TAU Phosphorylation Profile of hTAU Transgenic Mice

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BACKGROUND

Alzheimer's disease is characterized by phosphorylation and aggregation of the microtubule associated protein tau. Reliable *in vivo* models that mimic tau phosphorylation are therefore needed. The hTau transgenic mouse features expression of human tau combined with a knockout of murine tau and belongs to the best animal models to test compounds directed against human tau.

MATERIALS and METHODS

To evaluate the phosphorylation profile of tau (ptau), 3 - 15 months old hTau mice were analyzed for total tau, pThr181, pSer202/205, pThr231 and pSer396/404 compared to non-transgenic (ntg) littermates. Different brain regions were analyzed by immunofluorescent labeling. Additionally brain lysate was analyzed for ptau by MesoScale Discovery immunosorbent assay (MSD-ISA).

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SUMMARY and CONCLUSION

hTau transgenic mice are a valuable model to study human phosphorylated tau and to test compounds that are directed against this target.

RESULTS

Our results show a progressive increase of soluble total tau, pThr231 and pThr181 while phosphorylation of the same residues does not increase in the insoluble brain fraction. Immunofluorescent labeling showed an increase in pSer202/205 tau levels in the cortex and hippocampus already at the age of 3 months with further signal increase at 12 months of age. Analyzing the same brain regions for pSer396/404 levels revealed a highly increased phosphorylation already at the age of 3 months that stabilized at this level. Our data suggest that total and ptau in hTau mice progressively increases while insoluble tau does barely change.

Total tau, ptau Thr231 and Thr181 by MSD-ISA

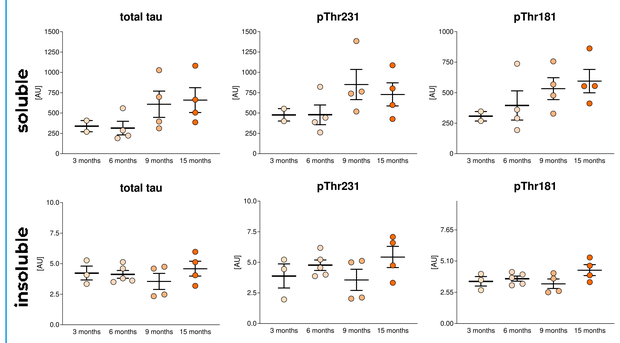

Figure 1: Soluble and insoluble total and phosphorylated tau levels in the brain of hTau mice. Soluble and insoluble tissue fractions of 3, 6, 9, and 15 months old animals were analyzed for total, pThr231 and pThr181 levels by MSD-ISA. One-Way ANOVA with Newman's Keul's multiple comparison test. Mean ± SEM; n = 2 - 4.

RESULTS

ptau Ser202/205

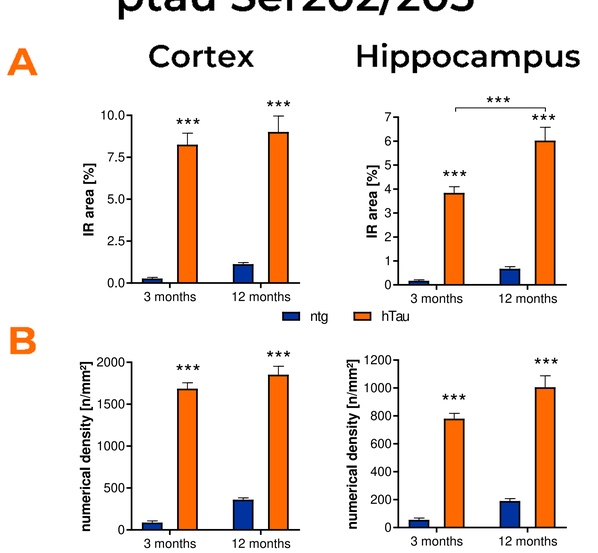

Figure 2: Quantitative analysis of ptau Ser202/205 tau levels in the cortex and hippocampus of 3 and 12 months old hTau mice compared to non-transgenic littermates by EPR2402 antibody. A: Immunoreactive area in percent; B: Object density in n/mm2. n = 8 per group. Mean + SEM; Two-way ANOVA with Bonferroni's *post hoc* test; **p<0.01; ***p<0.001.

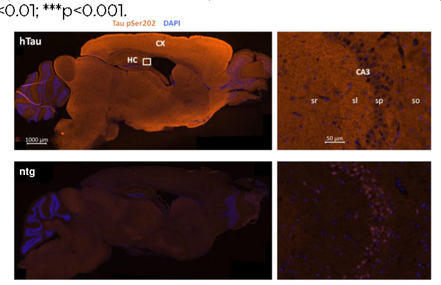

Figure 3: Immunofluorescent signal in the brain of a hTau transgenic mouse and ntg control. Representative example of immunofluorescent labeling of pSer202/205 tau on sagittal sections. Very high signal is evident in the frontal cortex of hTau mice. Note that immunofluorescence is absent from ntg tissue except of a bit of unspecific signal in nuclei. The location of the magnified area showing hippocampal CA3 is indicated by the rectangle in the whole slide scan. Nuclei are labeled with DAPI.

ptau Ser396/404

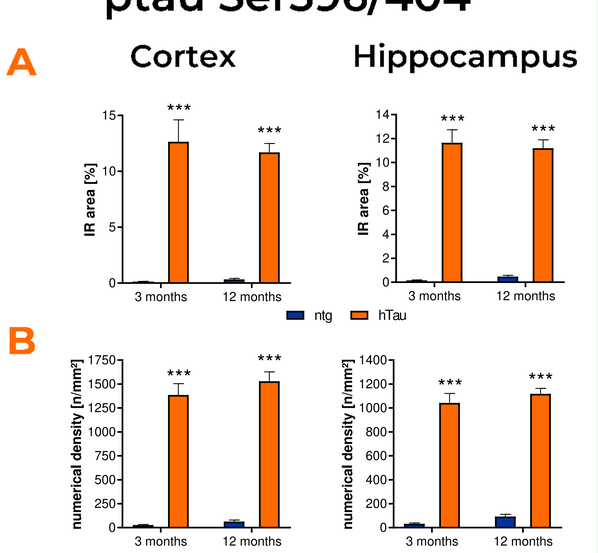

Figure 4: Quantitative analysis of ptau Ser396/404 level in the cortex and hippocampus of 3 and 12 months old hTau mice compared to non-transgenic (ntg) littermates by PHF13 antibody. A: Immunoreactive area in percent; B: Object Intensity in arbitrary units. n = 8 per group. Mean + SEM; Two-way ANOVA with Bonferroni's *post hoc* test; ***p<0.001.

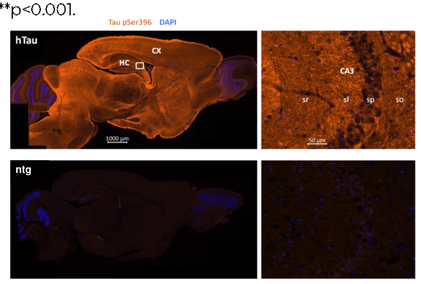

Figure 5: Immunofluorescent signal in the brain of a hTau transgenic mouse and ntg control. Representative example of immunofluorescent labeling of pSer396/404 tau on sagittal sections. Very high signal is evident in the frontal cortex of hTau mice. Note that immunofluorescence is absent from ntg tissue except of a bit of unspecific signal in nuclei. The location of the magnified area showing hippocampal CA3 is indicated by the rectangle in the whole slide scan. Nuclei are labeled with DAPI.