3xTg-AD mice (-13% object recognition index). **Conclusions:** As deterioration of metabolic perturbations coincides with behavioral deficit in the 3xTg-AD mouse, we suggest that AD pathology aggravates metabolic consequences of diet-induced obesity leading to a pathological self-amplifying loop.

O1-02-04 TAU DELETION RESCUES NEURONAL DEATH IN APP/PS1 MICE

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Background: Recent results have shown that lack of tau expression protects against excitotoxicity and prevents the development of memory deficits in mice overexpressing mutant APP. In these mice, mutant PS1 enhances generation of Aß42, and inhibits cell survival pathways. It is however unknown if the deficient phenotype induced by concomitant expression of mutant PS1 is also rescued by absence of tau. **Methods:** To investigate this issue, we have analyzed the effect of tau deletion on the behavioural deficits and the development of pathology in mice expressing mutant forms of APP and PS1. APP/PS1/tau+/+ mice were compared to APP/PS1/tau-/-, tau-/- and tau+/+ mice. Motor deficits and spatial memory were analyzed with the rotarod test and the Y maze. Neuronal death was analyzed at 12 months using the optical fractionator method. The amyloid load was analyzed by immunocytochemistry, western blotting and ELISA. **Results:** Although APP/PS1/tau+/+ mice had a reduced survival, developed spatial memory deficits at 6 months and motor impairments at 12 months, these deficits were rescued in APP/PS1/tau-/- mice. Neuronal loss observed in the hippocampus and the spinal cord of APP/PS1/tau+/+ mice was not observed in the APP/PS1/tau-/- mice. The amyloid plaque burden was decreased in the cortex and the spinal cord of the APP/PS1/tau-/- mice compared to APP/PS1 mice. The levels of soluble and insoluble Aß38, Aß40, Aß42, and the Aß42/Aß40 ratio were reduced in APP/PS1/tau-/- mice. Levels of phosphorylated APP, of ß-CTFs and levels of BACE1 were also reduced, suggesting that ß-secretase cleavage of APP was reduced in APP/PS1/tau-/- mice. **Conclusions:** Our results indicate that tau deletion had a protective effect against amyloid induced toxicity also in presence of a mutant PS1 protein and led to a reduction of the production of Aß in an APP/PS1 transgenic model.

O1-02-05 LOSS OF GABAERGIC INTERNEURON IN A MOUSE MODEL FOR TAU PATHOLOGY RESULTING IN ALTERED SYNAPTIC PLASTICITY AND BEHAVIOR

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Background: Tau pathology is involved in multiple neurodegenerative disorders, for example in Alzheimer's disease, Parkinson's disease, and Frontotemporal dementia (FTD). Tau is a neuronal protein that binds microtubules and is thought to be involved in the stabilization of microtubules. Over 50 different mutations within the MAPT gene, the gene encoding for Tau, have been associated with inherited FTD. FTD is thought to involve deficits in the communication between neurons and in the mechanisms neuronal adaptation to experience, synaptic plasticity. The role of Tau in mechanisms of synaptic plasticity is not well-understood. To address this gap in the field, we have investigated synaptic plasticity and behavior in P301L mice, a mouse model for tau pathology that over-expresses human Tau protein carrying an inherited human mutation. **Methods:** Long-lasting forms of plasticity, late-phase long term potentiation (L-LTP) were examined in P301L (JNPL3) mice and age-matched controls by measuring field excitatory postsynaptic potentiation (fEPSP) in the CA1 hippocampal region after high frequency electrophysiological stimulation. Two behaviors associated with GABAergic function were assayed, prepulse inhibition of startle response (PPI) and susceptibility to epileptic seizures. GABAergic interneurons were stained using two markers; paravalbumin and somatostatin. **Results:** By examining long-lasting forms of plasticity in aged (>18 months old) in hippocampal brain slices we found surprisingly enhanced L-LTP in P301L mice compared to age-matched controls. The enhanced L-LTP in P301L slices was rescued by treatment with a GABA agonist, Zolpidem. These results suggest a loss of GABAergic neurons in P301L mice. Next we examined PPI and susceptibility to epileptic seizures in P301L and control mice. We found an altered PPI response and differences in epileptic seizures grades. Finally, we stained GABAergic interneurons in the hippocampus using two markers that identify GABAergic cell types showing a decrease in GABAergic neurons in the hippocampal CA1 region. **Conclusions:** Our results suggest that GABAergic interneurons are more vulnerable to molecular lesions caused by pathological Tau, which may result in the selective loss of hippocampal GABAergic interneurons.The molecular mechanisms involved in this specific GABAergic loss remains to be resolved, but may help to explain the pathophysiological symptoms of diseases like FTD, which involve altered Tau function.

O1-02-06 THE ALZHEIMER'S BETA-SECRETASE ENZYME BACE1 IS REQUIRED FOR ACCURATE AXON GUIDANCE OF OLFACTORY SENSORY NEURONS AND NORMAL GLOMERULUS FORMATION IN THE OLFACTORY BULB

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Background: The β-secretase, β-site amyloid precursor protein cleaving enzyme 1 (BACE1), is a prime therapeutic target for lowering cerebral β-amyloid (Aβ) levels in Alzheimer's disease (AD). Clinical development of BACE1 inhibitors is being intensely pursued. However, little is known about the physiological functions of BACE1, and the possibility exists that BACE1 inhibition may cause mechanism-based side effects. Indeed, BACE1-/- mice exhibit a complex neurological phenotype. Interestingly, BACE1 co-localizes with presynaptic neuronal markers, indicating a role in axons and/or terminals. Moreover, recent studies suggest axon guidance molecules are potential BACE1 substrates. Here, we used a genetic approach to investigate the function of BACE1 in axon guidance of olfactory sensory neurons (OSNs), a well-studied model of axon targeting in vivo. **Methods:** We bred BACE1-/- mice with gene-targeted mice in which GFP is expressed from the loci of two odorant-receptors (ORs), MOR23 and M72, and olfactory marker protein (OMP) to produce offspring that were heterozygous for MOR23-GFP, M72-GFP, or OMP-GFP and were either BACE1+/+ or BACE1-/-. **Results:** BACE1-/- mice had olfactory bulbs (OBs) that were smaller and weighed less than OBs of BACE1+/+ mice. In wild-type mice, BACE1 was present in OSN axon terminals in OB glomeruli. In whole-mount preparations and tissue sections, many OB glomeruli from OMP-GFP; BACE1-/- mice were malformed compared to wild-type glomeruli. MOR23-GFP; BACE1-/- mice had an irregular MOR23 glomerulus that was innervated by randomly oriented, poorly fasciculated OSN axons compared to BACE1+/+ mice. Most importantly, M72-GFP; BACE1-/- mice exhibited M72 OSN axons that were mis-targeted to ectopic glomeruli, indicating impaired axon guidance in BACE1-/- mice. **Conclusions:** Our results demonstrate that BACE1 is required for the accurate targeting of OSN axons and the proper formation of glomeruli in the OB, suggesting a role for BACE1 in axon guidance. OSNs continually undergo regeneration and hence require ongoing axon guidance. Neurogenesis and the regeneration of neurons and axons occur in other adult populations of peripheral and central neurons that also require axon guidance throughout life. Therefore,