Oxidative Stress in Aging: Measurement of Glutathione in the Human Brain In Vivo Using Selective Multiple Quantum Chemical Shift Imaging

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INTRODUCTION

A long-standing theory of aging, the free radical theory, describes that oxidative stress plays an important role in aging and aging-related pathophysiology [1]. Glutathione (GSH), a major antioxidant, plays a central role in the protection against reactive oxygen species generated in the brain. However, the effects of oxidative stress in the aging brain *in vivo* have not been clearly described to date. We have developed a selective multiple quantum (MQ) chemical shift imaging (CSI) of GSH for equivocal detection of GSH [2, 3]. This study aims to determine the effect of aging on the cerebral GSH content, which may serve as a sensitive indicator of increased susceptibility to oxidative damage, ongoing mitochondrial dysfunction, and further, as a sensitive *in vivo* biomarker to assess progression of aging in the living human brain.

METHODS

Twenty-two healthy subjects (9 young adults, 31 ± 3 years old; 13 elderly, 69 ± 2 years old) were studied at a 3 Tesla SMIS system using a circularly polarized ^{1}H RF coil. For the selective MQ CSI of GSH, a double-band frequency selective 180^o pulse was used during MQ preparation period to ensure spectral selectivity for the strongly coupled cysteine protons of GSH at 4.56 ppm and 2.95 ppm. GSH CSI was performed with 8 × 8 phase encoding steps, FOV of 20 cm × 20 cm, and slice thickness of 3 – 3.5 cm. The nominal voxel size of GSH CSI is 2.5 cm × 2.5 cm × 3 cm without zero-filling. The CSI slice was positioned to across the frontal to parietal regions in the axial slices of the human brain *in vivo*. GSH concentration was determined from the regions of interest (frontal and parietal lobes) using the external reference method.

RESULTS AND DISCUSSION

The excellent selectivity of *in vivo* GSH of the human brain using the selective MQ CSI method was demonstrated in Fig. 1. The unequivocal detection of *in vivo* GSH at 2.96 ppm was consistently observed in all subjects. The unique spectral pattern of *in vivo* GSH doublet with frequency separation of ~4 Hz showed excellent match with that of *in vitro* indicating effective suppression of other overlapping signals such as creatine, GABA and macromolecules 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). The estimated GSH concentration in the parietal region of the elderly, 0.6 ± 0.1 μmol/g (mean ± SD, n = 13), was significantly lowered by 25% (p = 0.05) compared to that of the young controls, 0.8 ± 0.1 μmol/g (n = 9), confirming our hypothesis that reduction of cerebral GSH occurs in aging.

To further investigate cerebral GSH as a potential indicator of cognitive decline associated with oxidative stress in the aging brain, we compared the GSH contents in the frontal and parietal regions of four healthy elderly subjects (71 ± 5 years old, mean ± SD) with neuropsychological test scores. Our preliminary quantitative analysis showed that GSH contents in the frontal and parietal regions of these four elderly subjects were 0.8 ± 0.1 and 0.7 ± 0.1 (mean ± SD, n = 4), respectively (Fig. 2, left). The representative results of two neuropsychological tests ("Vocabulary" and "Delayed Recall") are shown in Fig. 2. While all four subjects scored in the normal range, interestingly the neuropsychological test scores of "Vocabulary" (middle) and "Delayed Recall" (right) show a similar pattern with GSH contents. While these results are quite preliminary, they are consistent with the possibility that biochemical changes due to increased oxidative stress contribute to cognitive decline. In various neurodegenerative diseases, the pattern of GSH reduction and its regional specificity may be different depending on the onset of oxidative damage and accompanying cognitive decline.

In conclusion, we report the noninvasive measurements of cerebral GSH contents in aging for the first time using *in vivo* GSH CSI. The capability of *in vivo* measurements of GSH in the human brain should allow us to monitor the progression of aging and diseases related to the concept of oxidative stress and the effect of pharmaceutical interventions directed at the antioxidant treatments.

REFERENCES: [1] Beckman et al., *Physiol Rev* **78**: 547 (1998). [2] Choi, *Proc ISMRM* **11**: 522 (2003). [3] Choi, *Proc ISMRM* **12**: 683 (2004).

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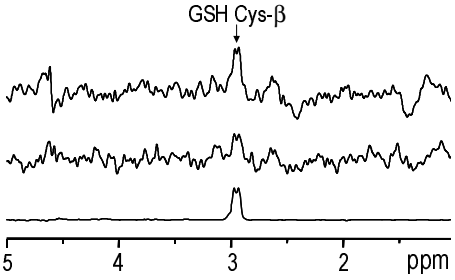

Fig. 1 *In vivo* measurements of cerebral GSH in aging using the selective MQ CSI. GSH spectra from the frontal region of the young adult (top) and the elderly (middle), and of the GSH solution phantom (bottom).

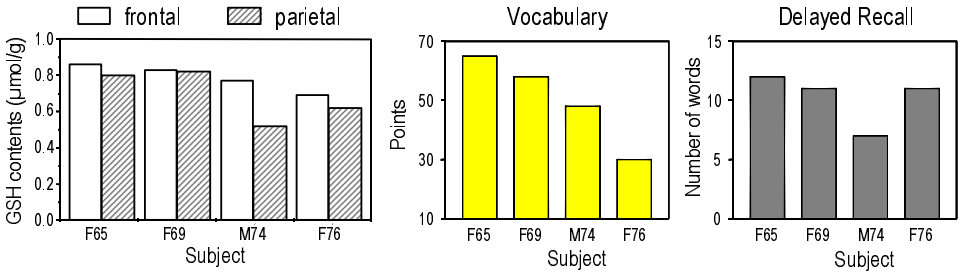

Fig. 2 GSH measurements in the frontal and parietal regions of the aging brain *in vivo* (left). The corresponding neuropsychological test scores of vocabulary scores (middle) and delayed recall (right) show a similar pattern with GSH contents in these elderly subjects. In the x-axis, F and M indicate female and male, respectively. Numbers next to the F or M indicate ages.