Dynamic and High-Resolution Metabolic Imaging of the Rat Brain *In Vivo* Using Hyperpolarized [1-^{13}C]-Pyruvate

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Introduction

Hyperpolarized [1-^{13}C]-pyruvate has been widely applied to the investigation of cancer and cardiac metabolism *in vivo* [1], but rarely to study brain metabolism. We have previously reported results using single-time point phase-encoded chemical shift imaging (CSI) [2] suggesting that transport of pyruvate through the blood-brain barrier (BBB) is sufficiently fast to detect metabolic products. Here we apply time-resolved spiral chemical shift imaging (spCSI) [3] to investigate the brain uptake dynamics. Additionally, metabolic imaging at higher spatial resolution was performed to better characterize the spatial origin of the metabolite signals.

Materials and Methods

All measurements were performed on a clinical 3T MR scanner (GE Healthcare, Waukesha, WI) with a high-performance insert gradient coil (500 mT/m, 1865 mT/m/ms, 160-mm inner diameter) [4]. A custom-built dual-tuned (^{1}H/^{13}C) quadrature coil (∅ = 50 mm) was used for both RF excitation and signal reception. Healthy male Wistar rats (197 - 257 g) were anesthetized with 1-3% isoflurane in oxygen (~1.5 L/min). The rats were injected in a tail vein with 2.4-3 mL of an 80-mM solution of [1-^{13}C]-pyruvate that was hyperpolarized via dynamic nuclear polarization (~20% liquid state polarization) using HyperSense (Oxford Instruments Molecular Biotools, Oxford, UK).

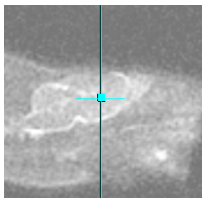

Fig. 1: Sagittal ^{1}H-MRI indicating the CSI slice position.

Dynamic metabolic imaging was performed using single-shot spCSI with a nominal in-plane resolution of 2.7 mm (FOV = 43.5×43.5 mm^2, 16×16 matrix, SW = 280 Hz, T_{acq} = 125 ms). A 10-mm axial (animal coronal) slice through the front and middle of the rat brain was excited as shown in Fig. 1. Sixteen data sets were acquired every 3 s starting 9 s after begin of injection. A variable-flip-angle scheme $\theta_i = \text{atan}\left(1/\sqrt{16-i}\right)$ [5] was applied to take into account the depletion of the magnetization due to the multiple excitations. To reduce partial volume effects and spatial blurring of vasculature signal originating outside the brain, high-resolution (1.5-mm nominal in-plane resolution) measurements at the 12-s and 24-s marks were performed (3 spatial interleaves, FOV = 48×48 mm^2, 32×32 matrix, 5-mm slice thickness, T_{acq} = 375 ms). A 35°-45°-90° flip-angle scheme was applied to increase the SNR by utilizing all longitudinal magnetization at that time point. Each measurement was repeated 2-4 times per animal to increase SNR and assess reproducibility.

After apodization of the undersampled spCSI data, "spectral tomosynthesis" reconstruction as described in [3] was performed. The data were gridded followed by 2D-FFT. Metabolic images of pyruvate (Pyr), lactate (Lac), alanine (Ala), and bicarbonate (Bic) were calculated by integrating the signal around each peak in absorption mode.

Results and Discussion

Representative metabolic images of the four metabolites from a single rat averaged over all 16 time points and three injections are shown in Fig. 2. Whereas Pyr and Ala have the highest signal intensity outside the brain, both Lac and Bic were detected predominantly inside the brain. In particular for Bic, the highest signal appears to be in the cortical structures. Figure 3 depicts the time course for Pyr, Lac, and Bic from a region-of-interest (ROI) in the cortex suggesting a slower production of Bic compared to Lac. Note that in particular for the early time points the Pyr signal is affected by contributions from high Pyr in the sagittal sinus and the interior blood vessels. The data from 3 injections into the same rat were averaged and the standard deviations for each time point indicate high reproducibility. The results from the high-resolution metabolic imaging experiment with the expected lower SNR (averaged over 4 injections) in Fig. 4 show similar metabolite distributions as for the averaged dynamic data, but with reduced contamination from vascular metabolite signals. Higher Lac and Bic in cortical regions could be due to higher transport of Pyr through the BBB, faster substrate-to-product conversion, or both.

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References

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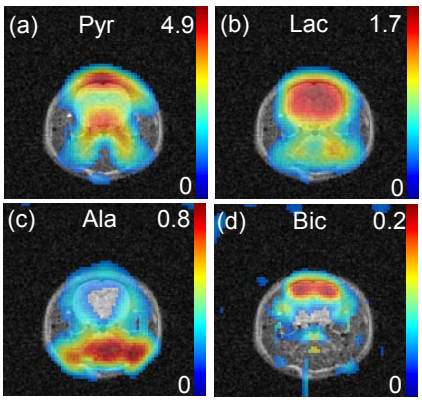

Fig. 2: Metabolic images of (a) Pyr, (b) Lac, (c) Ala, and (d) Bic from a single rat acquired with dynamic spCSI. The images (averaged over all 16 time points and 3 injections) are superimposed onto ^{1}H-MRI.

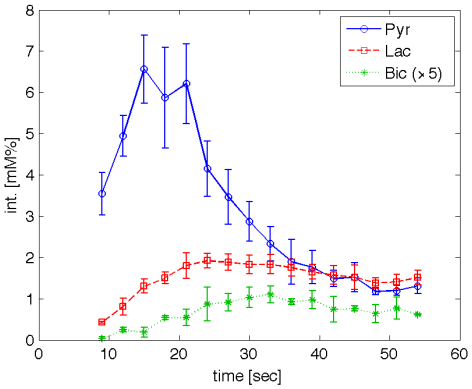

Fig. 3: Representative time course of Pyr (blue), Lac (red), and Bic (green, multiplied by 5) from an ROI predominantly in the cortex. Data were averaged over 3 injections and the error bars indicate the standard deviations across the 3 measurements.

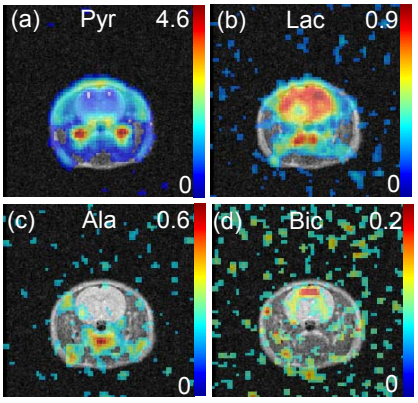

Fig. 4: High-resolution metabolic images (24-s mark) of (a) Pyr, (b) Lac, (c) Ala, and (d) Bic from a 5-mm slice through a rat brain. Data from 4 injections were averaged.