Longitudinal GluCEST Imaging in a Mouse Model of Tauopathy

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BACKGROUND: Tauopathies are dementia disorders such as Alzheimer's disease, Corticobasal degeneration, and Frontotemporal dementia (FTD), which are characterized by the presence of intracellular aggregates of tau protein. A mouse model has been developed which overexpresses mutated human tau, at P301S, a common mutation in FTD patients[1]. Previous studies in the PS19 mouse model using glutamate (Glu) chemical exchange saturation transfer (GluCEST) imaging and ^{1}H MR spectroscopy (MRS) have shown that Glu levels are reduced in degenerate regions of the hippocampus[2]. The goals of this longitudinal study are to determine the earliest stage at which transgenic mice can be distinguished from controls, and the concurrent histologic symptom, whether synapse loss or full neuronal loss in the PS19 mouse model of tauopathy.

METHODS: All animal studies were approved by the university's IACUC. Two cohorts were studied: cohort 1 included n=6 WT, n=6 PS19, imaged at 3, 7, and 13 months (mo.) of age; cohort 2 included n=3 WT, n=6 PS19, imaged at 9 and 13 mo. Imaging was performed on a 9.4T spectrometer (Agilent Technologies Inc., Santa Clara, CA). ^{1}H MRS was performed in the thalamus region using the PRESS pulse sequence (TR/TE 3000/28ms, 256 averages), with WET water suppression, while gating with respiration. GluCEST images were acquired from three slices (1mm thick) through the hippocampus, using previously published methods[2] (saturation duration = 1 sec., peak B_1 = 250 Hz, frequency offsets ± 2.5 – 3.5 with steps of 0.25ppm from water resonance). B_0 and B_1 maps were acquired to correct inhomogeneities. All images and spectroscopic data were processed as described previously. GluCEST maps were averaged across the entire brain region, from all 3 slices, after thresholding to remove the CSF (below 5% GluCEST asymmetry). Brain tissue was analyzed by a variety of immunohistochemistry techniques to correlate glutamate loss with tau pathology, synapse, and neuron loss throughout the brain.

Results: ^{1}H MRS in the thalamus shows N-acetyl aspartate (NAA, combined peaks from 2.0-2.2ppm) increases up to 9mo. of age, and decreases below WT levels by 13mo (Figure 1). This corresponds with immunostaining of neuron density in the thalamus, which shows delayed development at 3mo., and increased density up to 9mo. of age. Glu levels decrease significantly below WT by 13 mo. Choline (Cho) is reduced at all time-points. Myo-inositol (MI) increases throughout lifetime as tauopathy progresses. ANOVA revels a significant effect of genotype on Glu levels, and a significant interaction between time and genotype on Cho levels. Comparatively, GluCEST asymmetry maps, averaged over the whole brain, show a decreased trend in glutamate in PS19 mice (Figure 3). GluCEST increase as WT mice age to 7-9 mo. In PS19 mice, however, GluCEST decreases, and continues to be reduced out to 13mo. This corresponds with synapse density loss as early as 3 mo. in the hippocampus ($p \leq 0.05$), cortex ($p \leq 0.05$), and thalamus ($p = 0.07$).

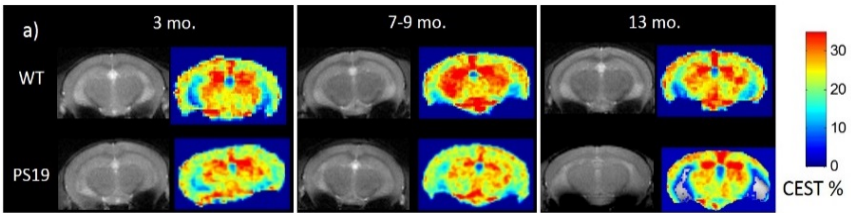
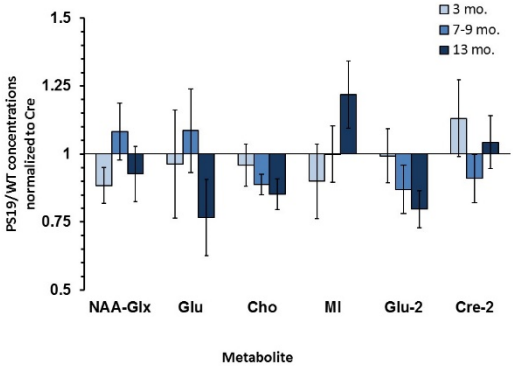


Figure 2. Representative anatomical slices and GluCEST maps showing the greatest distinction between normal and tauopathy mice at the 7-9mo. timepoint.



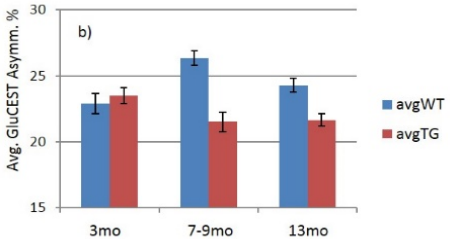


Figure 3. Average GluCEST asymmetry increases as WT mice develop, while decreasing with tauopathy.

CONCLUSIONS: Glutamate increases during neuronal development, and decreases with the progression of tau pathology, as determined by ^{1}H MRS and GluCEST imaging. PS19 mice can be distinguished from WT mice by GluCEST imaging as early as 7-9 mo. of age, when synapse loss has occurred (between 3-9 mo.), yet before neuron loss (after 9 mo.). In future studies, imaging glutamate will be useful to monitor pathology *in vivo* in response to therapy[3].

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