tissue homogenates with exogenous Aβ1-42 under multiple conditions. Samples were analyzed using acid urea gels followed by Western blotting. **Results:** The PDAPP mice study revealed Aβ42 to Aβ40 conversion over time reaching equilibrium by 72hr. Acid urea gel analyses demonstrated that over half of the Aβ1-42 peptide administered was converted to Aβ1-40. Furthermore, ELISA results from rat studies showed similar conversion rates from Aβ42 to Aβ40 regardless of the route of administration, centrally or peripherally. Ex-vivo studies using rat tissue homogenates incubated with exogenous Aβ1-42 peptide also exhibited Aβ conversion. This conversion was present in all tissues tested, cortex, kidney, liver, pancreas, and spleen, and was exacerbated when the pH was lowered to pH5 from pH7. The rate of conversion to Aβ40 was diminished when a c-terminal antibody or protease inhibitor was incorporated into the in-vivo/ex-vivo studies. **Conclusions:** We have identified in-vivo processing of the carboxyl-terminus of Aβ in rodents. The extent of in-vivo processing is exacerbated when an Aβ antibody extends the half-life of the peptide. The conversion of Aβ1-42 to Aβ1-40 occurs both centrally and peripherally. Although the potential for this conversion in human is unknown, these results suggest additional biology after secretase liberation of the Aβ from the APP may be important for the overall Aβ ratios being measured in CNS and periphery.

THURSDAY, JULY 28, 2016
ORAL SESSIONS
O5-04
MOLECULAR AND CELL BIOLOGY: BEYOND AMYLOID — THE CONSEQUENCES OF EXPOSURE TO ABETA AND OTHER APP METABOLITES

O5-04-01 MOLECULAR MECHANISMS OF ABETA-INDUCED TAU-PATHOLOGY: ANALYSIS OF CROSS-SEEDING OF ABETA AND TAU AND ITS ROLE IN PRION-LIKE PROPAGATION OF TAU-PATHOLOGY IN VITRO AND IN VIVO

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Background: Combined genetic, pathological and clinical data provided the basis for the amyloid cascade hypothesis, which is further supported by biomarker data and remains the major hypothesis for development of therapeutic strategies. In vitro and preclinical in vivo models have robustly recapitulated amyloid induced Tau-pathology providing support to the amyloid cascade hypothesis and providing tools to understand this event, generally considered to be crucial in the pathogenesis of AD. **Methods:** We previously reported a preclinical model with robust amyloid induced Tau-pathology, providing an experimental window for analysis of mechanisms of ABeta-induced Tau-pathology in vivo. In this model, we demonstrated the induction of Tau-pathology along functional connections, in regions relatively spared of amyloid pathology. The striking similarity between abeta-induced Tau-pathology in preclinical models and in our recently reported Tau-seeding model, provided the basis for our current analysis of Abeta-induced Tau-fibrillization by cross-seeding and its subsequent propagating potential, in vitro and in vivo. Cell –free assays were used to analyze Tau fibrillization by different forms of ABeta using ThioT, sedimentation analysis and electron microscopy. Furthermore, a previously characterized cellular assay of Tau-aggregation and in vivo seeding models, have been used to analyze cross-seeding of Tau fibrillization by ABeta and its subsequent propagation potential. **Results:** We demonstrate that different forms of pre-aggregated Abeta induce Tau-fibrillization in a cell-free assay, with varying efficiencies. In addition, we demonstrate that different forms of pre-aggregated ABeta induce Tau-aggregation in a cellular assay of Tau-seeding and Tau-aggregation with different efficiencies. The developed assays of cross-seeding are further used to analyze the molecular and cellular mechanisms of seeded Abeta-induced Tau-aggregation. Finally, we demonstrate that Abeta-seeded Tau provides potent seeds for induction and prion-like propagation of Tau-pathology in Tau transgenic mice in vivo. **Conclusions:** Different forms of pre-aggregated Abeta are demonstrated to cross-seed Tau fibrillization. Cross-seeding between ABeta and Tau provides a compelling mechanism for conversion of Tau-pathology from a silent to an aggressive propagating Tau strain associated with neuronal dysfunction. Cross-seeding of Tau-aggregation thereby presents as an attractive mechanism for Abeta-induced Tau-pathology observed in preclinical models and for the initiation of propagation of Tau-pathology observed in patients.

O5-04-02 ALTERED PROTEIN EXPRESSION IN AMYLOID PLAQUES IN RAPIDLY PROGRESSIVE ALZHEIMER'S DISEASE

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Background: Rapidly progressive Alzheimer's disease (rpAD) is a particularly aggressive form of Alzheimer's disease (AD). Survival is limited to 2-3 years after diagnosis. It is not yet known why AD develops so rapidly in these patients and previous research into this type of AD is limited. Studying cases of rpAD provides a unique opportunity to look for mechanistic factors associated with the development of AD pathology as these factors may be enhanced or distinct in the accelerated disease process. **Methods:** In this study we used our recently developed method to perform quantitative proteomics on amyloid plaques microdissected from formalin-fixed paraffin embedded hippocampal sections from patients with rpAD (n=22) and typical, sporadic AD (n=19). Plaque proteins were extracted after formic acid treatment and individual protein levels were quantified using label free LC-MS. **Results:** On average, 825 proteins were quantified in amyloid plaques, providing the most comprehensive dataset to date of proteins present in amyloid plaques. Our approach was validated by the abundant detection of known plaque associated proteins such as beta amyloid, apolipoprotein E, ubiquitin and tau. Importantly, we also discovered many novel plaque associated proteins. Quantitative LC-MS revealed that rpAD plaques had a significantly different protein composition than sporadic AD plaques. One striking observation that was generated using protein network analysis was that rpAD plaques contained significantly more neuronal proteins ($p<0.00001$), while sporadic AD plaques contained significantly more astrocytic proteins ($p<0.0001$). Examples of specific proteins with