MC1 content in the PHF from AD and Tg4510, the quantitative EM analysis shows that there is significant difference in the percentage helical structure between purified PHF from AD brain and Tg4510 mouse brain.

P3-072 IDENTIFICATION AND VALIDATION OF TAU-MODIFIERS, IDENTIFIED BY UNBIASED GENOME WIDE APPROACHES, USING AAV-BASED APPROACHES IN TAU TRANSGENIC MICE

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Background: Identification of Tau mutations linked to neurodegenerative Tauopathies have indicated that Tau-dysfunction is causally linked to neurodegenerative processes. Accumulating evidence furthermore corroborates a crucial executive role for Tau in the pathogenesis of AD, designating Tau as an important therapeutic target. Identification of modifiers of Tau that can modulate Tau-pathology and Tau-related phenotypic features and neurodegenerative processes observed in preclinical models has become an important research objective. **Methods:** A Tau-interactome mapping has been performed to identify proteins binding to Tau in an unbiased way. To further identify Tau-modifying potential of the identified interacting proteins, an AAV-based approach was used. AAV injections, driving neuronal expression of the protein of interest, were performed at P0 in previously characterized Tau transgenic mice, and in primary neuronal cultures. Biochemical and IHC analysis was performed to analyze the modifying potential of the protein of interest on Tau and Tau-pathology in vitro and in vivo. **Results:** Using this approach we demonstrate Tau-modifying potential for several novel proteins involved in protein degradation, more particularly in the ubiquitin proteasome degradation. **Conclusions:** Our findings are interesting in context of the findings in GWAS studies, pointing to the involvement of the Ubiquitin proteasome degradation pathways in AD and Tauopathies. Our findings may furthermore be interesting for the identification of therapeutic targets aiming at Tau.

P3-073 INTERVENTION OF TAU PATHOLOGY PREVENTS BEHAVIORAL CHANGES IN RTG4510 MOUSE MODEL OF TAUOPATHY

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Background: Although tau pathology, behavioral deficits, and neuronal loss are each observed in patients with tauopathies, the relationship between these endpoints has not been clearly established. **Methods:** Here we found that rTg4510 mice, overexpressing human mutant tau in the forebrain, develop progressive age-dependent increases in locomotor activity, which correlates with neurofibrillary tangle (NFT) pathology, hyperphosphorylated tau levels, and brain atrophy. To investigate whether attenuating the tau pathology in this animal model can prevent the progression of the behavioral deficits, we treated the rTg4510 mice with either doxycycline to reduce mutant tau expression or an O-GlcNAcase inhibitor Thiamet G, which has been shown to ameliorate tau pathology in animal models. **Results:** We found that both doxycycline and Thiamet G treatments starting at 2 months of age prevented the progression of hyperactivity, slowed down brain atrophy, and reduced brain hyperphosphorylated tau. Collectively, our results demonstrate a unique behavioral phenotype in the rTg4510 mouse model of tauopathy that strongly correlates with disease progression, and that early interventions which reduce tau pathology ameliorate the progression of the locomotor dysfunction. **Conclusions:** These findings suggest that investigation of the relationship between locomotor deficits and tau pathology in the rTg4510 model may improve our understanding of the mechanisms underlining behavioral disturbances in patients with tauopathies.

P3-074 THE RAFT-DERIVED TAU-ASSOCIATED VESICLES ARE INCORPORATED INTO PRETANGLES

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Background: Neurofibrillary tangles (NFTs) are aggregates of hyperphosphorylated tau protein, and one of the major pathological feature of neurodegenerative disorders such as Alzheimer's disease (AD). Recently, several other molecules, including flotillin-1, phosphatidylinositol-4,5-bisphosphate [PtdIns(4,5)P2], casein kinase 1(CK-1), and cyclin-dependent kinase 5 (CDK5), have also been revealed as components of NFTs. Flotillin-1 and PtdIns(4,5)P2 are considered markers of lipid raft microdomains, whereas CK-1 and CDK5 is a tau kinase. Therefore, we hypothesized that NFTs have a relationship with lipid raft domains and the tau phosphorylation that occurs in NFTs. **Methods:** With human brain tissue obtained at autopsy, we investigated six cases of AD, six cases of other non-AD neurodegenerative diseases with NFTs and three control cases. We examined the PtdIns(4,5)P2-immunopositive structures in detail using super-resolution microscopy and electron microscopy to reveal its pattern of expression. We also analysed the spatial relationship between the PtdIns(4,5)P2-immunopositive material and tau kinases through double immunofluorescence analysis. **Results:** PtdIns(4,5)P2-immunopositive small vesicles (mean diameter: approximately 1 μm) which topologically resembles granulovacuolar degeneration (GVD) bodies are present within pretangles and early stage of NFTs. Various combinations of these vesicles and GVD bodies, the latter of which are pathological hallmarks observed in the neurons of AD patients (mean diameter: 3- to 5- μm), were concomitantly found in hippocampal pyramidal neurons. These vesicles and GVD bodies were both immunopositive not only for PtdIns(4,5)P2 but also for several tau kinases such as glycogen synthase kinase-3β and spleen tyrosine kinase. Results from double immunofluorescence staining for PtdIns(4,5) P2 and anti-phosphorylated tau antibody (AT8) and electron microscopic images showed that scattered PtdIns(4,5)P2-immunopositive small vesicles are located adjacent to paired helical filaments (PHFs) formed by hyperphosphorylated tau protein in NFTs. **Conclusions:** These observations suggest that clusters of raft-derived vesicles that resemble GVD bodies are substructures of pretangles