In vivo editing of glutathione using doubly selective Hartmann-Hahn match at high magnetic field

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INTRODUCTION

Detection of glutathione (GSH), the major antioxidant, is particularly challenging due to its low concentration and overlapping resonances (macromolecules, creatine, and GABA). To date, GSH was measured *in vivo* mainly using multiple quantum filtering or J-difference editing methods [1-4], both of which are based on pulse-interrupted free-precession of J-coupling interactions to differentiate GSH from overlapping resonances. In this study, we developed a GSH editing method using a fundamentally different approach for reliable *in vivo* measurement of GSH in the Sprague-Dawley rat brain at 9.4 T. With this new approach, spectral editing was not based on the frequency profile of a conventional editing pulse, rather it was a result of the stringent requirement for doubly selective Hartmann-Hahn match (5). During spin-locking for generation of Hartmann-Hahn transfer, the rate of transverse magnetization decay is $T_1\rho$ which is substantially longer than T_2.

METHODS

The pulse sequence (Fig. 1) consists of the spectral presaturaion part followed by the Hartmann-Hahn transfer part. The spectral presaturation part eliminates thermal equilibrium signals of GSH cysteinyl methylene protons (β-H2), GABA C3 methylene protons (γ-H2) and macromolecules at ~3 ppm using optimized frequency selective CHESS pulses (Optimized asymmetric sinc, length = 10 ms, BW = 710 Hz). Interleaved outer volume suppression pulses were also used during this period. Then, a 0.5 ms adiabatic half-passage pulse applied along the y/-y axis was used for non-selective excitation. The doubly selective homonuclear Hartmann-Hahn match was created by simultaneous selective spin-locking of the GSH cysteinyl α-H at 4.56 ppm and GSH cysteinyl β-H2 at 2.93 and 2.97 ppm using a double band Gaussian pulse train (4 x 20 ms, 375 Hz) applied along the x-axis. During the doubly selective Hartmann-Hahn match, the thermal equilibrium signal of cysteinyl α-H is selectively transferred to cysteinyl β-H2. Localization was achieved using three slice-selective 180° refocusing pulses (mao, length = 1 ms, BW = 5.75 kHz) along x-, y- and z-dimensions immediately after spin-locking. Prior to data acquisition, a 1-1 echo was used for additional water suppression. The receiver phase was alternated according to the end-point phase of the adiabatic half-passage pulse used for excitation. *In vivo* GSH concentration was estimated using the external reference method using a phantom sample containing 10 mM GSH, 10 mM creatine and 10 mM NAA. All experiments were performed on a 9.4 T Varian system. The *in vivo* volume of interest (5 x 3 x 4 mm^3, 60 μL) was largely in the cerebral neocortex region.

RESULTS AND DISCUSSION

The editing yield of GSH cysteinyl β-H2 using the proposed Hartmann-Hahn transfer method was substantially greater than that of alternative methods at 9.4 T. For example, the maximum GSH cysteinyl β-H2 signal intensity achieved by multiple quantum filtering optimized for GSH was only ~50% of that by the Hartmann-Hahn transfer method.

Fig. 2 top trace shows the doubly selective Hartmann-Hahn transfer spectrum acquired from the phantom sample containing 10 mM GSH, 10 mM creatine and 10 mM NAA. Note the complete suppression of creatine methyl signal at 3.0 ppm. The creatine methylene signal at 3.98 ppm and NAA methyl signal at 2.0 ppm were also observed. The relative phase of the singlets was determined by the frequency and duration of the spin-locking pulses. Fig. 2 bottom trace shows the doubly selective Hartmann-Hahn transfer spectrum acquired from the rat brain *in vivo* (voxel size = 5 x 3 x 4 mm^3, TR = 2 s, NT = 1024). The *in vivo* spectral pattern of the GSH cysteinyl β-H2 was similar to that obtained from the phantom sample, which was line-broadened to match *in vivo* linewidth (Fig. 2 top & inset). However, the creatine and NAA singlets at 3.98 and 2.0 ppm were not observed in the *in vivo* spectrum due to relatively fast *in vivo* T_2^* relaxation at 9.4 T during the spin-locking period. The missing singlets in the *in vivo* spectrum could be recovered by shifting one of the slice-selective (and spectrally non-selective) 180° pulses into the center of the spin-locking pulse. In summary, we have demonstrated that it is feasible to use doubly selective Hartmann-Hahn transfer to edit the GSH cysteinyl β-H2 resonance in the rat brain *in vivo* at 9.4 T.

REFERENCES

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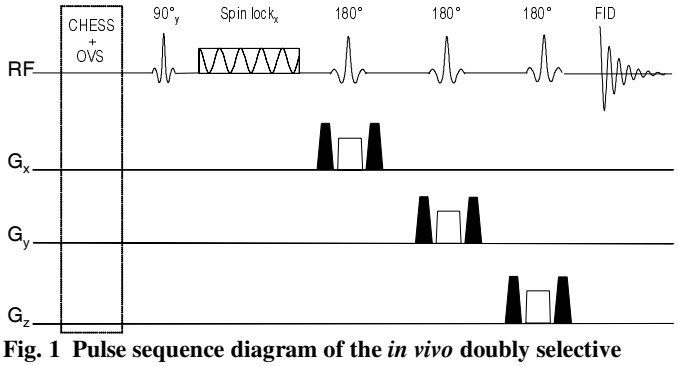

Fig. 1 Pulse sequence diagram of the *in vivo* doubly selective homonuclear Hartmann-Hahn transfer method.

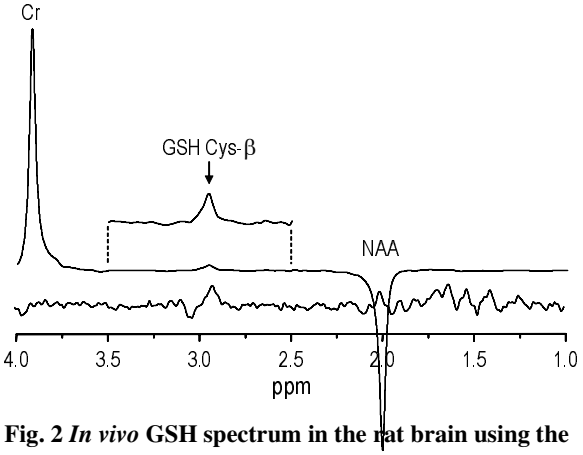

Fig. 2 *In vivo* GSH spectrum in the rat brain using the doubly selective Hartmann-Hahn transfer method. The *in vivo* spectal pattern of GSH cysteinyl β-H2 (bottom) matchs that acquired from a phantom of GSH solution (top). See the inset for an expanded view (x10).