Novel Applications of MRI Techniques in the Detection of Neuronal Dysfunction before Tangle Pathology in Tau Transgenic Mice

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Background: Tauopathic patients have significant cognitive decline accompanied by severe, irreversible brain atrophy. Neuronal dysfunction is thought to occur years before diagnosis. A major obstacle in the treatment of tauopathies is that current diagnostic tools are ineffective at detecting pre-pathological changes. We previously developed a MEMRI (manganese-enhanced magnetic resonance imaging) protocol coupled with R1-mapping to measure the extent of neuronal dysfunction that occurs before appearance of cognitive deficits and tau pathology associated with the rTg4510 tau model. In this study, we performed MEMRI with mangafodipir, an FDA-approved contrast. Additionally, we used amide proton transfer (APT), a type of chemical exchange saturation transfer (CEST) imaging, to detect aberrant protein in the brains of rTg4510 and non-transgenic mice.

Methods: We used MEMRI to measure neuronal dysfunction in rTg4510 mice tau transgenic mice at 2 months (no pathology/cognitive deficits), and 3 months (presymptomatic pre-tangle pathology detectable). We measured MEMRI R1 changes before (baseline) and after (time-course) injecting mangafodipir (50mg/kg) intraperitoneally. We focused on the superior cortex and hippocampal sub-regions. APT imaging was performed in the same areas before mangafodipir injection. APT involves collecting images at fixed frequencies around the resonant frequency of water to determine the chemical composition of an aqueous system.

Results: We found mangafodipir to be an effective contrast for MEMRI of mouse brains. Optimal enhancement of the cortex and hippocampus occurs 12-24 hours post-injection. We found APT imaging to be highly reproducible. Our APT studies found no significant differences in the wild type and rTg4510 mice at 2, 3, or 5 months.

Conclusions: This study builds upon our previous work showing that MEMRI (with MnCl2) reveals important functional differences between tau transgenic and non-transgenic mice. Here we found that mangafodipir is as effective as MnCl2 in performing MEMRI. Mangafodipir exhibits less toxicity than MnCl2 due to structural similarity to EDTA (used to treat manganese toxicity), making mangafodipir a target for translation of MEMRI for tauopathy into human subjects.