Uncovering Hidden In Vivo Resonances Using 1D-TOCSY-LASER Spectroscopy

M. Marjanska[1], P-G. Henry[1], P. J. Bolan[1], R. Gruetter[1], K. Ugurbil[1], M. Garwood[1]

[1]Center for Magnetic Resonance Research and Department of Radiology, University of Minnesota, Minneapolis, Minnesota, United States

Introduction

Low concentration metabolites in in vivo proton NMR spectra are often obscured by very strong resonances, e.g. glucose by water and lactate by lipids (in tumors). It has been proposed for biological systems that the recovery of underwater resonances that have been eliminated during water suppression can be accomplished through magnetization transfer using scalar or dipole interactions[1]. The purpose of the present work was to determine the feasibility of using polarization transfer between coupled spins for detection of resonances while eliminating strong overlapping signals.

Methods

The new pulse sequence (Fig. 1) has been designed for single shot editing which combines 1D-TOCSY with LASER localization[2]. Following water suppression with VAPOR, all resonances are excited using an adiabatic half passage (AHP). A frequency selective 180° gauss pulse together with three coherence selective gradients applied on one axis (dark gray shading) only refocus resonances within the bandwidth of that pulse. Then during the mixing period, a train of pulses (adiabatic tanh/tan (250 μs) pulses with mlev-16 phase cycling scheme) is applied to transfer the magnetization through homonuclear J-coupling. The filtering of the unwanted resonances comes from a gauss pulse, the coherence selection gradients, and the length of the mixing time. The LASER sequence that follows provides 3D-localization (stretched hyperbolic-secant-inversion (HS8) (2 ms) pulses). All the pulses except for pulses used in water suppression and gauss pulse are adiabatic.

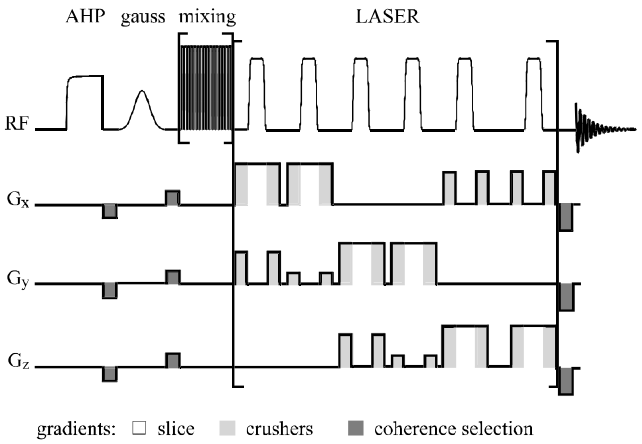

Figure 1. 1D-TOCSY-LASER sequence.

In vivo ^{1}H 1D-TOCSY-LASER edited spectra were recorded at 9.4 T (31 cm horizontal bore) magnet equipped with Varian INOVA console. The pulse sequence was optimized for the detection of the proton bound to C1 β-glucose. The center of the 5 ms gauss pulse was placed at 3.43 ppm to selectively refocus the source spin, a proton bound to C2 β-glucose which is J-coupled to the target spin. The mixing time was set to 63 ms (1/2J) according to the J-coupling between the coupled partners (between protons bound to C1 and C2 β-glucose).

Following an overnight fast, seven male Sprague-Dawley rats were intubated and both femoral veins and arteries were cannulated for glucose infusion and blood sampling. Blood gases and glycemia were measured every 15 minutes to ensure stable physiological conditions. During the course of the experiment the plasma glucose level was rapidly increased from ~5 mM to ~20 mM and maintained at this level for the duration of NMR measurement.

Results and Discussion

Without editing, the resonance of proton bound to C1 β-glucose is not observable due to the very strong water signal that resonates at the same frequency. In the 1D-TOCSY-LASER technique, water is suppressed to the noise level due to VAPOR and the narrow band-width of a frequency selective gauss pulse. Using this technique, the resonances from proton bound to C1 β-glucose (4.64 ppm) and to C1 α-glucose (5.23 ppm) were consistently observed (Fig. 2) in all animals. The time course during the infusion has been obtained to validate the fact that the signal observed at 4.64 ppm comes from β-glucose. Since the spectrum in Fig. 2 was obtained using mixing time optimized for β-glucose, the relative ratio of β- to α-glucose is not 6 to 4. Assignment of the resonance was reinforced by the disappearance of it in post-mortem.

It has been demonstrated that the considerably weaker signal of β-glucose can be detected under water. This single shot technique can be potentially used for detection of any metabolites that have J-coupled partners. Particularly useful application would be to obtain information about lactate (1.32 ppm) under lipids in tumors.

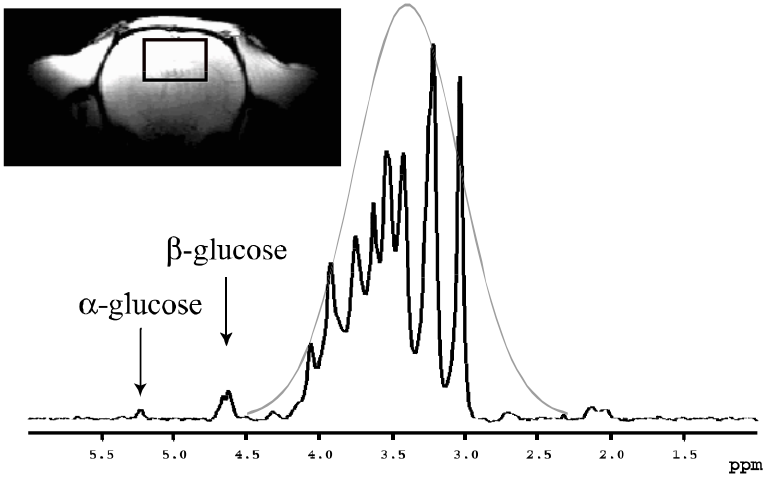

Figure 2. (a) Rat brain image obtained with gradient echo sequence. The bo shows the position of the localized volume (133 μL). (b) ^{1}H spectrum obtaine with 1D-TOCSY-LASER editing after 30 minutes of glucose infusion (plasm glucose concentration was 21 mM) with baseline-correction and 10-Hz lin broadening. Repetition time used = 4 s, 512 scans. The profile of the selectiv gauss pulse is displayed using a light-gray line.

Acknowledgements

The authors would like to thank D. Koski and K. Yue for technical support. This work was supported by P41 RR08079, WM Keck Foundation, Mind Institute, RO1 NS38672, RO1 NS42005, JDRF, and RO1 CA92004.

References

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