Injection of Patient-Derived Tau Seeds in the Hippocampus of hTau Mice Results in Tau Phosphorylation at Several Residues

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BACKGROUND

Tauopathies are a heterogeneous class of neurodegenerative diseases, including Alzheimer's disease (AD), which are characterized by intracellular inclusions of aggregated tau protein. Mirroring the disease by injecting human patient-derived tau protein into a mouse brain is currently an active field of research as it recapitulates cell type specificity and structural tau aggregation features of the donors' tauopathy. Here we evaluated the seeding efficacy and phosphorylation pattern of tau protein in the hTau mouse model.

MATERIAL & METHODS

hTau transgenic mice, developed by K. Duff and colleagues, express human tau on a murine tau knockout background. Male mice at the age of 9-10 weeks were injected with the sarcosyl-insoluble fraction of tau seeds isolated from human AD brains of Braak stage VI (AD-tau seeds) or vehicle into the right dorsal hippocampus and overlying cortex. Brain tissue was collected after 12 weeks, and coronal sections were prepared from the injection site. Sections were immunofluorescently labeled for tau phosphorylated at residues tyrosine 18, serine 202/threonine 205, threonine 231, and serine 396, as well as NeuN and GFAP which were subsequently evaluated qualitatively and quantitatively.

RESULTS

Phosphorylation was increased at all analyzed tau residues in the injected area compared to the contralateral hemisphere. Intriguingly, also spreading of tau protein to the contralateral site was detected. Although the granule cell layer of the dentate gyrus was structurally damaged by the injections, no neuronal loss due to AD-tau seeds was observed. Additionally, astrogliosis could be observed in the hippocampus after injection of AD-tau seeds.

pSer202/pThr205 and pThr231 Tau Phosphorylation

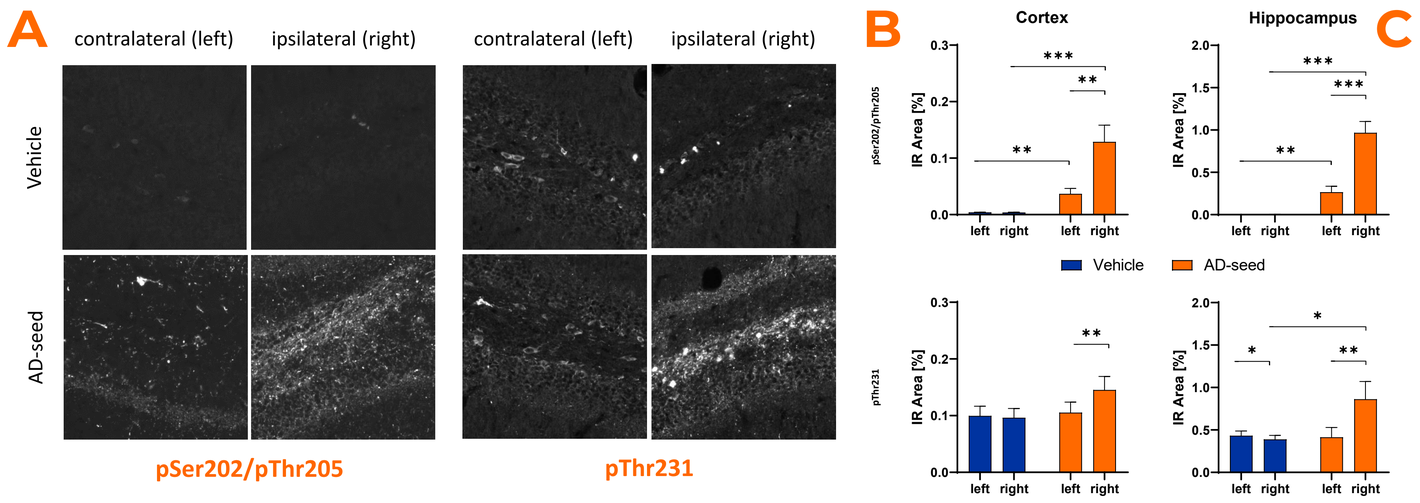

Figure 1: Tau phosphorylation at residues pSer202/Thr205 and pThr231 after unilateral tau seed injection into the hippocampus of hTau mice. A and C: Representative images of labeling. B: Quantification of labelings. Two-way ANOVA with Bonferroni's *post hoc* test; n = 8; Mean+SEM; *p<0.05; **p<0.01; ***p<0.001.

pSer396 and pTyr18 Tau Phosphorylation

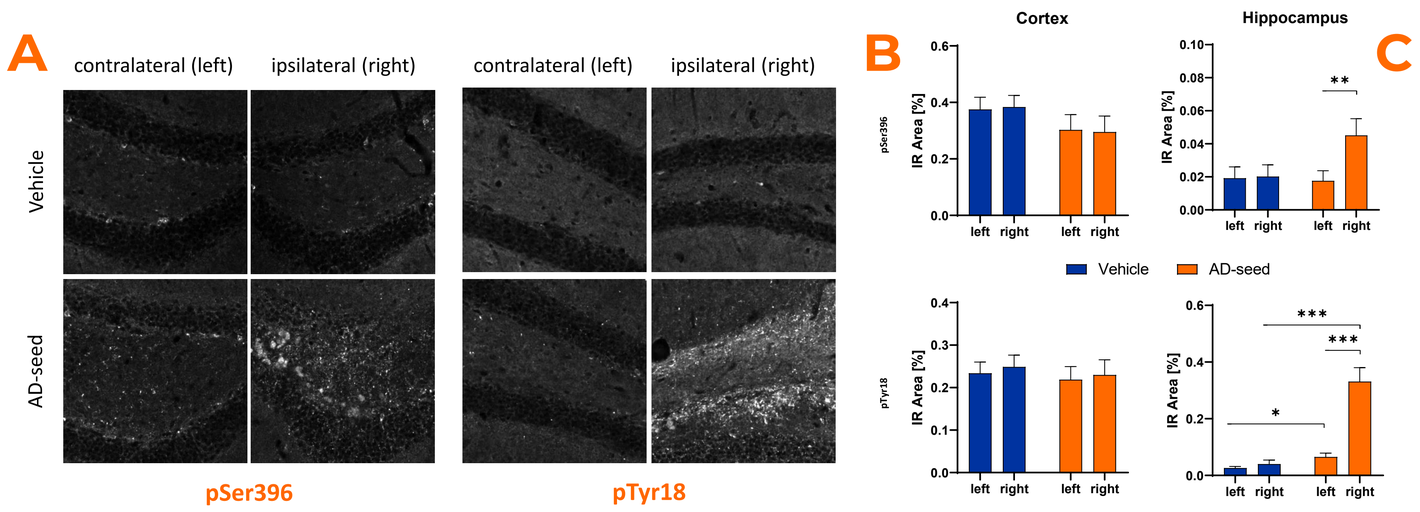

Figure 2: Tau phosphorylation at residues pSer396 and pTyr18 after unilateral tau seed injection into the hippocampus of hTau mice. A and C: Representative images of labeling. B: Quantification of labelings. Two-way ANOVA with Bonferroni's *post hoc* test; n = 8; Mean+SEM; *p<0.05; **p<0.01; ***p<0.001.

Astrogliosis and Neuronal Loss

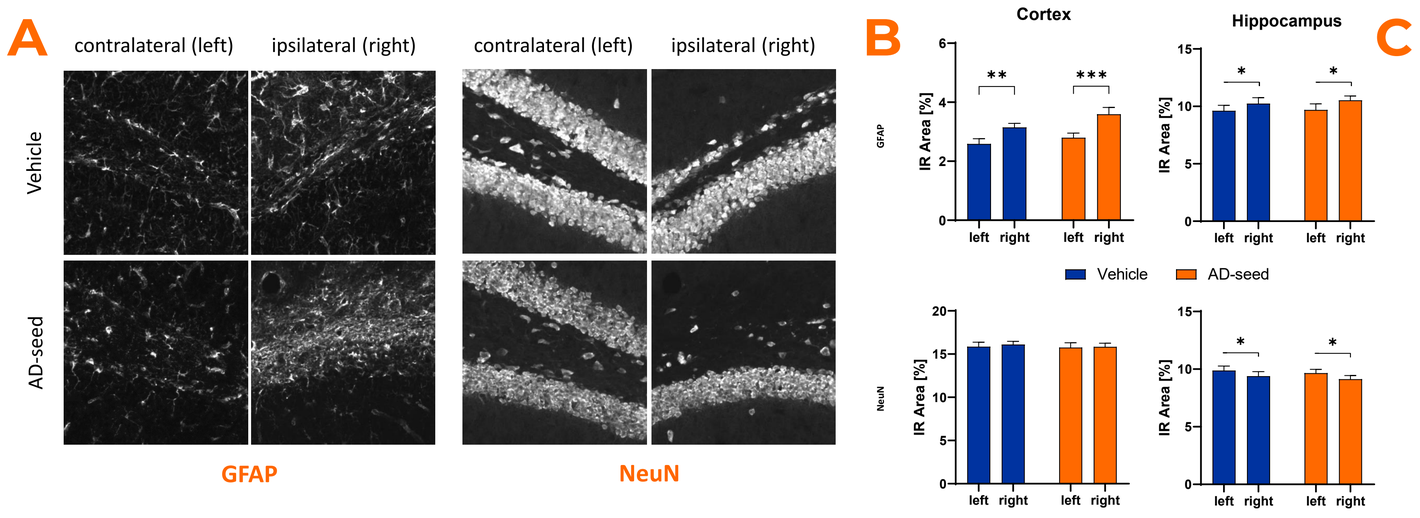

Figure 3: GFAP and NeuN labeling after unilateral tau seed injection into the hippocampus of hTau mice. A and C: Representative images of labeling. B: Quantification of labelings. Two-way ANOVA with Bonferroni's *post hoc* test; n = 8; Mean+SEM; *p<0.05; **p<0.01; ***p<0.001.

SUMMARY and CONCLUSION

The presented *in vivo* tau seeding mouse model is suitable to study tau pathology as well as the efficacy of new tau-related therapeutic interventions.

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For more information about the models please visit:
www.qpsneuro.com or send us an e-mail: office-austria@qps.com