Diffusion-weighted Spectroscopy of ^{13}C-Labelled Lactate in Rat Glioma *In Vivo*

Josef Pfeuffer, Joseph Lin, Kamil Ugurbil, Michael Garwood
Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, MN, USA

Purpose

The purpose of this study was to demonstrate the feasibility of diffusion-weighted {^{1}H-^{13}C} spectroscopy *in vivo* and to examine the multi-exponential diffusion characteristic of ^{13}C-labelled, metabolically-active lactate in a rat tumor model *in vivo*.

Introduction

Due to the low concentration of cerebral metabolites, diffusion-weighted ^{1}H NMR spectroscopy is difficult to perform *in vivo*. Only few studies of diffusion-weighted ^{13}C spectroscopy were reported *in vitro* with very long acquisition times not possible *in vivo* [1]. In this study, indirect ^{1}H detection of ^{13}C label with the ACED sequence (*'adiabatic carbon editing and decoupling'*) is used to measure, for the first time, diffusion attenuated signals of ^{13}C-labelled lactate *in vivo* at very large *b* values. Diffusion experiments with ^{13}C-labelled lactate are expected to provide valuable information regarding its compartmentation in tumors.

Methods

Diffusion-weighted ^{13}C-edited ^{1}H-detected NMR spectra were acquired at 9.4 T (Magnex/Varian) based on the ACED-STEAM sequence described previously [2]. Diffusion gradients were applied in the TE/2 periods (δ = 8 or 5 ms, t_D = 120 ms, G variable) to achieve *b* values from 0 to 50 ms/μm^2. Male Fischer rats were injected with 9L glioma cells. Voxel of ~60 μL volume were chosen to include the whole tumor tissue. 100% [1-^{13}C] enriched glucose was continuously infused i.v., which was metabolized to [3-^{13}C] lactate in the tumor.

Results

Phantom experiments were performed on a 20 mM [3-^{13}C] lactate solution at 23°C. Carbon-13 signals were inverted with an editing pulse during TM (Fig. 1a). Subtraction of alternately recorded spectra (see Fig. 1a, 1b) yielded proton signals of lactate connected to [3-^{13}C], which are more sensitive than direct ^{13}C detection. With decoupling in the ^{13}C channel, single resonance proton spectra of lactate were obtained representing total lactate concentration (^{12}C+^{13}C, Fig. 2a) or solely ^{13}C lactate (Fig. 2b). In addition to ACED, diffusion weighting was applied from *b* = 0 to 1.9 ms/μm^2 (see Fig. 1+2, 8 scans each), whereby strictly mono-exponential attenuation curves were found for {^{1}H-^{12}C} and {^{1}H-^{13}C} signals.

In the rat glioma tumor *in vivo*, signal from [3-^{13}C] lactate could be observed up to very large diffusion weighting of *b* = 50 ms/μm^2 (Fig. 3). ^{13}C fractional enrichment of lactate was about 70% after 1 hour of [1-^{13}C] glucose infusion. The apparent diffusion coefficient was ~0.10 μm^2/ms in the range *b* = 0 to 5 ms/μm^2. At very large *b* values, bi-exponential curves were found with $D_{1,2}^{app}$ = (0.2, 0.01) μm^2/ms and volume fractions p_1:p_2 ~ 1:1.

Discussion

In several respects the use of [1-^{13}C] glucose infusion is advantageous for the detection of [3-^{13}C] lactate in a tumor model. Only signal from metabolically-active tissue (metabolizing glucose to lactate) is observed giving an intrinsic selectivity and localization in the tumor. The editing technique eliminates unwanted lipid signals often found concomitant with the lactate signal in ^{1}H NMR spectra of tumors. The high concentration and fractional enrichment of lactate is advantageous for spectroscopic methods. Multi-exponential diffusion attenuation can be used to distinguish intra- from extracellular signals due to a different diffusion characteristic (restricted and hindered diffusion). Based on a comparison with metabolites known to be intracellular, the intra/ extracellular compartmentation of lactate in tumor appears similar to a previous study focused on glucose in healthy rat brain [3].

References

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3. Pfeuffer, J et al., *Proc ISMRM*, pg. 564; 1999.

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