Neurochemical changes in olfactory system and hippocampus regions of Tau transgenic mice using 1H MRS

J. Kim[1], I-Y. Choi[1,2], K. Duff[3], and P. 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 & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, United States

INTRODUCTION

Neurofibrillary tangles (NFTs) are the most common intraneuronal inclusion in the brains of patients with neurodegenerative diseases such as Alzheimer's disease, and have been implicated in mediating neuronal death and cognitive deficits. Neurochemical measurements can provide unique information on biochemical and pathologic processes during the disease progression. Effects of tauopathies in neurochemical levels are not well described. To understand the disease mechanisms, several animal models of AD tauopathy have been generated. Among those, a novel animal model of AD tauopathy, rTau, expresses a repressible human tau variant develop progressive age-related NFTs, neuronal loss, and behavioral impairments [1]. In this study, we characterized neurochemical alterations associated with the development of Tau pathologies in the hippocampus and the olfactory bulbs of rTau transgenic mice using ultra-short echo time ^{1}H MRS at 9.4T.

METHODS

Nine rTau and ten littermate wildtype (wt) mice were studied at 5 months age (5mos). At about 5 months of age, rTau mice show cognitive deficits, neuronal loss and NFT formations [1]. Mice were anesthetized with isoflurane mixed with air and O_2.

The ^{1}H MRS experiments were performed on a Varian 9.4 T MR system (Varian Inc., Palo Alto, CA). A quadrature coil was used for the left hippocampal region (HPL) and a 7-mm single loop surface RF coil for the olfactory bulbs (OB). Spectroscopy voxels of 6 μl (2.2x1.2x2.4 mm^3) and 2 μl (1.7x1.0x1.2 mm^3) were localized in the HPL and OB, respectively, using T_2-weighted MR images (Fast spin echo, ETL=16, echo spacing/TR/TE = 11/4000/11ms, matrix = 256x256, FOV = 2.56x 2.56 cm, thk = 0.5mm, NT = 2). First- and second-order shim currents were adjusted using FASTMAP [2] and the resulting FWHM of water resonances was in the range of 18-20 Hz for the OB and 13-15 Hz for the HPL. ^{1}H MRS was performed using a spin echo, full intensity acquired localized (SPECIAL) sequence [3] (TR/TE=4000/3 ms). Metabolite concentrations were estimated using the LCModel [4] with unsuppressed water signals as a concentration reference signal. Student t-tests were performed to compare neurochemical concentrations in the rTau and wt mice.

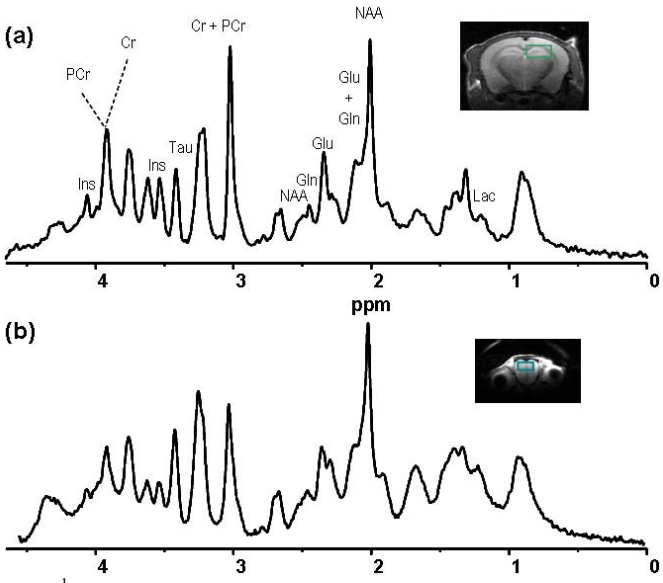

Fig. 1. ^{1}H MRS of the (a) HPC (b) OB of the Tau mouse brain *in vivo*. The inset shows the voxel location in the HPL and OB.

RESULTS AND DISCUSSION

Figure 1 shows spectra acquired from the (a) HPL and (b) OB as indicated in the MRI insets. The spectrum from the HPL showed separation of creatine and phosphocreatine at 3.9 ppm demonstrating the quality of data.

The strong susceptibility effect due to the proximity of the OB voxel to the air and tissue interface and nasal cavity caused broader spectral linewidth although we used strong second order shims possible.

The 18 metabolites were quantified and their concentrations in the HPL and OB were compared between rTau and wt mice (Fig. 2). At 5mo, taurine (Tau) levels were significantly lower in the HPL (p=0.004) and in the OB (p=0.007) compared with those in wt mice. In the OB, PCr (p=0.01), GABA (p=0.002), Glu (p=0.006), and NAA (p=0.0002) were also significantly lower in rTau mice compared with wt mice.

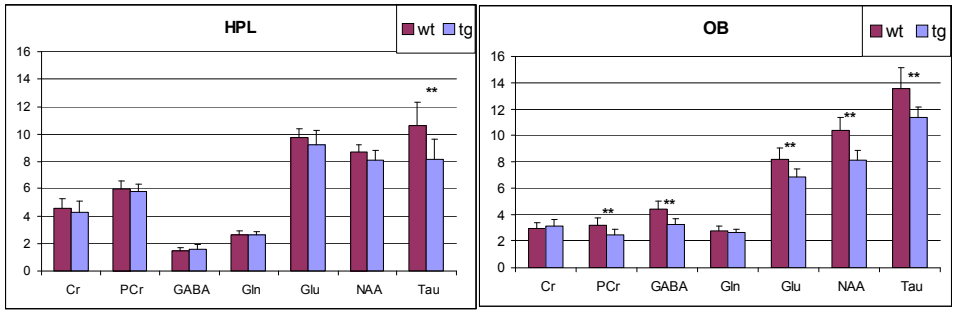

Fig 2. Comparisons of neurochemical concentrations in the OB and HPL between rTau (tg) and wt at 5 months of age. (**p < 0.05)

Our results demonstrate that ^{1}H MRS in the mouse OB region can be reliably measured and quantified with good spectral resolution. Interestingly, neurochemical changes in the OB appear to be more pronounced than the HPL of rTau mice, suggesting potential early pathologic development of Tau pathology in the OB region. Therefore, the neurochemical profile measured by *in vivo* ^{1}H MRS would provide an insight to the neurological effect in development and progression of Tau pathology.

REFERENCES

[1] SantaCruz et al, Science 309:476-481 [2] Gruetter et al., *Magn Reson Med* 29, 804 (1993) [3] Mlynarik et al. *Magn Reson Med* 56:965-970 (2006) [4] Provencher, *Magn Reson Med* 30, 672 (1993). This work is supported by Alzheimer's Association (NIRG-07-60405) and partly by NIH (C76 HF00201, P30 HD002528) and the Hoglund Family Foundation.