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2506-Pos

The Interaction with β-Amyloid Impairs the Mechanical Stability of Polymer Cushioned Membrane

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The mechanism of neurodegeneration caused by β-amyloid (Aβ) in Alzheimer's disease is still controversial. Neuronal toxicity is exerted mostly by various species of soluble Aβ oligomers. Recent data depict membranes as the main sites where proteins/peptides are recruited and concentrated, misfold, and nucleate amyloids; at the same time, membranes are considered key triggers of amyloid toxicity.

We demonstrated the capability of Aβ to penetrate and destabilize stacked lipid bilayers in a previous work. In this study, in order to maintain the natural fluidity of the membrane, polymer cushioned lipid bilayers have been used as a model for neuronal membrane. Layer-by-layer technique was used for the fabrication of the polymer cushion of charged poly-electrolytes, the lipid membrane is built on the polymer film by unilamellar vesicle fusion. Neutron reflectivity was used to monitor the kinetics of adsorption of the lipid bilayer onto the polymer surface; the conditions for the best surface coverage have been determined. The structure of the lipid bilayers is modified by the interaction with Aβ1-42; Neutron reflectivity showed a change of the scattering density profile in the direction perpendicular to the membrane plane, suggesting penetration of Aβ in the double layer. Atomic force microscope (AFM) has been used to test the lipid packing of the membrane through film rupture experiments and to compare the bilayer morphology in the presence or in the absence of Aβ. We demonstrated that the presence of Aβ weakens the lipid packing in the model membranes.

We compared the results obtained on polymer cushioned lipid bilayers with those obtained using a rigid substrate (freshly cleaved mica) for membrane preparation.

2507-Pos

The Effect of Mutant Aβ Peptide Aggregation on the Stability of Model Lipid Bilayers

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A hallmark of Alzheimer's disease (AD) is the rearrangement of the β-amyloid (Aβ) peptide to a non-native conformation that promotes the formation of toxic, nanoscale aggregates. One of many potential pathways for Aβ toxicity may be modulation of lipid membrane function on cellular surfaces. There are five mutations clustered around the central hydrophobic core of Aβ near the α-secretase cleavage site (the A21G Flemish mutation, E22K Italian mutation, E22G Arctic mutation, E22Q Dutch mutation and the D23N Iowa mutation). These point mutations are associated with hereditary diseases ranging from almost pure cerebral amyloid angiopathy (CAA) to typical Alzheimer's disease pathology with plaques and tangles. We hypothesizethat these point mutations alter the Aβ aggregation pathway and its interaction with cellular lipid membranes, resulting in altered disease progression and phenotypes. Brain lipid extract was used to form bilayers that are physiologically relevant models of neuronal cell surface. Intact lipid bilayers are exposed to different mutant forms of Aβ, and Atomic Force Microscopy was used to follow the aggregation of Aβ and membrane integrity over a 24 hour period. The goal of this study was to determine how point mutations in Aβ alter electrostatic interactions between the Aβ and the lipid surface. These interactions may affect aggregation, morphological characteristics, and bilayer disruption of Aβ on the model lipid membranes which may play a role in Aβ-related toxicity.

2508-Pos

A Molecular Dynamics Study of Amyloid-β (1-42) Peptide Dimer Formation on the Surface of Phospholipid Bilayers

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The Amyloid-β (Aβ) peptide is an integral aggregate species in the progression and neurotoxicity of Alzheimer's disease. While Aβ fibrils were historically considered the toxic species in Alzheimer's disease, recent evidence has shifted the focus towards oligomers as the most dangerous aggregate structure for neurons. In this aggregation process, the conversion of monomeric Aβ into a dimer constitutes the first step in oligomer formation. Further work has shown that cell membranes may play a substantial role in promoting aggregation through facilitating the protein-protein interactions that drive aggregation. We have used extensive replica exchange molecular dynamics simulations to demonstrate that monomeric Aβ does not adopt stable secondary structure over timescales that have allowed for significant structure formation in solution. Further, to characterize dimer formation on the surface of a model lipid bilayer, we have used a thermodynamic cycle to indirectly calculate free energies of dimerization on the bilayer surface. Use of a thermodynamic cycle helps to decrease bias due to initial conditions that would occur through directly calculating a dimerization free energy. We have calculated the free energies of dimerization for a preformed dimer containing a single antiparallel β-sheet or a pair of β-hairpin monomers. While these structures are representative of predicted fibril structures, comparison of dimerization free energies provides insight into the effect of the bilayer on the dimerization process. We have found that the bilayer does affect dimerization free energy depending on the dimer structure and bilayer surface charge. Our work demonstrates that a lipid bilayer is able to substantially hinder Aβ monomer structure formation and influence Aβ dimer formation.

2509-Pos

Protective Role of 17-β-Estradiol in LDL Amyloidogenesis

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In early atherogenesis, subendothelial retention of lipidic droplets is associated with an inflammatory response-to-injury, culminating in the formation of foam cells and plaque. Low density lipoprotein (LDL) is the main constituent of subendothelial lipidic droplets. LDL can be sketched as an inner lipidic core surrounded by a phospholipid monolayer, with the protein (apoB-100) wrapped around the particles' surface and partly seeping into the phospholipid monolayer and the inner cholesterol core.

We found that in a naturally occurring subpopulation of LDL (electronegative LDL-), the apoB-100 is misfolded and is capable of triggering the formation of aggregated, amyloid-like LDL structures. LDL- can be produced in human plasma by secretory phospholipases A2.

Both protein misfolding and LDL amyloids can well represent modifications able to transform this cholesterol carrier into a trigger for a response-to-injury in the artery wall.

Furthermore, by using Small Angle X-ray Scattering we furnish further evidences that the hormone 17-β-estradiol (E2) binds to a single highly specific site in apoB-100 and stabilizes its structure, even if the formation of LDL- is not altered by E2 binding. This results in an increased ellipticity of apoB-100, an overall volume shrinkage with modifications both in the outer shell and lipidic core, and an increased resistance to structural and conformational loss. Notably, also the formation of LDL amyloid aggregates is hindered by E2. Our findings converge to a picture where a possible explanation of the beneficial effect of E2 in the protection against the vascular response-to-injury can find its mechanism.

In addition, our results add arguments to the stringent lipid-protein structural interplay in LDL, with modifications in lipids being paralleled with apoB-100 structural and functional modifications, and vice versa.

2510-Pos

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Increasing evidence implicates interactions between Abeta peptide and lipid in the development of Alzheimer's disease. More generally, Abeta peptide interactions with membranes seem to depend on the composition of the lipid bilayer and the structural features of the peptide. One key parameter should be pH since one site of intracellular Abeta peptide production and/or accumulation is likely to be endosomes. This intracellular endosomal accumulation was suggested to contribute to disease progression.

In this workr, we report a study on the 11-22 amphiphilic domain of Abeta in interaction with model membrane; this region contains most of the charged residues of the N-terminal domain of Abeta. We show that the peptide charge, and more precisely the protonation state of histidines 13 and/or 14 is important for the interaction with lipids. Hence, it is only at endosomal pH that a conformational change of the peptide is observed in the presence of negatively charged lipid vesicles, i.e. when both lipid headgroups and histidines can interact through electrostatic interactions. Specific interactions of the fragment with phosphatidylserine and to a lesser extent with phosphatidylcholine, but not