Kinetic Modeling of Hyperpolarized $^{13}C_1$-Pyruvate Metabolism Using Dynamic Magnetic Resonance Spectroscopy

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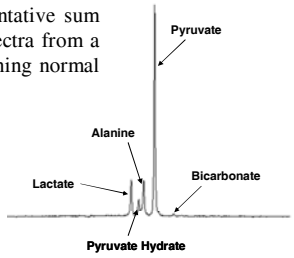
INTRODUCTION:

Dynamic nuclear polarization (DNP) has been shown to increase ^{13}C signal intensity by more than 10,000-fold[1]. By estimating metabolite levels from dynamic hyperpolarized ^{13}C MR spectroscopy, it is now possible to monitor real time changes in tissue parameters. Using normal rats, a modeling method that estimates rate constants for ^{13}C metabolism was evaluated in terms of robustness of the fitted parameters. This method was further tested on a transgenic adenocarcinoma of the mouse prostate (TRAMP) model in an attempt to assess tumor progression.

METHODS:

Using a 3T GE scanner with custom designed multinuclear RF coils, dynamic spectroscopic data were acquired from both normal rats and a TRAMP mouse with repeated 5 degree RF excitations every 3 seconds for a total of 189 seconds. Hyperpolarized $^{13}C_1$-pyruvate (~20% polarized) was injected over a 12 second duration for all studies. A 15mm slice through a rat kidney was used to acquire three dynamic data sets from different rats (2048 pts, BW=5kHz) for kinetic modeling. The same sequence was also used to acquire two dynamic datasets in one TRAMP mouse 22 days apart with a 10mm slice through tumor. Free induction decays were apodized with a 10Hz Lorentzian filter and then fourier transformed.

Figure 1. Representative sum of dynamic ^{13}C spectra from a 15mm slice containing normal rat kidney.



The spectral data showed five peaks (see Fig.1) corresponding to lactate, alanine, pyruvate, pyruvate hydrate, and bicarbonate. Absolute values of peak heights for lactate, alanine, and pyruvate were used for kinetic modeling of ^{13}C metabolism. Each metabolite peak height was assumed proportional to concentration with an additional fixed T1 decay term. All metabolites were assumed to be in one pool with metabolism, RF excitation, and T1 decay being the key factors in driving signal kinetics. The following equations show how the signal was modeled (the lactate model was used for alanine fitting as well):

$$C_{pyr}(t)=\begin{cases}\dfrac{rate_{inj}}{k_{pyr}}\left(1-\exp(-k_{pyr}t)\right) & , \quad t_{inj\_pyr}\le t<t_{end}\\ C_{pyr}(t_{end})\exp(-k_{pyr}t) & , \quad t\ge t_{end}\end{cases}$$

$$C_{lac}(t)=\begin{cases}rate_{inj}k_{pyr\to lac}\left(\dfrac{1}{k_{pyr}k_{lac}}+\dfrac{\exp(-k_{pyr}t)}{k_{pyr}(k_{pyr}-k_{lac})}+\dfrac{\exp(-k_{lac}t)}{k_{lac}(k_{lac}-k_{pyr})}\right) & , \quad t_{lac}\le t<t_{lac\_end}\\ \dfrac{C_{pyr}(t_{end\_lac})\left(\exp(-k_{pyr}t)-\exp(-k_{lac}t)\right)}{k_{lac}-k_{pyr}}+C_{lac}(t_{end\_lac})\exp(-k_{lac}t) & , \quad t\ge t_{lac\_end}\end{cases}$$

$$S_{pyr}(t)=C_{pyr}(t)\exp\left(-t\left(\frac{1}{T_1}+\frac{1-\cos\alpha}{TR}\right)\right) \quad , \quad t>t_{inj\_pyr}$$

$$S_{lac}(t)=C_{lac}(t)\exp\left(-t\left(\frac{1}{T_1}+\frac{1-\cos\alpha}{TR}\right)\right) \quad , \quad t>t_{inj\_pyr}$$

Three parameters ($rate_{inj}$, k_{pyr}, and t_{inj_pyr}) were first fit using the equation for pyruvate signal (S_{pyr}) with the assumption that reverse metabolism was negligible[2]. The signal equation was used to estimate concentration by inputting fixed values for T1 (15sec)[1] and the known constant flip angle (α=5°) and repetition time (TR=3sec). Lactate and alanine data were then both fit with the model for lactate signal (S_{lac}). Three parameters were estimated in each fit: $k_{pyr\text{-}lac}$ (or $k_{pyr\text{-}ala}$), k_{lac} (or k_{ala}), and t_{lac} (or t_{ala}). It should be noted that the T1 decay term starts at the same time for all metabolites (t_{inj_pyr}). This is necessary because T1 decay is constantly acting on all ^{13}C nuclei. Conversions of pyruvate to lactate ($k_{pyr\text{-}lac}$) and pyruvate to alanine ($k_{pyr\text{-}ala}$) were analyzed to see the robustness of the model fitting technique in the normal rat kidney. These parameters were also used to examine whether there were differences in metabolism of the TRAMP mouse as the tumor progressed.

Table 1. Metabolic rate constants and standard errors for normal rat kidney and TRAMP mouse.

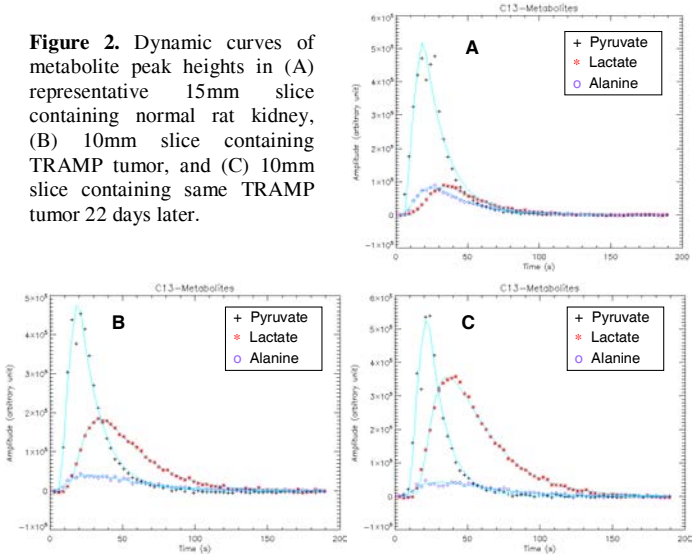
Normal Rat Kidney Metabolic Rate Constants (s^{-1})				
Rat	$k_{pyr\text{-}lac}$	SE_{kpl}	$k_{pyr\text{-}ala}$	SE_{kpa}
1	0.0225	1.34E-03	0.0203	1.22E-03
2	0.0225	6.76E-04	0.0120	9.80E-05
3	0.0324	7.64E-04	0.0150	3.91E-04
Mean	0.0258	9.25E-04	0.0158	5.69E-04
SD	0.0057		0.0042	

TRAMP Mouse Metabolic Rate Constants (s^{-1})				
Day	$k_{pyr\text{-}lac}$	SE_{kpl}	$k_{pyr\text{-}ala}$	SE_{kpa}
0	0.0434	5.01E-04	0.0039	3.43E-04
22	0.0730	1.30E-03	0.0039	3.56E-04

RESULTS:

Estimates for $k_{pyr\text{-}lac}$ and $k_{pyr\text{-}ala}$ in three normal rat kidney datasets showed mean values of 0.0258 and 0.0158 s^{-1}, with mean relative standard error of 3.77 and 3.14%, respectively. The standard deviations of the rate constants in the rats showed CV's of 22.2 and 26.9%, respectively. Conversion of pyruvate to lactate was much higher and conversion of pyruvate to alanine was much lower in the TRAMP mouse than in normal rat kidney. After 22 days, the same TRAMP tumor showed a further increase in conversion of pyruvate to lactate but a similar difference in conversion of pyruvate to alanine when compared to normal rats (see Table 1).

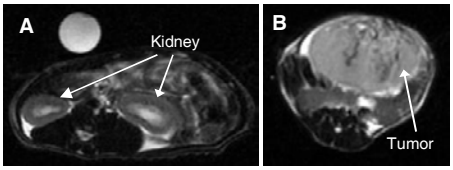
Figure 2. Dynamic curves of metabolite peak heights in (A) representative 15mm slice containing normal rat kidney, (B) 10mm slice containing TRAMP tumor, and (C) 10mm slice containing same TRAMP tumor 22 days later.



CONCLUSION:

These results show that by using a relatively simplistic model of the changes in MR signal intensity of hyperpolarized ^{13}C metabolites it is possible to obtain robust estimates of conversion rates from $^{13}C_1$-pyruvate to lactate and alanine. The results also suggest that as a TRAMP tumor progresses, lactate production increases. The T1 values at 3T may be different from the 15s reported by Golman, et al. at 1.5T. However, fixed T1 values do not have a strong effect on relative metabolic rates between subjects, and similar results were obtained using T1 values of 30s.

Figure 3. Representative images of slice used for dynamic spectroscopy in (A) normal rat kidney, and (B) tumor in TRAMP mouse.



REFERENCES AND ACKNOWLEDGEMENTS: This study was supported by UC Discovery grants LSIT01-10107 and ITL-BIO04-10148, in conjunction with GE Healthcare. [1] Golman K, et al. PNAS. Jul 103(30), 11270-11275 [2] Terpstra M, et al. Cancer Research. 1998 Nov (58) 5083-5088.