solvent, zwitterionic and anionic micelles, as well as monolayers. Tryptophan oxidation was found to