A New Localized Double Quantum Coherence Filter for the in Vivo Detection of Glutathione (GSH)

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Introduction

Glutathione (GSH), which is critical to the normal function of the brain, is a major antioxidant and plays a significant role in detoxification of reactive oxygen species. Normal GSH in the human brain (from 0.8 to 3.1 mM) is difficult to measure in vivo using proton magnetic resonance spectroscopy (MRS) due to its severe overlapping with more intense peaks from other metabolites such as creatine (Cr). Multiple-quantum filter editing overcomes this difficulty by suppressing the singlet resonances in a single acquisition via detecting only parts (25 ~ 50 %) of the available NMR signal from the J-coupled metabolites. In this work, a new combination of double-quantum filter with PRESS [1] was introduced and successfully demonstrated using the GSH phantom and in healthy volunteers.

Methods

The new localized double-quantum filter is shown in Fig. 1. For clarity, the symmetric crusher gradients around the 180° pulses, the initial water saturation pulses and its associated crusher gradients are not shown. The 90° excitation pulse and the two 180° pulses, which form the PRESS sequence, were used to achieve spatial localization. The duration of the first echo, t_1, was fixed and was kept as short as possible. A frequency selective 90° Gaussian pulse was applied symmetrically at each side of the last slice selective 180° pulse. The two 90° Gaussian pulses were 13 ms in duration (bandwidth 70 Hz at half-height) and were tuned to the CH proton of the cysteine moiety of GSH at 4.56 ppm. Since the two Gaussian pulses only acted on the CH proton, the chemical shifts of CH_2 protons of the cysteine moiety during TE and TM periods were refocused by the last slice-selection 180° pulse. Therefore only J-coupled signal is detected in the final measured GSH signals. During the first TE/2 period, the CH_2 protons of the cysteine moiety evolved into antiphase terms via its J-coupling with the CH proton, which was subsequently converted into multiple quantum coherences by the first selective 90° Gaussian pulse. In contrast, the signal started from the CH proton of the cysteinyl group, which had been severely reduced by the water saturation pulses, was left in antiphase state by the first frequency selective 90° Gaussian pulse and was prevented from being converted into observable CH_2 signals around 2.95 ppm by J-coupling. This minimized the potential contamination of the CH proton signal in GSH quantification if the CH proton was incompletely suppressed by the water saturation pulses. The gradients G_1 and G_2 were used to crush magnetizations that did not originate from the double quantum coherence. Other coherence orders, such as single quantum coherence from uncoupled metabolite resonances (e.g., 3.0 ppm creatine resonance line), were dephased by the gradients. A four-step phase cycling scheme, which alternately cycles the phases of the two 90° Gaussian pulses and the receiver, was implemented to further suppress unwanted coherence. The key differences between the new double quantum filter and the usual double-quantum filter are (1) that two selective pulses, instead of one, are applied, eliminating the need for additional phase calibration procedures and preventing potential contamination of signals from CH proton if the water saturation pulses are used and (2) that the effects of chemical shift and inhomogeneous B_0 field during TM periods are also refocused.

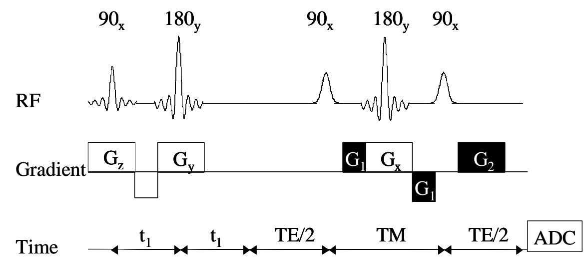

Fig. 1 Volume selective double quantum coherence filter with two frequency selective 90° Gaussian pulses.

All experiments were carried out on a 3.0 T scanner (Siemens) using a standard head coil for excitation and quadrature detection. Spectra were acquired with a repetition time of 2.0 s, 2048 complex data points and a 2000 Hz spectral bandwidth. Preceded by four dummy scans, 64 scans and 256 scans were averaged for in vitro and in vivo studies, respectively. After acquisition, the time signals were zero-filled to 4096 data points and multiplied with a 6-Hz (in vivo)/20-Hz (in vitro) exponential filter. The spectra were DC corrected before quantification. Water signal from the same VOI was acquired without water saturation using PRESS sequence (TE = 30 ms, TR = 2.0 s, 16 scans) and was used as an internal standard.

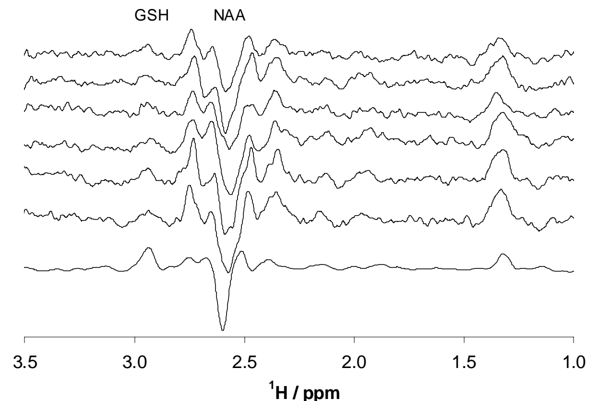

Fig. 2 In vivo ^{1}H NMR spectra of GSH using the new double quantum coherence filter. The bottom spectrum was a sum of the spectra from the following phantoms by first scaling their concentrations to the following concentrations: GSH 1.5 mM, ASP 1.0 mM, Cr 10.0 mM, NAA 10.0 mM, GABA 1.0 mM, Lactate 1.0 mM.

Results and Discussion

The maximum yield of the new double quantum filters from the GSH phantom was 36.8 %, which is close to that of previous methods [1]. The selectivity of the new sequence for GSH was evaluated using individual phantoms containing GSH, creatine, GABA, aspartate and NAA, respectively. The sum of all phantom spectra is displayed at the bottom of Fig. 2. Measurements were also performed in five males and one female healthy volunteers (ages from 29 ~ 45) who provided written informed consent. VOI (30×30×30 mm^3) was placed in the parietal lobe. The in vivo spectra, which were analogous to the sum of phantom spectrum, are shown in Figure 2. The GSH peak is clearly visible around 2.95 ppm. The GSH concentration from the in vivo spectra of the six healthy volunteers was estimated to be 1.4 ± 0.3 mM, in agreement with previous studies.

Conclusions

A new approach for double quantum filtering, combined with PRESS, for GSH editing was developed and demonstrated with both in vitro and vivo studies on a 3.0 T scanner. Compared to the conventional double quantum coherence filter, this new sequence does not require the additional phase calibration procedures to minimize the signal loss, making it convenient for routine use. Effects of chemical shifts and B_0 inhomogeneity during the double quantum mixing time were also refocused without the need of additional RF-pulses. This further improves the robustness of the new sequence. In phantoms, the new sequence was shown to have an efficiency of demonstrated 36.8% for GSH editing. GSH concentration in the parietal lobe from the in vivo spectra of the six healthy volunteers was estimated to be 1.4 ± 0.3 mM, in agreement with previous studies [1-3].

References

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