Longitudinal Changes in Glutamate in a Mouse Model of Tauopathy Measured by GluCEST

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BACKGROUND: Tauopathy is a broad category of dementia disorders characterized by the presence of intracellular aggregates of tau protein, which includes Alzheimer's disease (AD), Corticobasal degeneration, and Down's syndrome. The PS19 mouse model is a transgenic mouse which overexpresses mutated human tau, at P301S, a common mutation in FTDP-17 patients [1]. When expressed in a congenic background, PS19 mice develop pathology between 6-9 months of age, and with progressive synapse and neuron loss up to 15 months. Here we have studied this quickly progressing mouse model longitudinally, using GluCEST and ^{1}H MRS to measure the effects of progressive tau pathology on glutamate levels.

METHODS: All animal studies were approved by the university's IACUC. Glutamate was measured in congenic PS19 mice and age-matched wild-type mice at 3 and 7 months old (Cohort 1: n=6 WT, n=6 PS19), and another cohort at 10 and 13 months old (Cohort 2: n=3 WT, n=6 PS19). *In vivo* measurement of glutamate levels from 3mm of the hippocampus was carried out using proton magnetic resonance spectroscopy (^{1}H MRS) and glutamate chemical exchange saturation trasfer (GluCEST) MRI. Imaging was performed on a 9.4T spectrometer (Varian Inc., Palo Alto, CA). MRS was performed using the PRESS pulse sequence (TR/TE 3000/14ms, 256 averages), with VAPOR water suppression, while gating with respiration. GluCEST imaging was performed using a custom-programmed RF spoiled gradient echo readout pulse sequence, with a frequency selective continuous wave saturation preparation pulse. CEST images were collected using a 1 second saturation pulse at peak B_1 of 250 Hz for the frequencies ± 2.5 – 3.5 with steps of 0.25ppm from water resonance. B_1 and B_0 maps were acquired to correct inhomogeneities. All images and spectroscopic data were processed as described previously [2]. Cohort 1 will complete two additional time-points of imaging, and immunohistochemistry will be used to analyze pathologic correlates from all brains.

RESULTS:

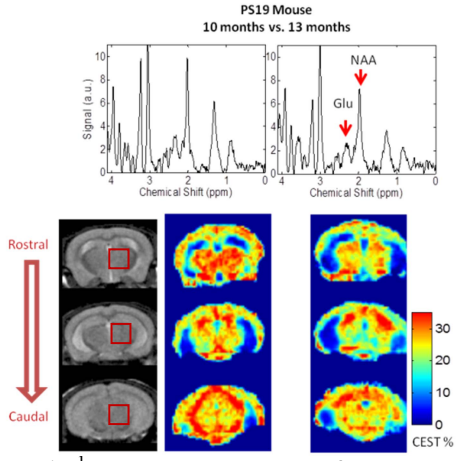

Figure 1. ^{1}H MRS shows loss of N-acetyl-aspartate (NAA, neuron loss) and glutamate at 2.35ppm in the thalamus (region outlined in red). This corresponds to decreased GluCEST contrast in the thalamus of all three slices in this mouse at 13mo. old compared to its 9mo. time point. Severe neuron loss is also apparent in the anatomy of the hippocampus.

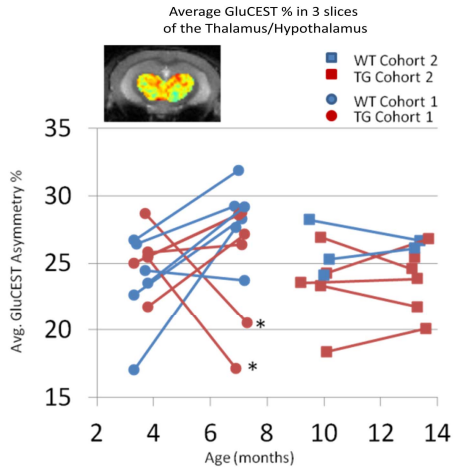

Figure 2. Average GluCEST asymmetry in the thalamus region is similar between young WT and PS19 mice. While glutamate levels increase as mice age to 7mo., PS19 mice show a shallower increase. *The two PS19 mice which have severely diminished glutamate levels at 7mo. have already reached a moribund state, and have been sacrificed for histological analysis. Glutamate appears to level off as mice continue to age to 13mo.

CONCLUSIONS: Glutamate increases during neuronal development of adolescent mice, and decreases in the thalamus/hypo-thalamus with the progression of tau pathology. In two cases, extremely low GluCEST values predicated early disease onset. Continuing study of cohort 1 will confirm whether glutamate changes after pathology increases in severity. Immunohistochemistry will be performed to correlate glutamate loss with tau pathology, synapse, and neuron loss throughout the brain.

REFERENCES:

[1] Hurtado, D. *et. al.,* Neurobiology, 177: 1977-1988, 2010.

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