In vivo Hyperpolarized ^{13}C MRS/MRSI Using ^{13}C-lactate as the Pre-polarized Substrate

A. P. Chen[1], J. Kurhanewicz[1], R. Bok[1], D. Xu[1], D. Joun[1], V. Zhang[1], S. J. Nelson[1], R. E. Hurd[2], and D. B. Vigneron[1]

[1]Radiology, UCSF, San Francisco, CA, United States, [2]GE Healthcare, Menlo Park, CA, United States

Introduction: It has been shown by using $^{13}C_1$-pyruvate as the substrate for hyperpolarized ^{13}C MRS/MRSI experiment, real time cellular metabolism can be studied in normal and diseased tissues in vivo (1-3). These studies have shown the ability to detect the metabolic conversion of the hyperpolarized ^{13}C-pyruvate into ^{13}C-lactate, ^{13}C-alanine and ^{13}C-bicarbonate after in vivo injection in animal models. However, if ^{13}C-lactate were the hyperpolarized substrate, ^{13}C MRS/MRSI could then probe the reverse enzymatic conversion of hyperpolarized ^{13}C lactate into the unlabeled pyruvate pool. The goal of this study was to develop a hyperpolarized MR probe based on $^{13}C_1$-lactate as the substrate for *in vivo* ^{13}C MRS/MRSI studies and to determine if metabolic products could be detected following injection in animal models.

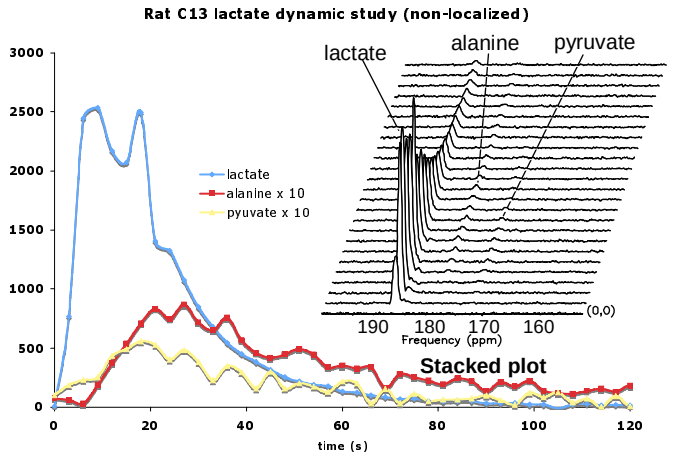


Figure 1. Dynamic MRS data from a normal rat after injection of hyperpolarized ^{13}C lactate. Both a stacked plot of individual spectra from each time points (first 25 time points, top right) and a time course graph (bottom left) of the ^{13}C lactate, ^{13}C alanine and ^{13}C pyruvate peak amplitude were shown.

Materials and Methods: Polarization of ^{13}C lactate**:** A HyperSense DNP polarizer (Oxford Instruments, Abingdon, UK) was used in this study. The preparation for pre-polarization developed in this project was a mixture of $^{13}C_1$-lactate (Isotec, Miamisburg, OH), water, DMSO and OX63 trityl radical (Oxford Instruments, Abingdon, UK). The mixtures contained 38.5% ^{13}C-lactate 30% DMSO and the concentration of the trityl was 15mM. A normal saline and 100mg/L sodium EDTA solution was used as the dissolution medium. The ^{13}C-lactate concentration in the hyperpolarized lactate solution was 44 mM. Polarization levels achieved in these studies were 6.9% - 12.4% (mean 10%).

Hardware, MRS/MRSI, and animals**:** All studies were performed using a 3T GE Signa™ scanner (GE Healthcare, Waukesha, WI) and custom built ^{1}H/^{13}C dual-tuned rat/mouse coils. ^{13}C dynamic MRS studies were performed in five healthy Sprague-Dawley rats, a C57BL6/FVB male wild type mouse and Transgenic Adenocarcinoma of mouse prostate (TRAMP) mice using a double spin-echo pulse sequence with a non-selective 5 degree flip angle RF excitation pulse and a pair of 180 degree hyperbolic secant refocusing pulses; TE/TR used was 35ms/3s (3-4). 3D ^{13}C MRSI data were acquired in both rats and TRAMP mice using a double spin-echo pulse sequence with a slice selective small tip angle excitation pulse and a flyback echo-planar readout trajectory (3-4).

Results: Representative data in Figure 1 shows a stacked plot of dynamic ^{13}C data (first 25 time points, each 3 seconds apart) and a graph of the signal amplitude vs time from one of the dynamic studies in healthy rats. Resonances for ^{13}C lactate, ^{13}C alanine, and ^{13}C pyruvate were observed in the spectra (Fig. 1). Pyruvate signal appeared in the spectra prior to alanine signal, and pyruvate time to peak was also earlier compare to that of alanine (7.0s vs 14.4s on average). ^{13}C bicarbonate resonance was also observed in the dynamic MRS studies in healthy rats (Fig. 2). In one of the TRAMP mouse studied with late stage tumor (Fig. 3), the 3D MRSI data demonstrated similarly high level of ^{13}C lactate in tumor, kidney and liver, while the metabolic product from ^{13}C lactate was observed only in liver and kidney voxels.

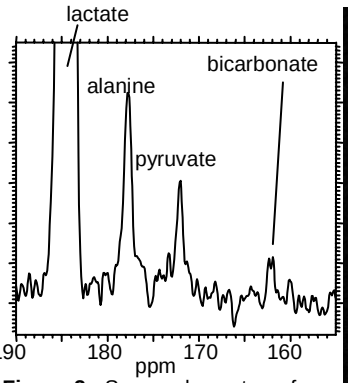
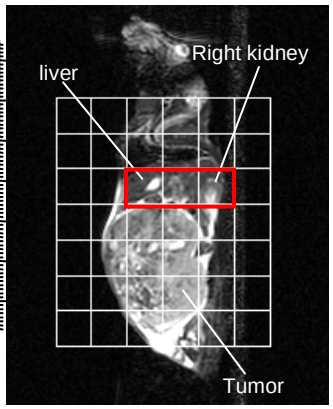


Figure 2. Summed spectrum from the first 16 time points of a dynamic MRS study in a healthy rat. In addition to ^{13}C lactate, alanine and pyruvate, ^{13}C bicarbonate was also observed.



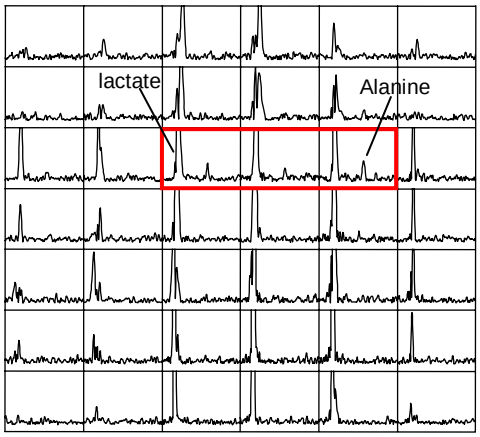


Figure 3. Sagittal T2-weighted FSE image from a TRAMP mouse (left) and the corresponding ^{13}C MRSI data (right). Similar levels of ^{13}C lactate were observed in regions of tumor compare to voxels containing kidney and liver, while metabolic products of ^{13}C pyruvate and ^{13}C alanine were only observed in kidney and liver, not in the tumor.

Discussion: This study demonstrated feasibility of using $^{13}C_1$-lactate as a substrate for pre-polarized MRS and MRSI *in vivo*. Hyperpolarized $^{13}C_1$-lactate MR provides a unique opportunity to study the conversion of lactate to pyruvate *in vivo* and to detect the secondary conversions to alanine and bicarbonate through pyruvate. When applied to a mouse model of prostate cancer, the tumor region demonstrated high lactate uptake but undetectable levels of the metabolic products of ^{13}C pyruvate and ^{13}C alanine.

References:

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