Decrease of glutathione levels in a transgenic mouse model of Alzheimer's disease expressing both β-amyloid and tau pathology

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INTRODUCTION

The levels of neurochemicals can be altered through various pathological mechanisms, thus providing insights into the disease progression. ^{1}H MRS has been employed to investigate biochemical abnormalities in Alzheimer's disease (AD) in humans and transgenic mouse models. During AD progression, Aβ deposition is continually increased with increased neuronal loss and mitochondrial dysfunction. The overall cellular integrity can be addressed by the measurement of the neurochemical profile. Significant loss of GSH has been reported in the APP mouse brain *in vitro*, indicating decreased neuronal cell viability and neuronal cell death, possibly due to Aβ-induced oxidative stress and neurotoxicity.

In this study, ultra-short echo time ^{1}H MRS [1] was employed to measure biochemical abnormalities in AD at 9.4 T using a triple transgenic (3xTg-AD) mouse model of AD [2], which has mutations in amyloid precursor protein (APP) and presenilin 1 (PS1) as well as a tau mutation to generate the neurofibrillary tangles found in humans. After subsequent quantification using LCModel [3], concentrations of 18 metabolites of the transgenic mice were compared with those of age-matched and gender-matched wild type control mice.

METHODS

Triple-transgenic (tg) mice (n = 4) and their wild-type (wt) littermates (n = 4) of 19 months old were studied. The ^{1}H MRS experiments were performed on a Varian 9.4 T MR system equipped with an 12-cm gradient coil (40 G/cm, 250 μs) and a shim coil (Magnex Sceintific, Abingdon, UK) with second-order shim strength up to 0.4 G/cm^2. The magnet was interfaced to a Varian INOVA console (Varian Inc., Palo Alto, CA). A quadrature surface RF coil consisting of two geometrically decoupled loops was placed on animal head for transmitting and receiving at 400 MHz proton frequency. During the experiments, the animals were anesthetized (air:oxygen = 1:1 with 1-2% isoflurane) and their core temperatures were maintained at 37˚C. First- and second-order shims were adjusted using FASTMAP [4]. Ultra-short echo-time STEAM (TE = 2 ms, TR = 5 s, TM = 20 ms) [4] was used to acquired spectral data from a voxel (2.2 x 1.2 x 2.4 mm^3) in the hippocampus. The voxel was localized using T_2-weighted MRI (ETL = 8, echo spacing 18 ms, TE/TR = 72/4000 ms, 256 phase encoding steps, 30x30 mm field of view, 1 mm slice thickness, and transients NT = 2). The water signal was efficiently suppressed using variable power RF pulses with optimized relaxation delays (VAPOR) technique [1]. The acquired spectra were corrected for phase and frequency drift based on the Cr signal at 3.03 ppm before LCModel [3] analysis. Paired t-test was performed between tg and wt mice.

RESULTS AND DISCUSSION

Figure 1 shows the spectrum obtained from the hippocampus of a wt mouse. The FASTMAP shimming resulted in a spectral resolution in the range of 13 – 16 Hz in water linewidth. Figure 2 shows the concentrations of metabolites including aspartate (Asp), γ-aminobutyric acid (GABA), glutamine (Gln), glutamate (Glu), glutathione (GSH), *myo*-inosital (Ins), lactate (Lac), N-acetylaspartate (NAA), taurine (Tau), and total creatine (Cr+PCr) in both wt and tg mice. The concentration of GSH in the wt brain (1.0 μmol/g) was decreased by 26.2% (p = 0.03) in the tg mouse brain, indicating increased oxidative stress in AD. At the age of 19 months, all other neurochemicals showed only marginal changes in the tg mouse brain. For example, the concentration of GABA in the tg brain was decreased by 19% (p=0.07) compared to that in the wt brain (2.4 μmol/g). Concentrations of Gln and Glu in wt were 2.9 and 10.4 μmol/g, and changed by +50% (p = 0.2) and -10% (p = 0.2), respectively, which showed the same trend as those shown in the PS/APP mouse brain [5]. Ins and NAA also showed a trend of decreases in tg by 4.2% (p = 0.6) and 3.7% (p = 0.5), respectively.

Our preliminary study shows the feasibility of non-invasive investigation of neurochemical abnormality in the AD brain. Interestingly, GSH, a critical antioxidant, showed the most significant changes in the hippocampus of the triple transgenic mouse model of AD. This result is consistent with the notion that GSH decreases as oxidative stress increases by the disease process and the loss of GSH is known to represent a measure of ongoing oxidative stress in aging and neurodegeneration.

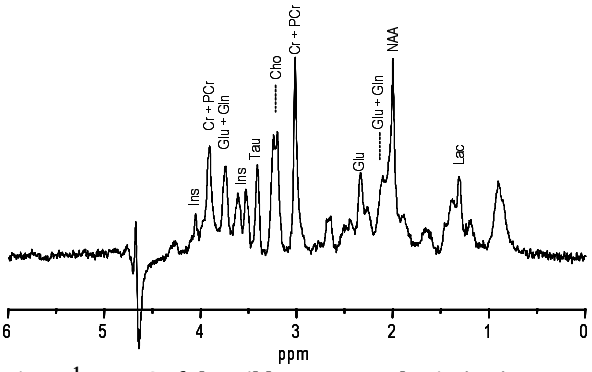

Fig. 1. ^{1}H MRS of the wild type mouse brain *in vivo* using ultra-short echo-time STEAM (TE = 2 ms).

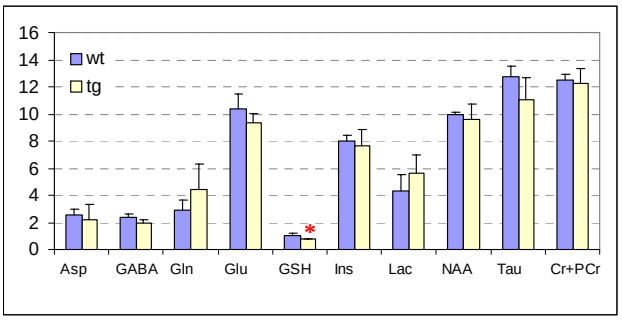

Fig. 2. Neurochemical changes in the mouse brain *in vivo* in control and in AD group. Error bars denote standard deviation and * denotes the significance level p < 0.05.

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