Role of neurochemistry in amyloid pathology using 5xFAD transgenic mouse model of AD: A single-voxel Magnetic Resonance Spectroscopy (MRS) study

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Background

Changes in cerebral metabolic concentrations are markers of aging and are also associated with various neurological disorders. Neurotransmitter and membrane metabolisms are affected in Alzheimer's disease (AD). These metabolic alterations are suggested to occur in the hippocampus and rhinal cortex during the early stages of AD pathology. Higher levels of glutamine (Gln) in the blood and cerebral spinal fluid are associated with an increased risk of developing AD. Since Gln is capable of crossing the blood-brain barrier and is involved in the metabolic cycle with glutamate (Glu), elevated levels of Gln in the presence of Aβ pathology may suggest a protective role of Gln in the early stage of the disease. Therefore, alteration in Glu/Gln cycle may serve as an early biomarker in the pathogenesis of AD. Choline-containing compounds (tCho) are essential for phospholipid synthesis and degradation of cell membranes. Abnormal alterations of tCho levels are indicative of imbalanced cell membrane phospholipid metabolism. At the early stage of Aβ pathology, high levels of tCho in conjunction with elevated levels of Gln may suggest the involvement of compensatory mechanisms to counter declining acetylcholine. Thus, investigating metabolic changes in the hippocampus may improve our understanding of metabolic mechanisms associated with Aβ pathology.

Material and Methods

Male 5xFAD mice (N=4) at 6-months-old and age-matched littermates (N=5) were used in this study. Single-voxel MRS was acquired on a 9.4T Biospec micro-MRI system equipped with a ^{1}H cryogenic surface coil. STEAM (TE/TM/TR = 3/10/2500 ms, avg = 256) spectra was acquired from a 2mm^3 voxel positioned on the left hippocampus region. Glu, Gln, tCho and total Creatine (tCr) levels were estimated with LC Model. A general linear model (GLM) was used to estimate group-wise differences in Glu/Gln ratio, tCho.Gln and tCr levels.

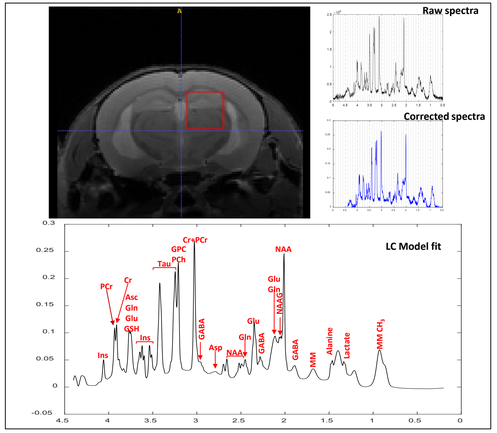

Figure 1: Invivo ^{1}H spectroscopy in mouse brain at 9.4 T in 8μL voxel (representative image).

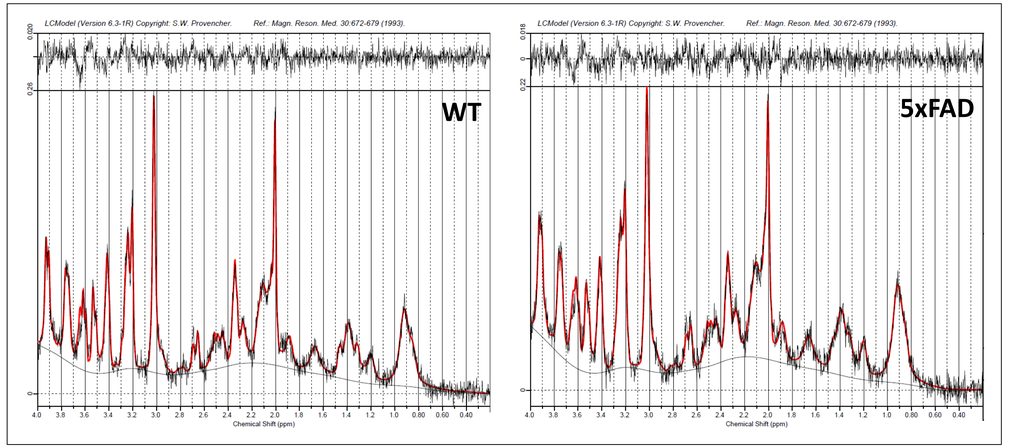

Figure 2: Spectra quantification using LC model. Model fit range 0.2 – 4.0 ppm. The black lines show the frequency, phase and eddy current distortion corrected spectra. The red lines indicate the fitted spectra. The top panels show the residuals of the fitting. Quantification reliability was assessed using Cramer-Rao lower bounds (CRLB). Metabolite data with CRLB >15% were considered unreliable and excluded from analysis.

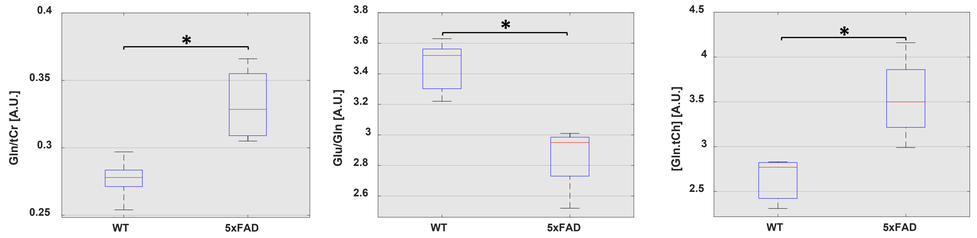

Figure 3: Quantitative results of post-hoc group comparison using general linear model (GLM) with metabolite levels/(ratios) as dependent variables and group as independent variable. * p_{FWE}<0.05

Results

Cerebral metabolic concentration levels suggest group-level differences between wild-type (WT) and 5xFAD mice. Glu/Gln ratio was significantly higher in WT mice than 5xFAD (p_{FWE}<0.05; d=3.4) and tCho.Gln was significantly lower in WT than 5xFAD (p_{FWE}<0.05; d=2.8).

Conclusion

Single-voxel MRS in the hippocampus region can identify the neurochemical profile of multiple cerebral metabolites, which may be sensitive to the Aβ burden at the early stages of the pathology.

Abbreviations:

Asc: aspartate; Aβ: beta-amyloid; AD: Alzheimer's disease; Ch: choline; Cr: creatine; FWE: family-wise error; GABA: gamma-aminobutyric acid; Glu: glutamate; Gln: glutamine; GSH: glutathione; GPC: glycerophosphocholine; Ins: myo-inositol; NAA: N-acetyl aspartate; NAAG: N-acetyl aspartyl glutamate; PCh: phosphorylcholine; Tau: taurine; tCh: total choline; WT: wild type

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