Manganese-Enhanced Magnetic Resonance Imaging (MEMRI)-Based Identification of Neuronal Dysfunction before the Appearance Tau Pathology in rTg4510 Mice

9a

Ryan Cloyd[1] • Sarah Fontaine, PhD[1] • Danielle Lyons, PhD • Alexandria Ingram[1] • Shelby Meier[1] • Michelle Bell[1] • David Powell, PhD[2] • Moriel Vandsburger, PhD[1] • Jose Abisambra, PhD[1]

[1]Physiology • [2]Anatomy and Neurobiology

Tauopathic patients have significant cognitive decline accompanied by irreversible and severe brain atrophy, and it is thought that neuronal dysfunction occurs years before diagnosis. Current diagnostic tools are ineffective at detecting robust pre-pathological changes in the brain. We developed a manganese-based imaging technique to perform quantitative measurement of broad neuronal dysfunction. We used ME-MRI (manganese-enhanced magnetic resonance imaging) coupled with R1-mapping to measure the extent of neuronal dysfunction that occurs before the appearance of cognitive deficits and tau pathology that are characteristic of the rTg4510 tau model.

Methods: We used MEMRI to reveal alterations in distribution of manganese in rTg4510 mice tau transgenic mice in a longitudinal time course: 2 months (no pathology/no cognitive deficits), 3 months (pretangle pathology, detectable but not-significant cognitive decline), and 10 months (overt tangle pathology and significant cognitive impairment). We measured and compared MEMRI changes in the superior cortex and different sub-regions of the hippocampus of rTg4510 and non- transgenic mice.

Results: We show that at 3mo, rTg4510 mice have dramatic changes in MEMRI patterns (significantly increased ΔR1 values) compared to the non-transgenic mice; these MEMRI signatures are further pronounced at 4 and 6 months. The magnitude of change in the rTg4510 mice was different in the cortical and hippocampal ROIs. However, no significant changes were observed in the non-transgenic mice.

Conclusions: This study establishes early detectable calcium-based neuronal dysfunction of tau pathogenesis in one of the most commonly used tau transgenic models. These results confirm that pre-pathological mechanisms can be identified much sooner than expected, and it will be crucial to focus on earlier time points to identify pathogenic events. In addition, our findings will help frame an effective therapeutic window for future studies using disease-modifying compounds.