Quantification of Undecoupled ^{13}C NMR Spectra in the Brain

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Introduction

^{13}C NMR spectroscopy with the use of ^{13}C-enriched substrates is a unique tool to study metabolic pathways for energy and neurotransmitter metabolism non-invasively in the brain. Almost all *in vivo* ^{13}C NMR spectroscopy studies have used decoupling during acquisition in order to improve signal-to-noise ratio and reduce spectral overlap. However at high fields, decoupling is challenging due to constraints imposed on power deposition for human studies. Thus far, no ^{13}C NMR in humans has been reported except for one preliminary study at 7T [1]. In this work we evaluated the feasibility to quantify ^{13}C labeled of glutamate and glutamine in the brain using ^{13}C NMR spectroscopy *without* the application of ^{1}H decoupling during acquisition.

Methods

Four male Sprague-Dawley rats were infused with labeled glucose (either [1-^{13}C] or [1, 6-$^{13}C_2$]) based on a protocol used previously [2] under morphine sulfate anesthesia (50mg/kg). *In vivo* ^{1}H-localized ^{13}C NMR spectra from the brain (VOI of 400µl) were measured on a 9.4T horizontal magnet using a semi-adiabatic DEPT sequence. In all experiments, proton decoupling (WALTZ-16) was switched on and off in an interleaved fashion after every block of 5.33min. *In vivo* spectra were analyzed using LCModel with J-couplings values from one-bond and long-range CH in glutamate, glutamine and aspartate determined from high-resolution ^{13}C spectra (acquired at 14.1T; temperature=37°C, pH=7.15). The accuracy and precision of LCModel quantitation of undecoupled and decoupled data was assessed by Monte-Carlo simulation.

Results

Undecoupled ^{13}C NMR spectra exhibit extensive splitting due to one-bond and long-range proton-carbon coupling constants. For example, undecoupled spectrum of [4-^{13}C] glutamate shows 12 distinct resonances (i.e. triplet of quadruplets) due to the two directly attached protons at C4 positions ($^{1}J_{CH}$=126.8 Hz) and the long-range couplings from protons at C2 and C3 carbon positions ($^{2}J_{CH}$=4.5 Hz and $^{3}J_{CH}$=4.3 Hz). The resonances corresponding to glutamate (C4, C3, C2), glutamine (C4, C3, C2) and aspartate (C2, C3) were clearly observed in both proton-decoupled and undecoupled *in vivo* ^{13}C spectrum, although the latter has more overlapping peaks primarily due to the one-bond J_{CH} coupling constant and the peak S/N was lower by about 2.5. The LCModel fit of the undecoupled *in vivo* spectrum, 3.5 hours after glucose infusion, showed nearly flat residuals, with small contributions from low concentrations amino acids such as GABA not taken into account at present in the basis set (Figure 1). The *in vivo* time courses of undecoupled data (open symbols) were in excellent agreement with that of proton-decoupled (filled symbols) for both glutamate and glutamine resonances (Figure 2), although the standard deviation of the metabolites concentrations was increased with no decoupling. Quantification of undecoupled spectra resulted in a coefficient of variation of 35% to 91% higher than that of decoupled spectra depending on the carbon resonance of interest, in agreement with Monte-Carlo simulations when administrating [1, 6-$^{13}C_2$] glucose. Similar results were obtained during infusion of [1-^{13}C] glucose (not shown).

Discussion

This study shows the feasibility of acquiring and accurately quantifying undecoupled ^{13}C spectra using LCModel with prior knowledge of chemical shifts and J-coupling values. The use of prior information on J-coupling and fitting the multiplets simultaneously in the LCModel improves accuracy of quantification so that errors in the quantification is significantly less than the loss in peak S/N suffered in the absence of decoupling. Using this approach the experimental setup can be simplified by alleviating constraints imposed on electrical isolation between ^{13}C and ^{1}H RF channels and the use of RF filters. Human studies are restricted at high fields due to SAR limitation imposed by RF decoupling and also the inhomogeneous B_1 field distribution which precludes the exact determination of the local SAR level in the brain due to subjects' anatomical variability. Therefore the proposed technique of acquiring undecoupled ^{13}C spectra is a safer approach since power deposition is significantly reduced. Furthermore some of the signal loss when not applying decoupling can be recovered by reducing the repetition time. In addition data could be collected anywhere in the brain without risk of damaging low-perfused tissues such as the eyes. In conclusion, the methodology of acquiring ^{13}C NMR *without* ^{1}H decoupling will be useful to study human brain metabolism at ultrahigh fields (> 4T).

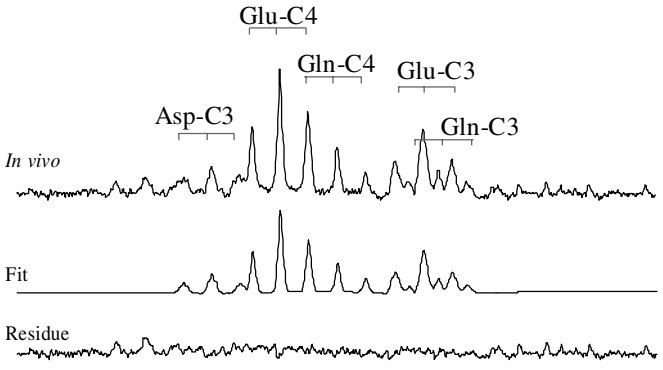

Figure 1: LCModel fit of the summed *in vivo* undecoupled ^{13}C spectrum. From top to bottom: the *in vivo* spectrum, the best fitted spectrum, the residue left after subtracting the reconstructed spectrum from the original one.

References

1. Gruetter R et al. Proc. Intl. Soc. Mag. Reson. Med. 2001; 9: 627.
2. Henry P-G et al. Magn. Reson. Med. 2003; 50: 684-692.

Acknowledgements

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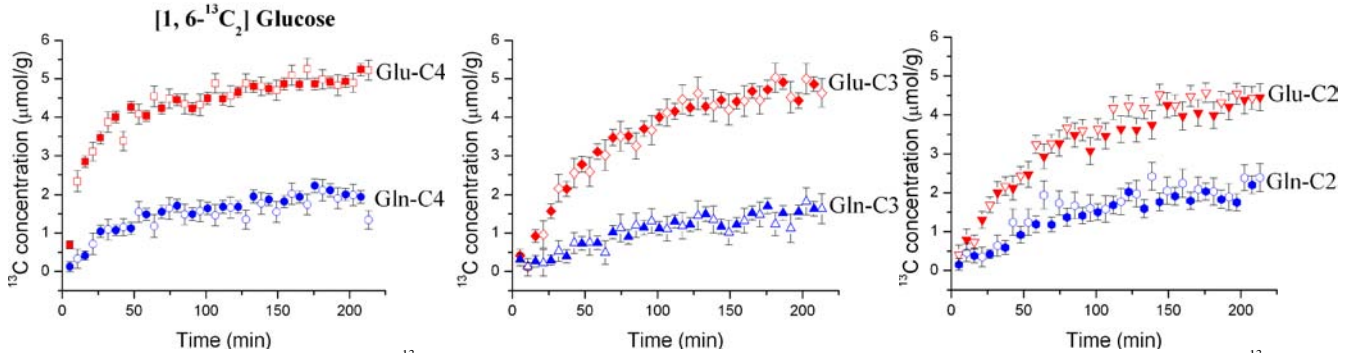

Figure 2: *In vivo* time course of incorporation of ^{13}C labels into C2, C3 and C4 glutamate and glutamine in the rat brain after administration of [1, 6-$^{13}C_2$] glucose. Filled and open symbols represent decoupled and undecoupled data respectively.