Background: Aberrant intracellular inclusions composed of hyperphosphorylated filamentous tau are a neuropathological hallmark of Alzheimer's disease, progressive supranuclear palsy and other sporadic neurodegenerative disorders, which have been collectively termed tauopathies. The discovery that pathogenic mutations in the tau gene (MAPT) can cause a familial neurodegenerative tauopathy has provided compelling evidence that tau dysfunction is sufficient to cause neurodegeneration. Therefore inhibiting potentially toxic events such as tau inclusion formation are attractive targets for therapeutic intervention and disease prevention. A string of recent in vitro and in vivo studies have shown that tau aggregates have 'prion-like' properties which not only allow them to transmit/seed further tau aggregation, but also spread to neighbouring cells or connected brain regions. This process is referred to as 'tau propagation' and might explain the stereotypic progression of tau pathology in Alzheimer's disease and other tauopathies. **Methods:** In this study, we report a novel in vivo model of tau propagation using young asymptomatic P301S transgenic mice that underwent unilateral hippocampal infusions containing brain extracts from older clinically impaired P301S mice, known to have florid tau aggregates. Detailed neuropathological examination was conducted in these mice (and controls) at various time-points post-infusion to investigate the presence and distribution of tau pathology. **Results:** Infusion-related tau pathology was induced rapidly (within 2 weeks) in the hippocampus of this model. Tau-positive neurofibrillary tangles increased in a stereotypic and progressive fashion, with robust Gallyas-positive tangles being observed 1 month post-infusion. Contralateral and anterior/posterior spread of tau pathology was also evident and appeared to be dependent on synaptic connectivity rather than spatial proximity. Tau biochemistry confirmed the induction and spread of tau pathology in this model. **Conclusions:** Previously reported models of tau propagation take several months to develop significant tau pathology attributable to propagation, therefore the rapid and robust propagation phenotype in our model will be instrumental to both basic research and the drug discovery process, with the ultimate aim to find intervention and prevention strategies for human tauopathies.

O1-07-05 *IN VIVO* TAU SPREADING RELIES ON THE TRANSSYNAPTIC TRANSFER OF SOLUBLE WILD-TYPE TAU SPECIES

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Background: Tauopathies represent a heterogeneous group of neurodegenerative diseases characterized by the intracellular accumulation of Tau, which results in neurofibrillary degeneration (NFD). In sporadic forms of tauopathies, such as Alzheimer's disease, argyrophilic grain disease and progressive supranuclear palsy, wild-type (WT) Tau progressively aggregates and affects brain regions following a spatio-temporal pathway. In mice, it is difficult to reflect this Tau spreading, since Tau variants bearing a FTDP-17 mutation are often used. Here, we present a new rat model using lentiviral vector (LV)-mediated WT Tau expression in pyramidal neurons of the CA1 field of the hippocampus allowing for NFD development. **Methods:** LV (WT Tau) Transduction of primary neurons in microfluidic chambers allowed the transport of Tau though axons and it transfer to secondary cells. Bilaterally intracerebral injections of LV (WT and P301L Tau) into the CA1 field of the ventral hippocampus of Wistar rats were performed using standard stereotaxic procedures. Rat brains were processed 2, 4, and 8 months post-injection for immunohistochemistry using ADx215 (human specific), AT8 (phospho-Tau), MC1 (conformational Tau) and AT100 (aggregated Tau) antibodies. **Results:** Through this combination of in vivo and in vitro experiments, it appears that WT Tau overexpressed by neurons located in the infected region is transported over long distance and actively transferred to secondary neurons in anatomically-connected brain areas (for instance from ventral CA1 field to olfactory bulb and frontal areas). This cell-to-cell transfer of WT Tau protein occurs in an anterograde direction, following well defined neuronal pathways. Furthermore, following Tau protein spreading to other brain regions, a Tau pathology is also observed. Finally, we did not observe a distant Tau spreading using the P301L mutant suggesting that the faster nucleation and aggregation of such mutant do not allow for its propagation in the present time window (2-8 months post-injection). **Conclusions:** To conclude, we observed a two-step mechanism that may explain the spatio-temporal progression of sporadic tauopathies 1) a direct toxicity of Tau in injected primary areas but also in secondary neurons, and 2) a conversion of the endogenous Tau protein into a pathological form in these secondary neurons.

O1-07-06 WILD-TYPE AND MUTANT TAU EXPRESSION AFFECTS APP PROCESSING

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Background: The effect of APP/PS1 and amyloid pathology on the development of tau pathology has been investigated in several models. Although the lack of tau expression has been shown to protect against some aspects of the deficient phenotype observed in APP transgenic models, the effect of wild-type or mutant tau expression on APP processing has been less investigated. **Methods:** To investigate this issue, we have analyzed and compared the development of amyloid pathology in APP/PS1 mice (5xFAD) expressing wild-type mouse tau (5xFAD/tau+/+), deleted for tau (5xFAD/tau-/-), or expressing a mutant tau (5xFADxTg30). The amyloid pathology was analyzed by immunocytochemistry, western blotting and ELISA. The tau pathology was analyzed in parallel in the 5xFADxTg30 and the Tg30 models. Motor deficits and spatial memory were analyzed with the rotarod test and the Y maze in all models. **Results:** The amyloid plaque burden, the levels of Aß40, Aß42, and the Aß42/Aß40 ratio were reduced in the cortex and the spinal cord of 5xFAD/tau-/- mice compared to 5xFAD/tau+/+ mice. Levels of phosphorylated APP, of ß-CTFs and levels of BACE1 were also reduced in 5xFAD/tau-/- mice. The 5xFAD x Tg30 mice showed a more severe deficient phenotype than Tg30 mice and developed with age a dramatically accelerated tau pathology in brain compared to Tg30 mice. However, the amyloid plaque load, Aß40 and Aß42, ß-CTFs and phosphorylated APP levels in the brain were lower in 5xFAD x Tg30 mice than in 5xFAD mice. **Conclusions:** Expression of a mutant tau protein or deletion of tau led similarly to a reduction of the amyloid load in these models, suggesting that this effect might be due to a loss of function of tau. Our results also demonstrate the existence of bidirectional crosstalks in development of tau and amyloid pathologies, with mutant APP/PS1 expression leading to increased tau pathology and expression of mutant tau leading to reduction of amyloid pathology.

ORAL SESSIONS: O1-08 BASIC SCIENCE: PROTEASES AND SECRETASES

O1-08-01 DUAL-PATHWAY CARBOXYPEPTIDASE ACTIVITY IS AN INTRINSIC PROPERTY OF GAMMA-SECRETASE

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Background: The presenilin-containing gamma -secretase complex produces not only 40- and 42-residue amyloid β- peptides (Aβ) but others