View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

aggregates slowly, than for Abeta42, which aggregates quickly. Furthermore, the rate of reconfiguration for Abeta42 speeds up at higher pH, which slows aggregation, and in the presence of the aggregation inhibitor curcumin. These results are commensurate with a model of the first step of aggregation, described here, that is a kinetic competition between reconfiguration and bimolecular diffusion.

331-Pos Board B111

The Ability of Polyphenols to Reduce Aβ-Induced Apoptosis Associated with Alzheimer's Disease

Kayla M. Pate, McCall Rogers, Melissa Moss.
Chemical Engineering, University of South Carolina, Columbia, SC, USA.

Alzheimer's disease (AD), the most common form of dementia, is characterized by extracellular plaques in the brain created when monomeric amyloid-β (Aβ) protein aggregates into fibrillar structures. Soluble Aβ aggregates, including oligomers that form along the reaction pathway, are believed to be the more toxic species and can increase the production of reactive oxygen species (ROS). Polyphenols have been suggested as a complimentary AD therapeutic based on epidemiological evidence that polyphenol-rich diets correlate with a reduced incidence of AD. In particular, many flavonoids, a subclass of polyphenols, have the ability to inhibit Aβ aggregation. Alternatively, polyphenols can counter Aβ-induced cellular responses by neutralizing ROS through their antioxidant properties. This study sought to identify polyphenols that can reduce Aβ-induced apoptosis by inhibiting Aβ aggregation and/or reducing ROS.
Polyphenols investigated include quercetin (QUE), rhamnetin (RHA), isorhamnetin (IRHA), and tamarixetin (TAM). Using SDS-PAGE and Western blot to evaluate oligomer size, only IRHA was unable to reduce Aβ oligomers 250 – 100 kDa in size, while QUE reduced these oligomers by 88.3 ± 2.4%. All compounds reduced Aβ oligomers <100 kDa in size, although IRHA was still the weakest inhibitor. Antioxidant capabilities were quantified *in vitro* relative to Trolox, a vitamin E analog. All compounds tested exhibited antioxidant capability similar to Trolox. To assess the effect of anti-aggregation and antioxidant properties on Aβ-induced apoptosis, human neuroblastoma cells were stained using TUNEL, which identifies breaks in the DNA strand. Polyphenols with anti-aggregation properties successfully reduced apoptosis, and it is hypothesized that antioxidant activity will also have a protective effect.

332-Pos Board B112

Self-Propagative Replication of Amyloid-β Oligomers in Alzheimer Disease

Dexter N. Dean[1], Amit Kumar[1], Kayla M. Pate[2], Melissa A. Moss[2], Vijayaraghavan Rangachari[1].
[1]Department of Chemistry and Biochemistry, The University of Southern Mississippi, Hattiesburg, MS, USA, [2]Department of Chemical Engineering, The University of South Carolina, Columbia, SC, USA.

The aggregation and deposition of the polypeptide Amyloid-β (Aβ) in the brain is implicated in the pathology of Alzheimer disease (AD). It has been known that soluble oligomeric forms of Aβ are the primary neurotoxic agents in AD, rather than insoluble fibrils. This has resulted in a plethora of research investigating the cellular mechanism of Aβ oligomer toxicity. However, how these toxic oligomers proliferate throughout the AD brain remains elusive. Emerging evidence implicates that a prion-like mechanism of propagation may cause the widespread proliferation of toxic Aβ oligomers in AD. We have observed that a specific oligomeric form of Aβ, called large fatty acid-derived oligomers (LFAOs), undergo self-propagative replication in a template-assisted manner, resulting in the formation of quantitatively more LFAOs. The current research investigates the experimental parameters governing the efficiency of LFAO replication by self-propagation, and shows that LFAOs specifically activate NF-κB in human neuroblastoma cells. Furthermore, structural characteristics of propagated LFAOs have been evaluated to assess the fidelity of the LFAO self-propagative replication process. This study is the first detailed investigation into the mechanisms governing self-propagating Aβ oligomers *in vitro*, revealing novel insight into the potential proliferation mechanism of toxic Aβ aggregates in AD.

333-Pos Board B113

Alzheimer's Protective A2T Mutation Changes the Conformational Landscape of the Aβ1-42 Monomer Differently than does the A2V Mutation

Payel Das.
IBM T J Watson research center, Yorktown heights, NY, USA.

The aggregation of amyloid-beta (Aβ) peptides plays a crucial role in the etiology of Alzheimer's disease (AD). Recently, it has been reported that an A2T mutation in Aβ can protect from AD. Interestingly, a non-polar A2V mutation has been also found to offer protection against AD in the heterozygous state, while causing early-onset AD in homozygous carriers. Since the conformational landscape of the Aβ monomer is known to directly contribute to the early-stage aggregation mechanism, it is important to characterize the effect of the A2T and A2V mutations on the Aβ1-42 monomer structure. Here, we have performed extensive atomistic replica exchange molecular dynamics simulations of the solvated wild-type (WT), A2V, and A2T Aβ1-42 monomers. Our simulations reveal that, although all three variants remain as a collapsed coil in solution, there exist significant structural differences among them at shorter timescale. An enhanced double hairpin population in A2V is noticed compared to WT, similar to those reported in the toxic WT Aβ1-42 oligomers. Hydrophobic clustering between the N-terminus and the central and C-terminal hydrophobic patches promotes such double hairpin formation in A2V. In contrast, the A2T mutation engages the N-terminus in unusual electrostatic interactions with distant residues, such as K16 and E22, resulting in ''unique'' population comprising only the C-terminal hairpin. These findings imply that a single A2X (X=V/T) mutation in the primarily disordered N-terminus of Aβ1-42 monomer can dramatically alter the β-hairpin population and switch the equilibrium toward alternative structures. The atomistically detailed, comparative view of the structural landscapes of A2V and A2T variant monomers obtained in this study can help understanding the mechanistic differences in their early-stage aggregation.

334-Pos Board B114

The Effect of Peptoids on Aβ Aggregation and NF-κB Activation in Alzheimer's Disease

Kelly Moore[1], **Lauren M. Wolf**[1], J. Phillip Turner[2], Melissa A. Moss[3,1], Shannon Servoss[2].
[1]Biomedical Engineering Program, University of South Carolina, Columbia, SC, USA, [2]Department of Chemical Engineering, University of Arkansas, Fayetteville, AR, USA, [3]Department of Chemical Engineering, University of South Carolina, Columbia, SC, USA.

Alzheimer's disease (AD) is a costly and devastating illness, which is characterized by progressive neurological degeneration, manifesting in memory and cognitive impairment until eventual death. Although the exact mechanism for AD is unknown, it is hypothesized that disease etiology lies within the aggregation of the protein amyloid-β (Aβ), whose aggregates are toxic to neuronal cells. Thus, inhibition of Aβ aggregation is one therapeutic strategy. Peptoids are peptide derivatives that resist proteolytic degradation through a structural modification in the backbone, while maintaining side chain chemistry. This study examines the therapeutic potential of three peptoids designed to mimic the hydrophobic core of Aβ and incorporate a neutral, positive, or negative spacer between aromatic side chains. These peptoids are assessed for their ability to abate Aβ aggregation and reduce the aggregate-induced NF-κB activation in neuronal cells.
To examine the effect of peptoids on small, oligomeric aggregate formation, Aβ monomer was solubilized in DMSO and diluted into PBS to initiate oligomer formation. Oligomer size was assessed via SDS-PAGE and Western blot; oligomer structure was evaluated using ANS. Finally, the effect of peptoids on Aβ physiological activity was assessed using activation of NF-κB in human neuroblastoma cells.
All three peptoids reduced the quantity and size of oligomers formed, with the peptoid containing the positively charged spacer possessing the greatest inhibitory capabilities. In contrast, only peptoids containing a neutral or negatively charged spacer also altered oligomer structure. NF-κB activation was significantly reduced for oligomers formed in the presence of all three peptoids. In addition, when peptoid was added post-oligomerization, peptoids with a neutral and negatively charged spacer both elicited a significant reduction in NF-κB activation. In sum, peptoids are capable of inhibiting Aβ oligomerization and associated physiological activity, demonstrating potential as AD therapeutics.

335-Pos Board B115

Effects of Carbon Nanoparticles on the Aggregation of Alzheimers Beta-Amyloid Peptide

Yunxiang Sun, Luogang Xie, Dongdong Lin, Xinju Yang, **Guanghong Wei**.
Physics Department, Fudan University, Shanghai, China.

Amyloid deposits are implicated in the pathogenesis of many neurodegenerative diseases such asAlzheimer's disease (AD). The inhibition of β-sheet formation has been considered as the primary therapeutic strategy for the AD. In this presentation, I will present our recent results of the influences of different carbon nanoparticles (CNPs) (including graphene oxides, pristine single-walled carbon nanotubes–SWCNTs, hydroxylated SWCNTs, fullerenes including C_{60} and C_{180}) on the aggregation of Aβ(16-22) and full-length Aβ peptides. Our replica exchange molecular dynamics (REMD) simulations show that CNPs shift the conformations of Aβ oligomers from ordered β-sheet-rich structures toward disordered coil aggregates. Atomic force microscopy (AFM) experiments further confirm the inhibitory effect of CNPs on Aβ