In Vivo Detection of Cerebral Glutathione in Aging and Alzheimer's Disease Using Selective Multiple Quantum Chemical Shift Imaging of GSH

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INTRODUCTION

Glutathione (GSH), a major antioxidant, is involved in oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, and altered oxidative metabolism in the mechanism of aging and most neurodegenerative diseases. GSH plays a major role in the cellular antioxidant defense mechanism to protect against cellular damage caused by reactive oxygen species. However, the *in vivo* measurement of GSH in the aging brain and/or the brain with Alzheimer's disease (AD) has been very scarce to date due to technical challenges. Recently, we have developed a selective multiple quantum (MQ) chemical shift imaging (CSI) of GSH in the human brain [2-4]. This study aims to investigate the effect of aging and AD on the cerebral GSH content, which may serve as a sensitive indicator of increased susceptibility to oxidative damage and as an *in vivo* biomarker to assess progression of aging and the neurodegenerative diseases in the living human brain.

METHODS

Total 55 subjects (9 young adults; 22 elderly; 4 AD patients) were studied for GSH measurement in the brain and blood. Among those, 23 subjects participated in MR studies using a 3 T SMIS system. ^{1}H MR spectra were acquired using a PRESS sequence (TE = 26 ms, TR = 4 s) from the fronto-parietal region of the brain. Measurement of GSH was performed using the selective MQ CSI of GSH with a double-band frequency selective 180^o pulse during MQ preparation period for spectral selectivity of GSH at 4.56 ppm and 2.95 ppm (8 ×8 phase encoding steps, FOV 20 cm ×20 cm, slice thickness 3 – 3.5 cm). An axial CSI slice was positioned across the frontal to parietal regions of the brain. GSH concentration was determined using the external reference method.

RESULTS AND DISCUSSION

Figure 1 shows representative PRESS spectra of subjects from each group: young, elderly and AD. Several metabolites including N-acetyl aspartate (NAA), creatine (Cr+PCr), choline (Cho), glutamate (Glu) and glutamine (Gln), *myo*-inositol (Ins) and lactate (Lac) were measured reliably with a consistent spectral pattern in all subjects. The concentration of NAA was decreased in the aging brain compared to the young, and further reduced in the brain with AD. The unequivocal detection of *in vivo* GSH at 2.95 ppm was also consistently observed in all subjects using the MQ GSH CSI technique as we demonstrated previously [2, 3]. The GSH spectra of the elderly (Fig. 1, middle) showed lower intensity than those of the young control (Fig. 1, top) and the signal intensity was further decreased in the AD brain. The estimated GSH concentration in the human brain of the elderly and AD patient was significantly lowered by 25% (p = 0.05) and ~48% compared to that of the young controls, suggesting increased oxidative stress and/or lowered antioxidant defence system in aging and neurodegenerative diseases.

In conclusion, we demonstrated the noninvasive measurements of cerebral GSH contents in aging and AD using *in vivo* GSH CSI. The capability of *in vivo* measurement of GSH in the human brain should allow us to monitor the progression of aging and neurodegenerative diseases such as AD and the efficacy of pharmaceutical interventions and treatments directed at the antioxidant treatments.

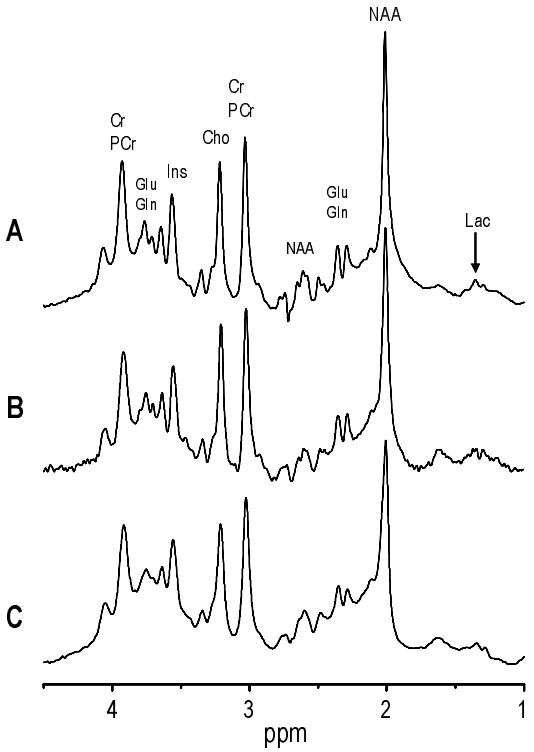

Fig. 1 *In vivo* PRESS spectra (TR = 4 s, TE = 26 ms) in the fronto-parietal regions of the brain of a young (A; 34 yrs old), elderly (B; 79 yrs old) and AD (C; 73 yrs old) subjects.

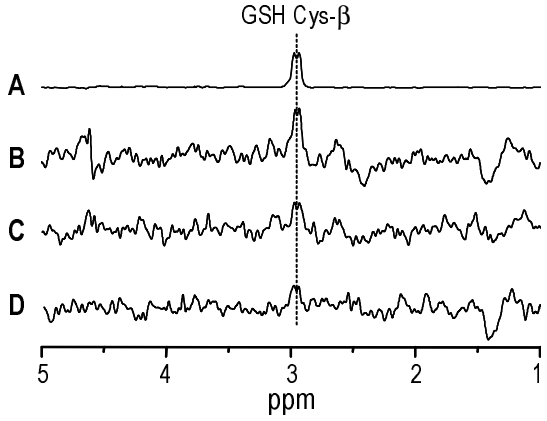

Fig. 1 *In vivo* measurements of cerebral GSH using the selective MQ CSI. GSH spectra from the GSH solution phantom (A), the frontal region of young adult (B), elderly (C) and AD patient (D).

REFERENCES: [1] Beckman et al., *Physiol Rev* **78**: 547 (1998). [2] Choi, *Proc ISMRM* **11**: 522 (2003). [3] Choi, *Proc ISMRM* **12**: 683 (2004). [4] Choi, *Proc ISMRM* **13**: 1168 (2005).This work is supported by American Health Assistance Foundation and NIH grants 8R01EB00315 and R03AG022193.