P1-031 AMYLOID CASCADE INDUCTION IN AN AAV-BASED MOUSE MODEL OF ALZHEIMER'S DISEASE

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Background: Evaluation of biomarkers and innovative therapies for Alzheimer's disease (AD) suffers from lack of models close to disease progression in human. Most of transgenic models express supraphysiological levels of APP metabolites to mimic AD lesions such as amyloid plaques and neurofibrillary tangles. Our goal was to develop a modelling strategy by gene transfer with two major objectives: (1) create a relevant mouse model closer to human physiopathology, (2) mimic the early stages of AD and thus allowing characterization of early events. We focused on the amyloid cascade and the APP processing to trigger in vivo the production of neurotoxic peptides such as βCTF and Aβ42. **Methods:** We used Adeno-Associated Viruses (AAVs) to express APP (with Swedish and London mutations) and PS1 (M146L mutation). We made a single stereotactic injection in the hippocampus of wild-type mice, followed by behavioral, biochemical and histological analysis. **Results:** Our strategy allows expression of human APP and PS1 and leads to βAPP production and its neurotoxic catabolites such as sAPPβ, βCTF, Aβ38, Aβ40 and Aβ42, as soon as one month post-injection. This production was stable during at least 12 months, without senile plaque formation. Interestingly, only co-injection of APP and PS1 increased the ratio Aβ42/Aβ40 and triggered hyperphosphorylation of the murine Tau protein which was correlated with increased levels of GSK3β. We also demonstrated a decrease of Beclin1 and NEP specifically observed in AD patient's brain. Finally, significant behavior impairments (Morris Water Maze and Openfield) appeared from 2.5 months after injection. **Conclusions:** This strategy induced amyloid pathology within the first month post-injection and overcame two major pitfalls of transgenic models, i.e. continuous expression of transgenes from in utero and limitations to the transfer to other species. Stable and more physiological amount of neurotoxic peptides derived from APP was produced and brought out an early link between the APP processing and Tau pathway.

P1-032 STEREOLOGICAL QUANTIFICATION OF PLAQUE PATHOLOGY IN THE HIPPOCAMPAL AND PARAHIPPOCAMPAL REGIONS OF THE MCGILL-R-THY1-APP TRANSGENIC RAT MODEL OF ALZHEIMER'S DISEASE

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Background: Alzheimer's disease is the most common cause of dementia and is a progressive neurodegenerative disorder characterized by senile plaques consisting of amyloid beta (A-beta), neurofibrillary tangles and neuronal death. Areas affected early in the disease include the hippocampal formation and parahippocampal region, structures that are strongly implicated in episodic memory and have been shown to be important for spatial memory and navigation in rodents. The McGill-R-Thy1-APP rat is one of the few transgenic rat models of Alzheimer's disease. This rat expresses human APP carrying the Swedish double and Indiana mutations under control of the murine Thy 1.2 promoter. Deficits in spatial memory have been reported by three months of age and these become more prominent in older animals. Intraneuronal A-beta accumulation reportedly occured as early as 1 week after birth (Leon et al, 2010). We aim to further characterize the McGill-R-Thy1-APP transgenic rat by quantifying the plaque load in the hippocampal and parahippocampal regions in different age groups. **Methods:** Transgenic and control rats (wild type Wistar) were transcardially perfused at different ages. The brains were removed, postfixed and cut coronally in 40 µm sections on a freezing microtome. One of six equally spaced series was incubated with the McSA1 antibody against human A-beta (MédiMabs) and visualized with peroxidase/DAB. Stereological estimates of the plaque load in areas of the hippocampus and parahippocampus were obtained with the area fraction fractionator using the StereoInvestigator software from MBF Bioscience. **Results:** In the control animals no intracellular or extracellular accumulation of A-beta was observed. At 6 months of age no plaques were seen in the homozygous transgenic rats but intracellular A-beta accumulation was evident. By 12 months early plaque pathology could be seen in the homozygous transgenic rats, particularly in the subiculum. At 18 months, the pathology spread to other areas of the hippocampus and parahippocampus, whith the heaviest plaque loads in the subiculum, CA1 and lateral entorhinal cortex. The hemizygous transgenic rats mainly displayed intracellular A-beta immunoreactivity. **Conclusions:** At 12 months of age the McGill-R-Thy1-APP rat starts to display plaque pathology in the subiculum, subsequently spreading to other areas of the hippocampus and parahippocampus.

P1-033 AMYLOID-INDUCED TAUOPATHY CONTRIBUTES TO SYNAPTIC AND COGNITIVE DEFICITS IN A TRANSGENIC MODEL FOR ALZHEIMER'S DISEASE

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Background: Brains of Alzheimer's disease patients are characterized by the presence of amyloid plaques and neurofibrillary tangles, as diagnostic hallmarks. Mouse models combining amyloidosis and Tauopathy and their parental counterparts are important tools to further investigate the interplay of abnormal Abeta and Tau species in pathogenesis, synaptic and neuronal dysfunction and cognitive decline. **Methods:** Crosses of APP/PS1 mice with 5 EOFAD mutations (5xFAD) and TauP301S (PS19) transgenic mice - denoted F+/T+ mice - were generated and phenotypically compared to their respective parental strains - denoted F+/T- and T+/F- respectively. **Results:** Tau pathology was invariably and very robustly aggravated in hippocampal and cortical brain regions in F+/T+ mice compared to the parental T+ mice. In contrast, amyloidosis was unaltered compared to the parental F+/T- mice. Most importantly, F+/T+ displayed aggravated cognitive deficits in a hippocampus-dependent spatial navigation task, compared to the parental F+/T- strain, while parental T+/F- mice did not display cognitive impairment. In F+/T+ mice basal synaptic transmission was impaired compared to non-transgenic mice and the parental strains. Finally, F+/T+ mice displayed a significant hippocampal atrophy compared to non-transgenic mice, in contrast to the parental strains. **Conclusions:** Our data indicate for the first time that pathological Abeta species induced changes in Tau contribute to cognitive deficits correlating with synaptic deficits and hippocampal atrophy in an AD model. These data lend further support to an executive role of Tau in the pathogenetic process of AD and to the amyloid cascade hypothesis with a role of pathological Abeta species as initiator and pathological Tau species as executor.

P1-034 AN INTRONIC TREM1 VARIANT INFLUENCES THE ACCUMULATION OF ALZHEIMER'S DISEASE-RELATED AMYLOID PATHOLOGY

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