

Detecting progression of Alzheimer's disease pathology in the triple transgenic mouse brain using ^1H MRS

J. Kim¹, S-P. Lee^{1,2}, M. L. Michaelis³, and I-Y. Choi^{1,4}

¹Hoglund Brain Imaging Center, University of Kansas Medical Center, Kansas City, KS, United States, ²Department of Molecular & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, United States, ³Department of Pharmacology and Toxicology, University of Kansas, Lawrence, KS, United States, ⁴Department of Neurology, Molecular & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, United States

INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder that involves significant structural and functional alterations in the brain. Cerebral glucose metabolism changes have also been reported. Neurochemical measurements can provide unique information on pathologic biochemical processes in the living brain using *in vivo* ^1H MRS. Among many transgenic mouse models of AD, the triple transgenic AD (3xTg-AD; mutations in PS1_{M146V}, APP_{Sw}, and tau_{P301L}) mice progressively develop both A β plaques and neurofibrillary tangle pathology with accompanying neuronal death in brain regions similar to those seen in human AD [1]. In this study, ultra-short echo time ^1H MRS was employed to characterize age-dependent neurochemical changes in AD pathology of 3xTg-AD mice.

METHODS

Thirty-seven 3xTg-AD and littermate wildtype (wt) mice were studied at three time points: 2 months old (2MO, n=5 in each group), 3 months old (3MO, n=8 in each group) and 15 months old (15MO, n=6 and 5 for 3xTg-AD and wt, respectively). The ^1H MRS experiments were performed on a Varian 9.4 T MR system (Varian Inc., Palo Alto, CA) equipped with a 12-cm gradient coil (40 G/cm, 250 μs) and a shim coil (Magnex Scientific, Abingdon, UK) with second-order shim strength up to 0.4 G/cm². A quadrature surface RF coil was placed on the mouse head for transmitting and reception of the NMR signal at 400 MHz proton frequency.

Mice were anesthetized with 4% isoflurane mixed with 4L/min air and 1L/min O₂ and maintained by 1-1.5% isoflurane during the experiments. Body temperature was maintained at 37°C using a hot water pad and monitored via a rectal probe. Respiration, heart rate and the blood oxygen level were also monitored via a respiration pillow and a mouse pulse oximeter.

First- and second-order shims were adjusted using FASTMAP [2] and a ^1H MRS sequence, spin echo, full intensity acquired localized (SPECIAL) [3], was used (TR/TE=4000/3 ms, TM=20ms). A spectroscopy voxel of 6 μl was localized in the left hippocampus (hpL) using T2-weighted MR images (Fast spin echo ETL=16, echo spacing/TR/TE = 11/4000/11ms, matrix=256x256, FOV=2.56x2.56cm, thk=0.5mm, NT=2). The water signal was efficiently suppressed using variable power RF pulses with optimized relaxation delays (VAPOR) technique [4]. Metabolite concentrations were estimated using the LCModel [5] with unsuppressed water signals as a concentration reference signal. T-test was performed to compare neurochemical concentrations in the 3xTg-AD and wt mice.

RESULTS AND DISCUSSION

Figure 1 illustrates the representative spectrum acquired from a 3xTg-AD mouse brain from a voxel (2.2 x 1.2 x 2.4 mm³) in the left side of the hippocampus (hpL) as indicated in the inset MRI. The automatic shimming routine resulted in the full-width at half-maximum of water resonances in the range of 13-15 Hz, providing excellent spectral resolution.

The concentration ratios of 18 metabolites against total creatine (Cr+PCr) were quantified and compared between 3xTg-AD and wt mice. Comparison of several metabolites in hpL is shown in Fig 2. At 2mo, only taurine (Tau) contents were significantly lower in 3xTg-AD ($p=0.00002$) compared with those in wt mice. Tau was persistently lower in 3xTg-AD in advanced ages ($p=0.034$ at 3mo, $p=0.016$ at 15mo). At 3mo, both lactate (Lac) ($p=0.037$) and NAA ($p=0.032$), started to show significant differences between two groups. The higher Lac ($p=0.017$) and lower NAA ($p=0.035$) contents in 3x-Tg were consistently measured at 15mo age. Glutamine was significantly higher in 3xTg mice ($p = 0.02$), which is complimentary to the lower Glu contents reported in APP mice [6], indicating alterations in glutamatergic neurotransmission.

Our results showed that neurochemical alterations in AD pathology were not pronounced at 2mo but started to be extensive at 3mo in the 3xTg-AD mice. The neurochemical profiles obtained by ^1H MRS would provide an insight to the neurological effect in development and progression of AD pathology.

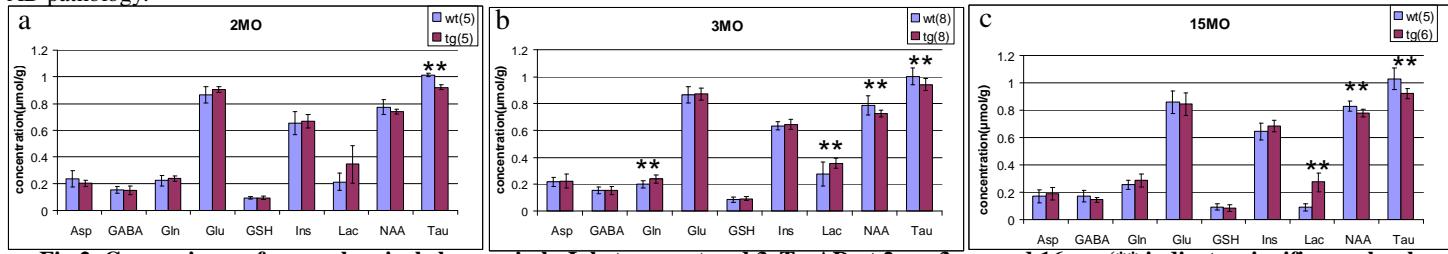


Fig 2. Comparisons of neurochemical changes in hpL between wt and 3xTg-AD at 2mo, 3mo, and 16mo. (** indicates significance level $p < 0.05$)

REFERENCES

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