Novel non-transgenic rat tauopathy model induced by injection of tau oligomers into the entorhinal cortex

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Transgenic mouse models have been extensively used in Alzheimer's disease (AD) research based on the amyloid hypothesis and have taken advantage of mutations in the genes for amyloid precursor protein (*APP*) and the presenilins (*PSEN1* and *PSEN2*) that cause familial forms of AD. However, while these models may mimic a range of AD-related pathologies, they are limited in their ability to replicate the complex process of the sporadic human disease fully, which concerns over 95% of all AD cases. Because efforts to treat or prevent AD have been unsuccessful, there exists an urgent need for the development of new approaches for *in vivo* modeling of AD. As emerging evidence suggests that the spread of tau pathology in the human brain reflects the propagation of misfolded tau along anatomically connected brain regions, initiating in the brain stem and entorhinal cortex with spreading to the hippocampus and association neocortical regions, we report on a novel non-transgenic rat tauopathy model of the spreading of tau pathology observed in the human brain.

The model was generated by stereotactic injections of tau proteins into the lateral entorhinal cortex of 4-month-old male Wistar rats. We assessed whether intracerebral injection of different forms of tau proteins (tau oligomers and synthetic preformed tau fibrils) would induce neurofibrillary degeneration and tau spreading in a time-dependent manner along known pathways within interconnected brain areas distant from the injection site, and whether these changes would correlate with the animals' cognitive performance on open field, T-maze task, novel object recognition, and object-location tests.

We assessed the progression of tau spreading after 4, 8, and 11 months post-injection using antibodies AT8 for hyperphosphorylated tau, and MC1 for misfolded tau, whereas possible amyloid changes were evaluated using the anti-amyloid antibody 4G8. Proteins isolated from the different ipsi- and contralateral regions to the injection site were analyzed by immunoblotting. To test for microglial uptake of tau, we also analyzed AT8 and MC1 colocalization with Iba1-expressing microglia. We discuss our results in the light of advantages and limitations of our approach in comparison to known transgenic mouse models and debate how our model may contribute to future AD preclinical testing and drug discovery.

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