properties; non-volatility and non-explosiveness. However, the safety of ILs in aquatic environment has not been fully assessed. In this work, we investigated the effects of ILs on ion channels when they are incorporated into a lipid bilayer. We chose gramicidin A (gA) as our model protein that selectively permeates cations. The ion permeability of gA varies depending on the type of ILs. In order to measure channel activities of gAs, we used two methods; fluorescence assay utilizing using stop-flow spectrometer and measurement of ion currents across lipid bilayers using a patch clamp instrument. Furthermore, we revealed that alkyl chain length of ILs and ion strength of buffer play important roles in ion permeability and confirmed how electrostatic effects due to charges on the membrane surface changed depending on ion strength of buffer using MD simulation. As a result, we should be able to design safer ILs by taking our results into account.

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Tug of War in Lung Surfactant Components: MiniB Dominates over Cholesterol during Lipid Domain Formation

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Lung surfactants (LS), a complex mixture of lipids and proteins present in the alveolar lining of lungs, help in lowering surface tension to near zero at expiration. Deficiency of this surfactant can lead to Neonatal Respiratory Distress Syndrome in infants, while a dysfunction of LS can cause Acute Respiratory Distress Syndrome (ARDS) that affects patients irrespective of age. Successful medical intervention such as surfactant replacement therapy (SRT) requires a good understanding of surfactant composition and function. Currently there is no consensus on the composition of LS used in SRT, particularly the interactions between components making up this mixture. Our objective was to understand the interaction of cholesterol (a component whose role and even presence in SRT is highly debated) and MiniB (a synthetic protein mimic of native surfactant protein SP-B) at air-water interface. We report the alteration in lipid domain formation of films containing 1,2-dipalmitoyl- sn- glycero- 3-phosphocholine (DPPC): 1- palmitoyl- 2- oleoyl- sn- glycero- 3- phosphatidyl-glycerol (POPG) in the ratio 7:3 under the influence of varying concentrations of MiniB and cholesterol. Fluorescence imaging under constant compression, along with analysis of domain size distributions, reveals that MiniB increases line tension between lipid domains, and prefers to stay in fluid POPG regions, making the liquid-ordered domains smaller in size. Small amounts of cholesterol prefer packed domains, stretching them into spirals during the process, lowering their line tension. In both cases, higher concentration yields more prominent consequences in terms of the stated changes. However, mixture containing both cholesterol and MiniB shows reduction in domain size with no changes in domain shape. This suggests the dominance of MiniB over cholesterol when interacting with lipid domains, which may have important effects on the performance of synthetic LS.

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Dynamic Measurements of Membrane Insertion Potential of Synthetic Cell Penetrating Peptide/pDNA/Ca^{2+} Complexes

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Noncovalent complexation of plasmid DNA (pDNA) using cell penetrating peptides (CPPs) has been less explored due to the relatively large complex size formed and the low-level gene expression. Here, condensing synthetic CPP polyplexes using CaCl2 produced small and stable complexes, which show higher level of in vitro gene expression. Anionic (i.e., POPS and POPG) or zwitterion (i.e., POPC) phospholipid monolayers at the air-water interface are used as model cell membranes to monitor the membrane insertion potential of synthetic CPPs. The insertion potential of complexes having different cationic (dTAT, H9, K9, R9, and RH9) and amphiphilic (RA9, RL9, and RW9) peptides were recorded using a Langmuir monolayer approach that records complexes adsorption to model membranes. Further, to mimic the pH of early endosome and late endosome and lysosome, phospholipid complex interactions were recorded at normal (pH 7.4) and low (pH 4.4) pH. All the complexes studied induced disruptions in phospholipid packing, which were most pronounced for the complexes having amphiphilic CPPs (i.e., RW9 and RL9). Particularly, the surface pressure of the complexes was significantly lower at normal pH when compared to acidic pH in the presence of POPC and POPS monolayers, except for RL9 and RW9 complexes. In contrast, the surface pressure of the complexes was significantly higher at normal pH when compared to acidic pH in the presence of POPG monolayer. Since the late endosomes contain an abundance of PC lipids and low pH, these results may be highly relevant to understand the efficiency of endosomal escape of these complexes.

Intrinsically Disordered Proteins (IDP) and Aggregates III

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Secondary Metal Binding to Amyloid-Beta Monomer is Insignificant under Synaptic Conditions

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Synaptically released Zn and Cu can reach high μM concentrations during neurotransmission. It is thought that multiple copper ions could bind to Aβ monomer and mixed Zn/Cu coordinated Aβ complexes may form. This could impact the Cu coordination to Aβ, and therefore may be of relevance to Aβ oligomerization and toxicity in the synapse. We investigated the kinetics of multiple Cu and mixed Zn/Cu binding to Aβ. We found that the second order association rate constants are on the order of 10^8 $M^{-1}s^{-1}$ and 10^5 $M^{-1}s^{-1}$, for the first and second Cu binding to Aβ, and 10^3 $M^{-1}s^{-1}$ for Zn binding to Aβ-Cu complex, respectively. Given that the metal ion concentration decreases by more than three orders of magnitude within 1 ms, based on our simulation of metal ion release from synaptic vesicle to the cleft, we conclude that only the first Cu binding would be of significance. Our study implies that although Zn could substantially perturb Cu coordination in Aβ, it has a negligible effect on the Aβ-Cu complex in the synapse, due to its slow association.

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Gas-Phase Conformations of a Huntingtin N-Terminal Peptide Reveal Condensed-Phase Heterogeneity with and without the Presence of a PPII Helix

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Huntingtin aggregate morphology and kinetics are modulated by the presence of two flanking sequences: a seventeen-residue α-helix (Nt17) which lies N-terminal to the amyloidogenic polyglutamine region; and a polyproline PPII helix that is C-terminal to the polyglutamine region. Nt17 is responsible for aggregate nucleation, and as such, represents an intriguing target for gaining structural insight into the early stages of N-terminal huntingtin aggregation. This study examined the secondary, tertiary, and quaternary arrangement of Nt17 using ion mobility-mass spectrometry (IMS-MS) coupled with condensed-phase covalent modification and gas-phase isotopic labeling. Monomeric Nt17 adopted two gas-phase conformations, which were derived from solution structures. These structures ranged from compact globular to elongated helical. Nt17 multimers followed the same pattern, again adopting structures varying from non-specific globule to bundled helix. Species ranging from the monomer up to the pentamer were observed. Covalent modification studies reveal threonine-3 and lysine-6 are solvent-exposed in the multimeric form. Additionally, polyproline, in a PPII helix conformation, was incubated with Nt17. Gas-phase isotopic labeling studies (hydrogen-deuterium exchange, HDX) on the two non-covalent complexes revealed nearly the same amount of deuterium uptake per Nt17 monomer in the complex, which suggests the same binding face is involved in Nt17 multimer and Nt17-Polyproline interactions. These results provide structural insight into Nt17 multimerization, and thus, the early stages of N-terminal huntingtin aggregation.

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Huntingtin N-Terminal Fragment Fibrils have a Rigid Amyloid Core Flanked by Non-Amyloid Domains with Increased Dynamics

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In Huntington's disease (HD) and several related disorders, the primary genetic cause is the expansion of a CAG repeat in a disease-specific gene. In HD the resulting expanded polyglutamine (polyQ) segment occurs near the huntingtin protein's N-terminus. The disease appears to reflect a gain of toxicity, with the toxic species involving a misfolded form of the mutant protein. However, the molecular details of the misfolded state remain unknown. In vivo studies have noted the presence of amyloid-like aggregates that are formed from