Longitudinal Neurochemical changes in brains of Tau transgenic mouse model

Jieun Kim[1], In-Young Choi[1,2], Karen Duff[3], and Phil Lee[1,4]

[1]Hoglund Brain Imaging Center, University of Kansas Medical Center, Kansas City, KS, United States, [2]Department of Neurology, University of Kansas Medical Center, Kansas City, KS, United States, [3]Department of Integrative Neuroscience, Columbia University Medical Center, New York, NY, United States, [4]Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, United States

INTRODUCTION Tauopathies are characterized by pathologic aggregation of the microtubule-associated tau protein and formation of neurofibrillary tangles (NFTs) and have been linked to neurodegeneration and cognitive decline. Neurochemical measurements can provide unique information on biochemical and pathologic processes during the disease progression. However, the effects of tauopathies on cerebral metabolism reflected in neurochemical level changes are not well described. In this study, we characterized neurochemical alterations associated with the development of tau pathologies in a novel animal model of tauopathy, rTg4510 transgenic mice using ultra-short echo time ^{1}H MRS at 9.4T.

METHODS rTg4510 mice express a repressible human tau variant and develop progressive age-related NFTs, neuronal loss, and behavioral impairments starting at 5 months of age (mos) [1]. Nine rTg4510 and 10 littermate wildtype (wt) mice were studied at 5, 9 and 12 mos.

The ^{1}H MRS experiments were performed on a Varian 9.4 T MR system (Agilent Technologies, Santa Clara, CA) and a quadrature surface coil was used. Spectroscopy voxel of 6 μl (2.2x1.2x2.4 mm^3) was localized in the left hippocampal region (HPL), using T_2-weighted MRI (FSE, ETL = 16, echo spacing/TR/TE = 11/4000/11ms, matrix = 256x256, FOV = 2.56x2.56cm^2, thk = 0.5mm, NT = 2). Shimming was performed using FASTMAP [2] and the resulting FWHM of water resonances was 13-15 Hz. ^{1}H MRS was performed using a spin echo, full intensity acquired localized (SPECIAL) sequence [3] (TR/TE = 4000/3ms). Metabolite concentrations were obtained using the LCModel [4]. Student t-tests were performed for statistical analysis.

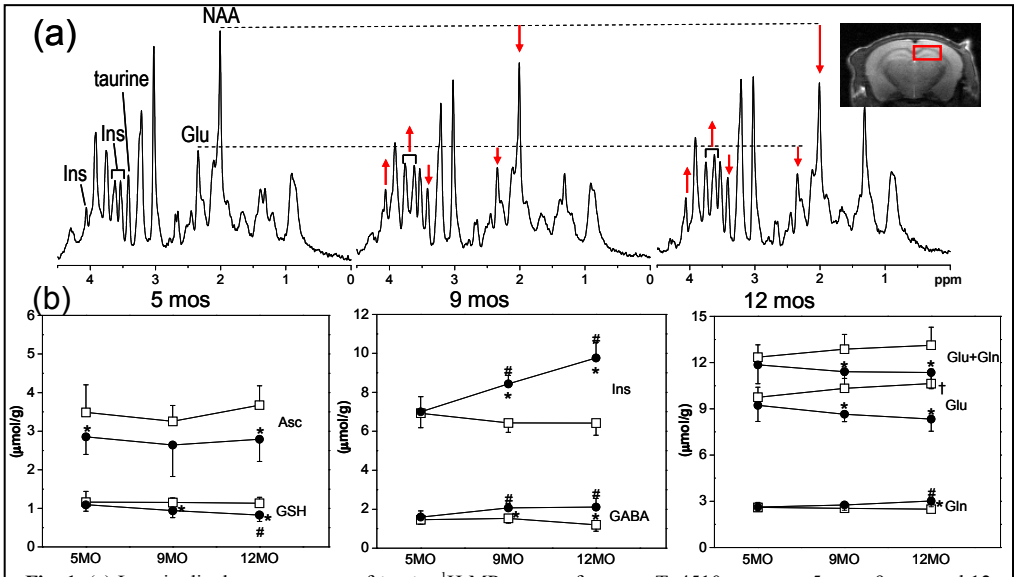

Fig. 1. (a) Longitudinal measurement of *in vivo* ^{1}H MR spectra from an rTg4510 mouse at 5 mos, 9 mos and 12 mos in the HPL. Alterations in NAA, Glu, Ins and taurine in this mouse are indicated by arrows. (b) Comparisons of neurochemical levels in the HPL between wt (□) and rTg4510 (●) groups at 5 mos, 9 mos and 12 mos (* $p < 0.05$ between wt and rTg4510 at each age; # $p < 0.05$ between 5 mos & 9 mos or 5 mos & 12 mos in rTg4510 mice; † $p < 0.05$ between 5 mos & 9 mos or 5 mos & 12 mos in wt mice). Error bar indicates standard deviation.

RESULTS AND DISCUSSION Figure 1(a) shows representative ^{1}H MR spectra from an rTg4510 mouse, demonstrating longitudinal changes of metabolites indicated by arrows. Reductions in NAA, Glu, and taurine and increase in Ins were clearly visible. Fig 1(b) shows comparisons of metabolite concentrations between rTg4510 and wt groups and longitudinal changes within each group. At 5 mos, Asc ($p = 0.035$) and taurine ($p = 0.004$) levels were significantly lower in the HPL of rTg4510 mice compared with those in wt mice. By 12 mos, NAA ($p < 0.001$), taurine ($p < 0.001$), Glu ($p < 0.001$), GSH ($p = 0.003$), Asc ($p = 0.004$) and PCr ($p < 0.001$) levels were significantly lower in the HPL of rTg4510 than those in wt mice; while GPC ($p < 0.001$), GABA ($p < 0.001$), Gln ($p = 0.005$) and Ins ($p < 0.001$) levels were significantly higher in rTg4510 than those in wt.. Changes of Ins ($p = .0003$), GABA ($p = 0.003$), taurine ($p = 0.012$) were significant at 9 mos compared to 5 mos of rTg4510 mice, indicating disease progression. Changes in Cr ($p = 0.026$), Ins ($p = 0.001$), taurine ($p = 0.02$), GPC ($p = 0.02$) and NAA ($p = 0.016$) of rTg4510 mice at 12 mos were also significant when compared to 9 mos indicating these metabolites association with further disease progression.

Figure 2 shows disease progression characterized by selected neurochemical levels (e.g., NAA and Ins) demonstrating gradual separation of rTg4510 from wt mice over 7 months. At 5 mos, wt (□) and rTg4510 (■) mice showed significant overlap of neurochemical levels. However, clear separation of rTg4510 from wt mice started from 9 mos (rTg4510:* and wt: ×) and was more pronounced at 12 mos (rTg4510: ● and wt: ○), indicating the progression of tau pathology. Neurochemical levels of wt mice remained within a dashed circle over time while those of rTg4510 mice showed gradual and consistent changes marked by solid circles that moved away from the initial data cluster. Longitudinal changes of neurochemical levels in each individual rTg4510 mouse could also be monitored during disease progression (dashed arrows in Fig. 2).

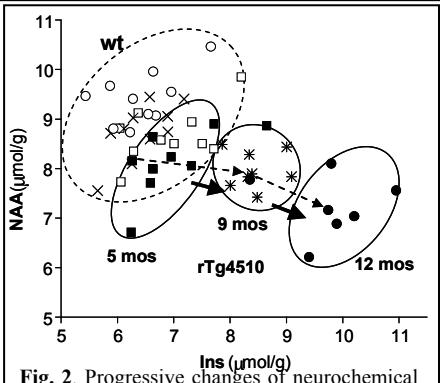

Fig. 2. Progressive changes of neurochemical levels in the hippocampus of rTg4510 (■ -5 mos, *-9 mos, ●-12 mos) during disease progression, compared with wt (□-5 mos, ×-9 mos, ○-12 mos) mice. The progression of tau pathology in rTg4510 mice can be identified at each age by following solid arrows. Dotted arrows show disease progression of an rTg4510 mouse over time as an example.

In summary, neurochemical changes in the hippocampus started at 5 mos, were pronounced at 9 mos and further progressed at 12 mos, indicating the sensitivity of ^{1}H MRS in detecting disease progression with age. The neurochemical profile measured by *in vivo* ^{1}H MRS can provide insights into the neurological effect in development and progression of Tau pathology. **Asc**: ascorbate; **GPC**: glycerophosphocholine; **Cr**: creatine; **PCr**: phosphoryl creatine; **GABA**: γ-Aminobutyric Acid **Gln**: glutamine; **Glu:** glutamate; **GSH**: glutathione; **Ins**: myo-inositol; **NAA**: N-acetylaspartate.

REFERENCES [1] SantaCruz et al, Science 309:476 (2005) [2] Gruetter et al, MRM 29:804 (1993) [3] Mlynarik et al, MRM 56:965 (2006). [4] Provencher, MRM 30: 672 (1993). This work is supported by Alzheimer's Association (NIRG-07-60405), NIH (C76 HF00201, P30 HD002528). The Hoglund Brain Imaging Center is supported by Hoglund Family and NIH (P30 HD002528, S10 RR29577, UL1 RR033179, and P30 AG035982).