Neurodegenerative disease related neuropathology in the retina and olfactory bulb of transgenic rodent models

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Background

Alzheimer´s disease (AD) is the most common form of neurodegenerative dementia. Major hallmarks of the disease are: (1) extracellular plaque deposits of the β-amyloid peptide (Aβ) and (2) intracellular neurofibrillary tangles of hyperphosphorylated Tau. Published research suggests an association between AD and functional impairments of sensory systems. The current study is designed to analyze the neuropathological changes occurring both in brain and retina of different AD animal models and address suitable biomarkers for early screening tests for AD.

Materials and Methods

Eyes and brains from the rodent AD models Tau mice (Tau 441/V337M; R406W-Thy1), APP mice (human APP_{SL}-Thy1), Tau rats (Tau 441/P301L-Thy1) and APP rats (APP_{SL}-Thy1), aged 6 and 12 months, were collected. Tissues were cryosectioned and histologically investigated by immunofluorescent microscopy (Zeiss AxioImager Z1 microscope) with focus on: 1) the visual system (visual cortex and retina) and 2) the olfactory system (olfactory bulb and piriform cortex). Different neuronal and neuropathological markers were evaluated utilizing the following antibodies: APP (6E10, BioLegend), Tau (PHF-6, Covance), GFAP (Abcam), IBA1 (Wako), ChAT (Millipore), GAD67 (1G102, Millipore) and TH (Novusbio).

Results

Microglia and astroglia were detected with antibodies against IBA1 and GFAP, respectively (**Figure 1**). Expression is detectable in all areas of interest and is currently subject to quantitative image analysis.

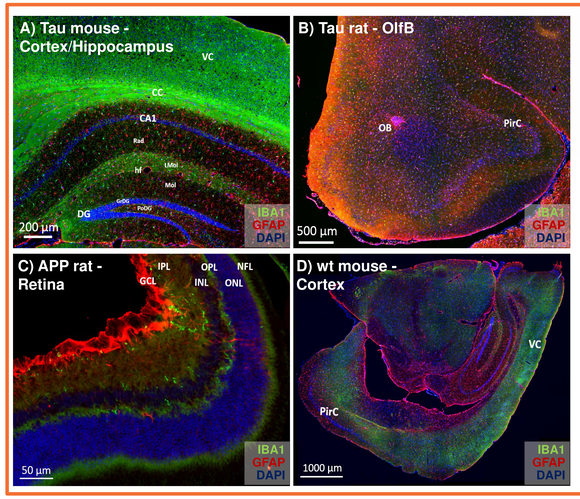


Figure 1: Gliosis in AD rodent models. Immunofluorescent labelling of IBA1 (green) and GFAP (red) in brain and retina. DAPI (blue) to stain cell nuclei. IBA1+ cells are distributed all over the brain (**A**, **B** and **D**), whereas in the retina IBA1 is mainly restricted to nerve fiber layer (NFL), ganglion cell layer (GCL), and inner and outer plexiform layer (IPL and OPL) (**C**). Regions significantly labelled by GFAP are the hippocampus, piriform area and olfactory bulb (OB) in the brain (**A**, **B** and **D**), whereas in the ocular tissue GFAP immunoreactivity is highest in the GCL (**C**).

pTau inclusions can be detected in the brain of Tau rat models (**Figure 2A**), as previously reported in Tau mice. In APP rodents, amyloid deposition is very low since no plaques are detected in the retina (data not shown) while in the brain plaques are common (**Figures 2E and 2F**).

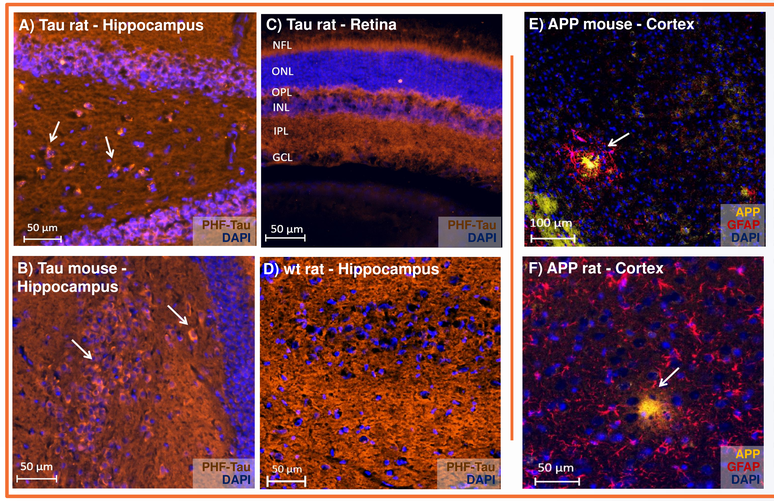
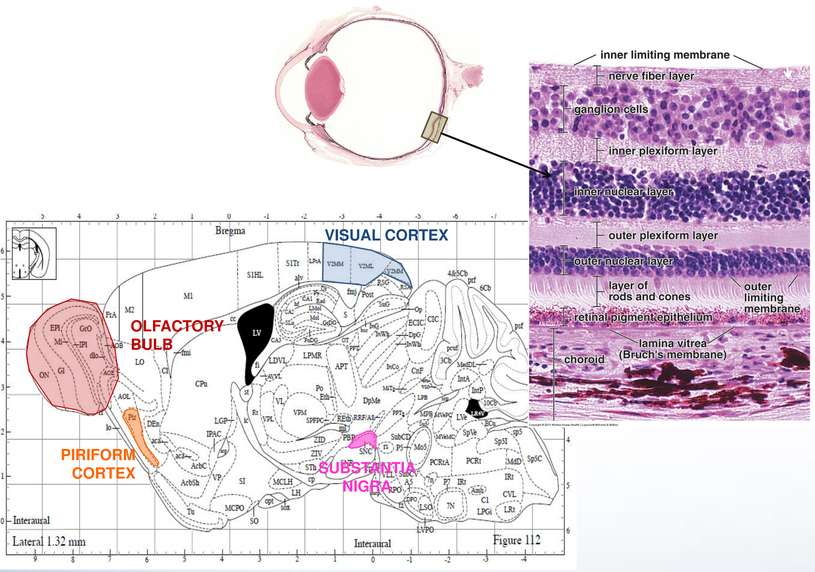


Figure 2: Tau and ß-amyloid deposition in AD models. Images **A**-**D** show PHF-Tau (brown). DAPI (blue) to stain cell nuclei. In the brain (**A**, **B** and **D**) Tau is distributed all over the hippocampus, whereas in the retina (**C**) p-Tau is detected in IPL, OPL and NFL. In Tau rats and mice aggregation of Tau leads to the formation of tangles in the hippocampus (white arrows in **A** and **B**), but not in the ocular tissue (**C**).

Double immunostaining of APP (yellow) and GFAP (red) shows ß-amyloid plaques (white arrows) in the cortex of APP models (**E** and **F**), but not in the retina (data not shown). Co-localization of GFAP and APP indicates that reactive astrocytes cluster around the plaques in AD rodents (**E** and **F**).



AD has a significant effect on the synthesis and secretion of different neurotransmitters. GABAergic, cholinergic and catecholaminergic neurons were labelled (**Figure 3**) and analysis of neurotransmitter systems is currently executed. Additionally, evaluation of other AD markers to study differences between physiological and pathological features of neurons and synapses has been started.

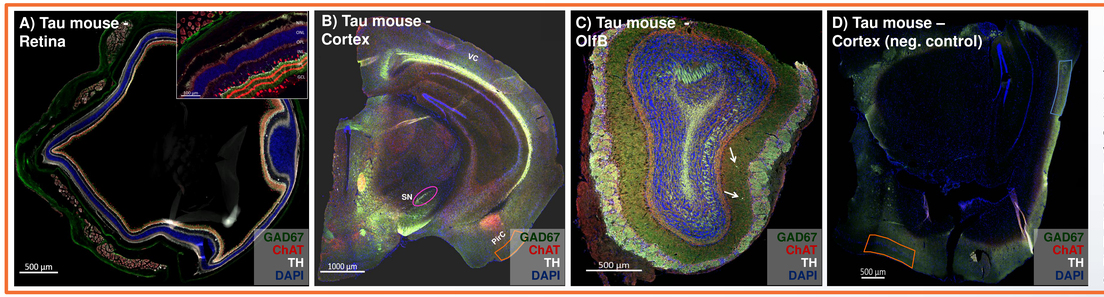


Figure 3: Detection of neurotransmitters in the brain and retina of Tau mice. Co-labeling of GAD67 (green), ChAT (red) and TH (white) in Tau mice: retina (**A**), visual cortex (**B**), piriform cortex (**B**), substantia nigra (**B**) and olfactory bulb (**C**). DAPI (blue) to stain cell nuclei. In cerebral tissue, ChAT evidences a high density of cholinergic cell fibers and axon varicosities, whereas in the retina it labels two cell populations, one in the IPL and one in the GCL whose dendrites form a double banded staining pattern in the IPL. GAD67 identifies GABAergic neuronal cell bodies in brain tissue (white arrows in **C**), and immunoreactivity in the retina is restricted to the IPL. Peak expression of TH is observed in substantia nigra, inner nuclear layer (INL) and inner plexiform layer (IPL) of the eye.

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Conclusion

AD models analyzed in this study, together with the specific antibodies tested, provide us with a powerful tool to analyze neuropathology in sensory systems. In fact, by means of triple immunofluorescent labeling performed in our target tissues, it is possible to 1) show whether gliosis occurs in AD-affected tissues, 2) detect Tau accumulation, 3) identify ß-amyloid plaques, and 4) evaluate if there is an alteration of neurotransmitter levels. Ongoing research will now focus on the quantitative analysis of all labeling. Lastly, further biochemical investigation of the tissues will be executed to receive a further characterization of neuropathology in the sensory system.