Unequivocal Detection of Glutathione in the Human Brain *In Vivo* Using Navigated Chemical Shift Imaging of Glutathione: Assessment of Regional Heterogeneity of Glutathione

I-Y. Choi[1]

[1]Medical Physics, The Nathan Kline Institute, Orangeburg, NY, United States

INTRODUCTION

Glutathione in its reduced form (GSH) is a major antioxidant in the brain and is suggested to be a sensitive indicator of oxidative stress in normal aging and many neurodegenerative diseases. To date, the regional heterogeneous distribution of GSH in the human brain has been investigated mostly from brain specimens obtained from autopsy or biopsy. Therefore, the development of *in vivo* methods to detect alterations and regional differences in GSH contents is of importance. The purpose of this study was (a) to develop a selective multiple quantum (MQ) chemical shift imaging (CSI) of GSH with a navigator for phase correction for equivocal detection of GSH throughout the axial section of the brain and (b) to quantify GSH concentration distribution in the human brain.

METHODS

Seven healthy subjects were studied (36 ± 8 yrs old, mean ± SD) at a 3 Tesla SMIS system using a circularly polarized ^{1}H RF coil. The MQ CSI of GSH pulse sequence consists of two parts: the MQ filtered GSH part (4) and the navigator water part with no further relaxation delay. For the MQ filtered GSH part, a double-band frequency selective 180^o pulse at 4.56 ppm and 2.95 ppm was used during MQ preparation period. The navigator water part selects the identical slice used for the MQ GSH CSI part. The flip angle of water was <5^o and an identical phase encoding scheme as MQ GSH CSI was used. GSH CSI was performed with 8 × 8 phase encoding steps, FOV of 16 cm × 16 cm, and slice thickness of 2.5-3.5 cm. The nominal voxel size of GSH CSI is 2 cm × 2 cm × 3 cm. The CSI slice was positioned in the axial slices in the plane of the cingulate sulcus of the human brain *in vivo*. GSH concentration was estimated using a phantom containing GSH (external reference method). In addition, T_1 of in vivo GSH was measured to optimize repetition time using an inversion recovery method.

RESULTS AND DISCUSSION

The excellent selectivity of *in vivo* GSH using the selective MQ filtering method with a double-band frequency selective pulse was demonstrated in Fig. 1A & B. The unequivocal detection of *in vivo* GSH doublet at 2.96 ppm (Fig.1A) was consistent with that of *in vitro* GSH (Fig. 1B). As we previously reported (4), the frequency separation of GSH doublet was ~4 Hz in both *in vivo* and phantoms indicating effective suppression of other overlapping signals such as Cr, GABA and macromolecules (MM) using the double-band selective pulse, which does not select GABA and MM. The T_1 value of *in vivo* GSH was 0.40 ± 0.02 s (mean ± SE, n = 5) at 3 Tesla, which was substantially shorter than other metabolites. Taking the advantage of the short T_1 value of GSH, the repetition time of GSH measurements was set to 1 sec to reduce total scan time. Figure 2 shows an *in vivo* GSH CSI of the human brain with nominal voxel size of 3 ml after one time zero-filling. The phase of each CSI voxel was corrected based on the phase of navigator water from the corresponding voxel, which is particularly appreciated for the measurements of MQ filtered CSI since all singlets are suppressed by MQ filtering. The GSH signals were clearly detected throughout the entire GSH CSI slice. The preliminary estimated concentration of GSH in frontal lobe was 1.0 ± 0.1 mM (mean ± SE) and that in limbic lobe (mainly cingulate) was 1.1 ± 0.1 mM. The concentration of GSH in parietal lobe showed the lowest GSH level of 0.7 ± 0.04 mM ($p<0.05$), which may indicate regional heterogeneity of GSH distribution in the human brain.

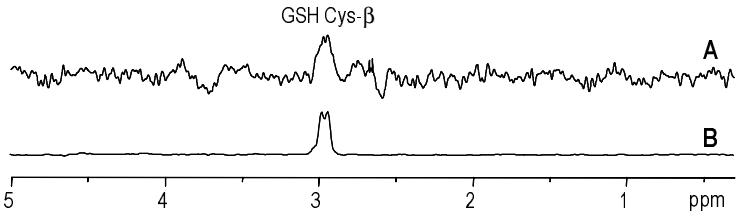

Fig. 1 Unequivocal detection of GSH using the selective MQ method. GSH spectra of (a) the human brain *in vivo* and (B) the phantom using single voxel MQ methods.

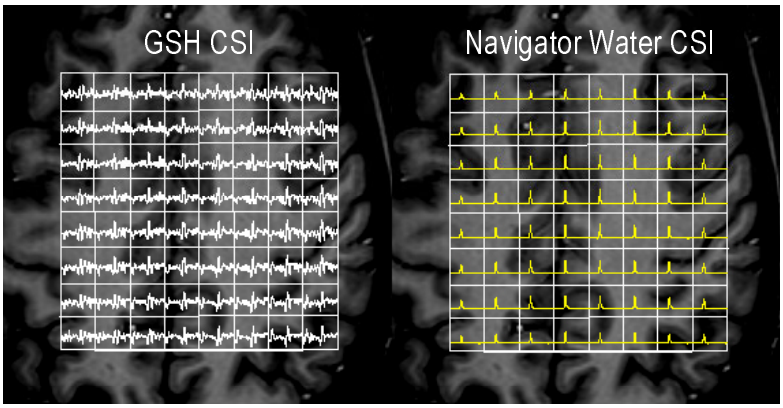

Fig. 2 Chemical shift image of GSH in the human brain *in vivo* at 3 Tesla with navigator water for phase correction

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

REFERENCES

1. Trabesinger et al, *MRM* **45**:708 (2001). 2. Terpstra and Gruetter, *MRM* **50**:19 (2003). 3. Choi et al, *Proc ISMRM* **11**: 522 (2003).

This work is supported by NIH grant 8R01EB00315 and R03AG022193.