Construction of a tau seed-injection model using hTau mice

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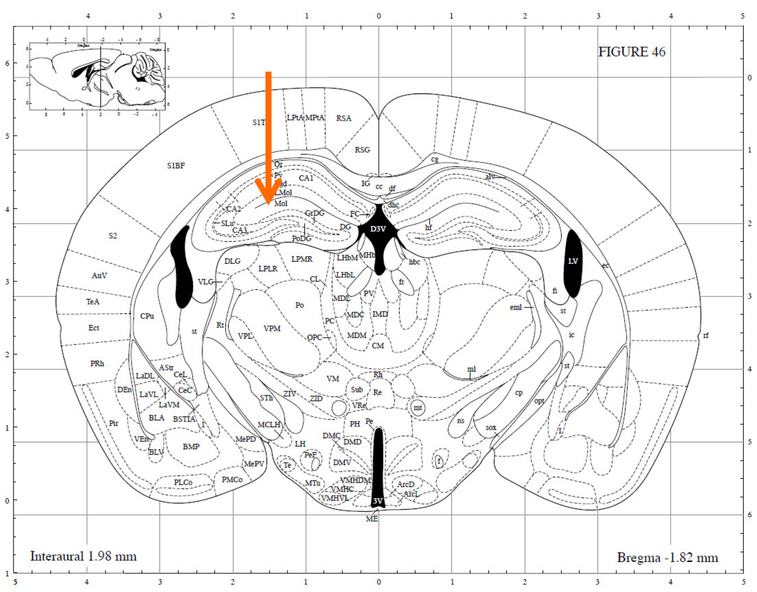
BACKGROUND

Under pathological conditions, the microtubule-associated protein tau can assemble into highly structured tangles to cause a variety of neurodegenerative diseases collectively termed tauopathies. Such diseases include Alzheimer's disease (AD), frontotemporal dementia (FTD) and corticobasal degeneration (CBD). The precise mechanism of tangle formation is not completely understood, but in recent years, evidence has accumulated that tau pathology can propagate through the brain via extracellular tau "seeds". Since most tau transgenic mouse models lack significant levels of insoluble tau or tangles, the development of tau-seeding models has gained increasing attention.

METHODS

To generate a tau-seeding model with highest translational value, we used the hTau transgenic mouse model. These mice are bred on a murine tau knockout background, hence lacking the endogenous protein. The hTau mice also overexpress all six human tau isoforms without mutations, therefore coming closest to human conditions. Six month old hTau animals received a single unilateral intra-hippocampal injection of one of three different tau seeds: (1) recombinant P301S tau, (2) sarkosyl-insoluble fraction from rTg4510 mouse tissue or (3) sarkosyl-insoluble fraction from human AD brains. Vehicle injected mice and non-injected mice served as controls. Three months after injection, the ipsi- and contralateral hippocampi and cortices were analyzed for changes in soluble and sarkosyl-insoluble tau species.



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RESULTS

Soluble tau levels were not influenced by any condition, whereas sarkosyl-insoluble tau increased in the human AD seed-injected hippocampi but not when recombinant P301S protein or rTg4510 material was used as exogenous seeds. The effect was significant in the ipsilateral cortex of both female and male mice from this group. Even in the contralateral hippocampus a tendency to increased insoluble tau levels was observed by Western blot and immunosorbent assay.

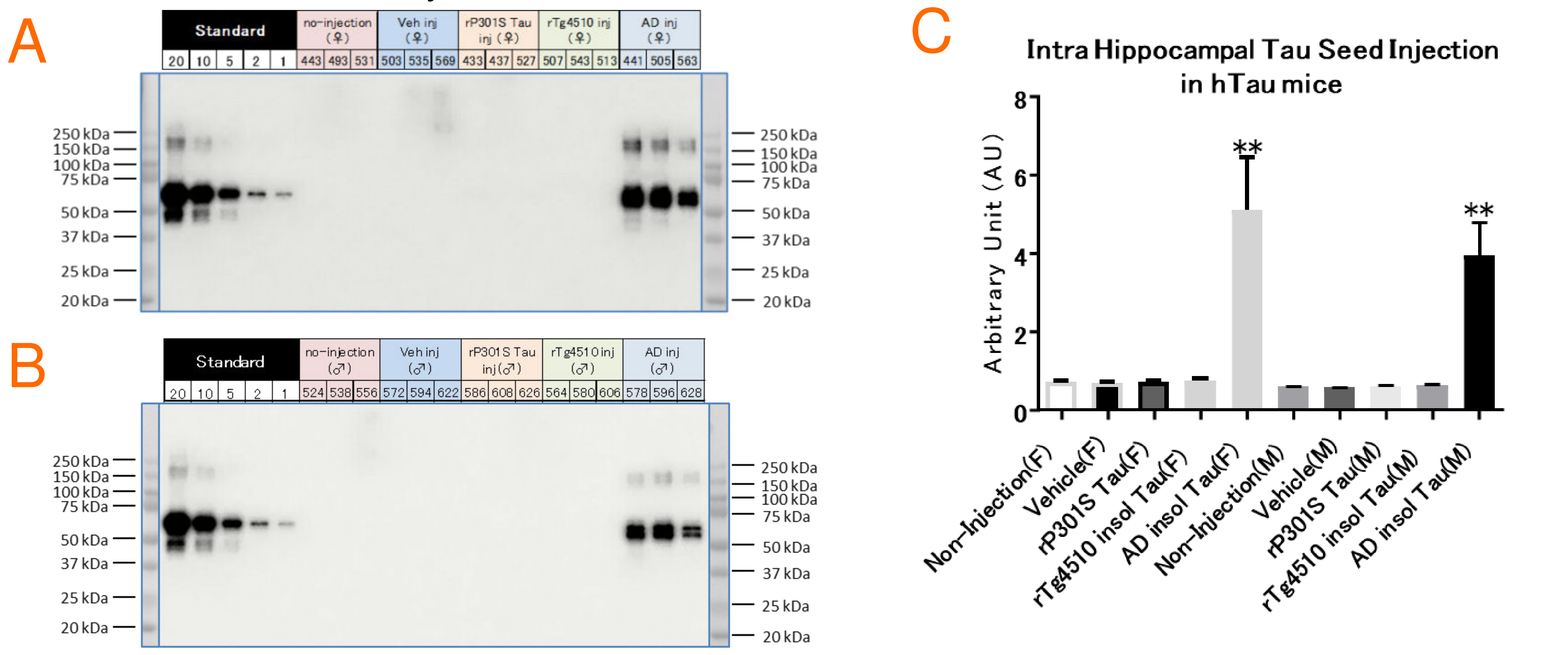

Figure 1. Western blot analysis of tissue from the ipsilateral hippocampus of seed-injected hTau mice. Total tau immunoreactivity of the sarkosyl-insoluble hippocampal fraction with HT7 antibody after 3 months incuabtion with different tau seed material. A: female, B: male animals. C: Quantification and statistical analysis of Western blots showing highly increased total tau levels in the ipsilateral hippcampus of hTau mice of both gender injected with human sarkosyl-insoluble fraction from AD brain. n = 6 per group. Mean±SEM.*p<0.05; **p<0.01 compared with vehicle by unpaired t-test. F: female; M: male.

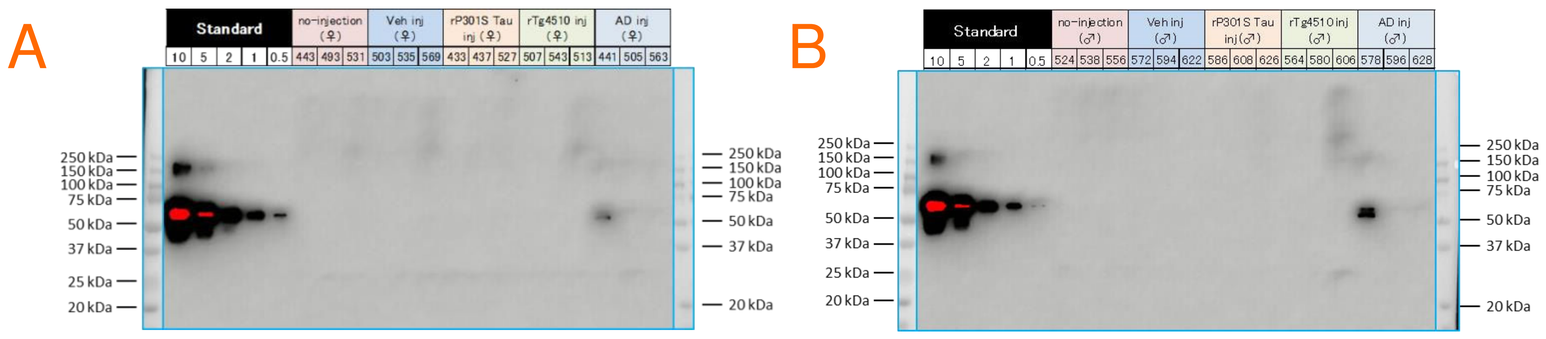

Figure 2. Western blot analysis of tissue from the contralateral hippocampus of seed-injected hTau mice. Total tau immunoreactivity of the sarkosyl-insoluble hippocampal fraction by HT7 antibody after 3 months incubation with different tau seed material shows weak signal in some human insoluble AD tau-injected animals. A: female, B: male animals.

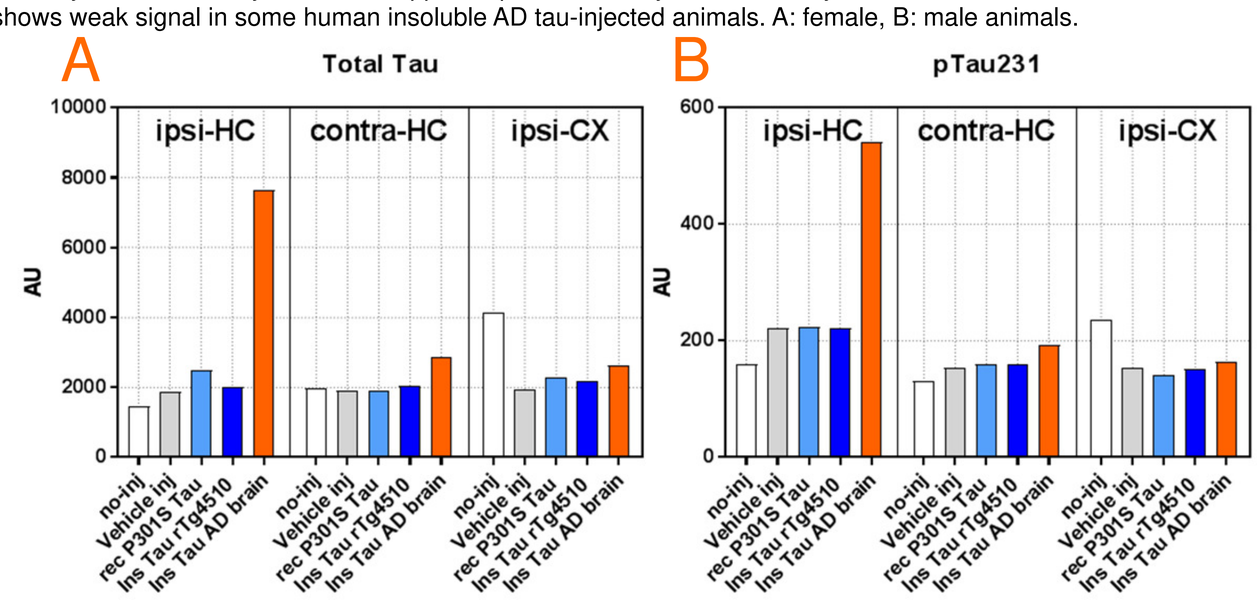

Figure 3. Quantification of total tau and ptau231 by Mesoscale Discovery immunosorbent assay. Total tau (A) and pTau231 (B) quantification of the sarkosyl-insoluble ipsilateral and contralateral hippocampus and cortex following 3 months incubation with different tau seed material. Samples of each group were pooled in this analysis.

Literature: Andorfer C, Kress Y, Espinoza M, de Silva R, Tucker KL, Barde YA, Duff K, Davies P. Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. J Neurochem. 2003 Aug;86(3):582-90.

CONCLUSION

Unilateral intra-hippocampal injection of insoluble tau from human AD brains into hTau mice represents a suitable model for further investigation of tau aggregation, seeding and spreading as well as associated interventions.

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