New Strategy for Detection of Glycine in Human Brain In Vivo

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INTRODUCTION

Glycine (Gly), an inhibitory neurotransmitter and co-agonist at N-methyl-D-aspartate receptors, has two uncoupled spins, resonating at 3.55 ppm. Because of its low concentration (~0.5 mM) and the abundant overlapping resonances of *myo*-inositol (mI), detection of Gly by proton MRS at short TE has proven to be very difficult. An alternative long-TE approach can be employed, with an advantage that TE optimization can suppress the scalar-coupled resonances of mI whilst maintaining the small Gly singlet measurable within the acceptable time frame. The complex behavior of the mI signal, primarily arising from strong coupling effects, requires rigorous investigation of the signal dependence on the sequence parameters. In a recently reported method based on TE averaging [1], Gly is detected as a shoulder on the larger mI multiplet. This incomplete resolution of Gly and mI indicates that further improvements to Gly measurement are needed.

METHOD and MATERIALS

Suppression of the strongly-coupled resonances of mI for detection of the Gly singlet can be achieved by exploiting signal degradation due to the effects of scalar coupling, which occurs more drastically in a PRESS than in a STEAM sequence. Antiphase coherences that play a major role in signal degradation pass through PRESS, whereas STEAM preserves the signal from strongly coupled spins due to its zero-quantum-filtering characteristics. A sequence with three consecutive 180° RF pulses has been explored for suppression of the mI resonances at ~3.55 ppm, i.e., 90 – 180 – 180 – 180. The 90° and two 180° pulses were slice selective for single-voxel localization. The second 180° pulse (19 lobes; 50 ms; bandwidth = 330 Hz) was applied for refocusing of resonances between 1.9 - 4.1 ppm, excluding water and lipid signals from the acquisition. Density-matrix simulation was employed to search for optimal sequence timings for mI suppression, based on the published chemical shift and coupling constants [2]. It turned out that the mI multiplet at ~3.55 ppm is minimal at TE = 198 ms, in which the individual echo times of the three 180° pulses were $\{TE_1, TE_2, TE_3\} = \{66, 57, 75\}$ ms. Fig. 1 demonstrates the performance of the Gly filter. The mI multiplet at ~3.55 ppm reduces substantially, the suppression ratio being 1000 in terms of peak area for the shaded region (10 Hz wide). For an mI-to-Gly concentration ratio of 8, following the filtering sequence, the height and area of the mI residual multiplet are 14% and 1% with respect to those of Gly, respectively. This result indicates that Gly can be estimated from peak area calculation directly with negligible contamination of mI.

The sequence was tested on two phantom spheres (d. = 6 cm); one with mI (50 mM) and Cr (50 mM), and another with Gly (10 mM), mI (80 mM), Cr (100 mM), Tau (20 mM), Glu (100 mM), Gln (20 mM) and GSH (20 mM). Spectra following a 90° pulse and the localized filter (25×25×25 mm^3) were both acquired from the phantoms (see Fig. 2). A preliminary in-vivo test of the sequence was conducted on two healthy volunteers. A 25×25×25 mm^3 voxel was positioned in the parieto-occipital lobe for one subject and in the occipital lobe for another. Experiments were carried out at 3.0 T in an 80-cm bore magnet, interfaced to a SMIS console. A 28-cm diameter quadrature birdcage coil was used for RF transmission and reception. The density-matrix simulation of the sequence was programmed with Matlab (The MathWorks, Inc.).

RESULTS and DISCUSSION

Fig. 2 presents phantom results from the Gly filter. For phantom 1, mI and Cr exhibit similar signal intensity in a 90°-acquired spectrum. However, the Gly filter suppresses the mI multiplet drastically, giving virtually null at 3.55 ppm. The 90°-acquired spectrum of phantom 2 indicates presence of several chemicals at the brain concentration ratio [2]. Due to its relatively low concentration, Gly is not visible in this spectrum. However, the small Gly singlet is clearly discernible in the filtered spectrum. Additional neighboring resonances of Tau and Glu also reduce due to the strong coupling effects and consequently do not interfere with Gly estimation critically. The Cr-to-Gly concentration ratio of 10 is reproduced from peak area estimation, within experimental limits. Fig. 3 displays a pair of *in vivo* spectra obtained from the parieto-temporal and occipital lobes of the human brain. For the two regions selected in this study, the ratio of the Gly peak area with respect to that of the Cr 3.03-ppm singlet was 3% and 5%, respectively. Assuming identical T_1 and T_2 between Gly and Cr, the concentrations of Gly in the parieto-temporal and occipital cortices were estimated as 0.4 and 0.6 mM, with reference to Cr at 8.0 mM.

In conclusion, we have demonstrated the feasibility of a sequence with three 180° RF pulses to suppress the strongly-coupled resonances of mI for detection of Gly in human brain. Further *in vivo* studies are currently underway.

REFERENCES

1. Prescot AP *et. al*. Magn Reson Med 2006;**55**:681-686.
2. Govindaraju V *et. al.* NMR Biomed 2000;**13:**129-153.

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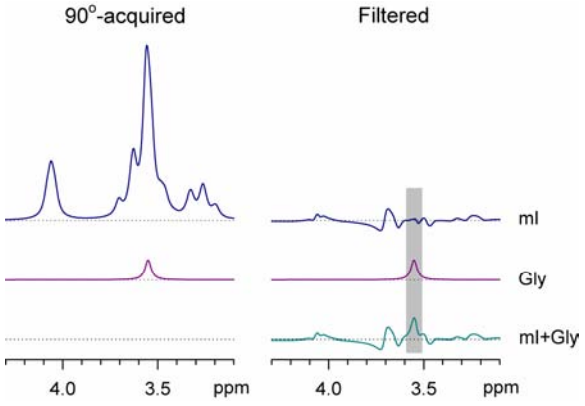

FIG 1. Calculated spectra of mI, Gly and mI+Gly for 90°-acquisition and the filtering sequence. Spectra are broadened to 5 Hz (FWHM). The concentration ratio [mI]/[Gly] = 8. For the shaded region, the mI-to-Gly peak area ratio is < 1%.

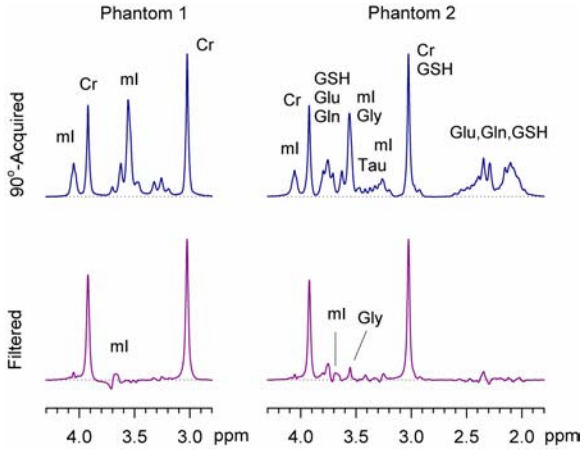

FIG 2. Phantom demonstration of the performance of the Gly filter. Data from phantom 1 illustrate suppression of mI. Gly in phantom 2 is revealed in the filtered spectrum. Spectra are each normalized with respect to the Cr 3.03-ppm singlet. The linewidth of singlets is 3.5 Hz. TR was 15 and 3.2 s in 90°-acquisition and filtering tests, respectively. The T_1 of the Cr 3.03-ppm singlet was 2 s in both phantoms.

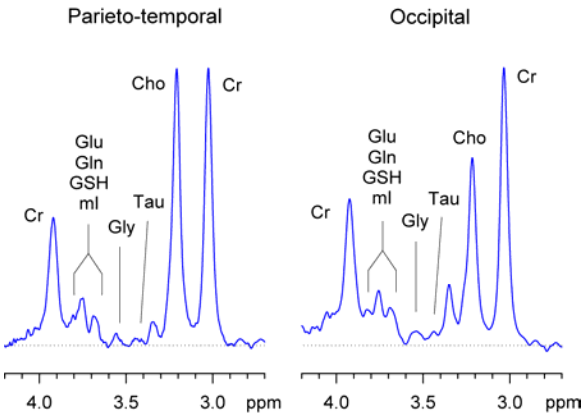

FIG 3. In-vivo filtered spectra obtained from the human parieto-temporal and occipital lobes, at 3T. The voxel size was 25×25×25 mm^3. TR = 2.4 s. NEX = 512.