Dynamic spectroscopy and modeling of response to 2-deoxyglucose using hyperpolarized [1-13C]-pyruvate

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Introduction

Tumor cells fulfill their energetic requirements primarily through aerobic glycolysis rather than mitochondrial respiration. As a result, therapeutic agents such as 2-deoxyglucose (2DG) offer a promising approach to intervention. Methods for early evaluation of biological efficacy and response to therapy could provide rapid feedback, promote personalized therapeutic plans, and inform on the development of newer anti-metabolic compounds. Hyperpolarized (HP) tracers (1) enable a powerful new platform for characterization of disease in vivo with unprecedented spatial and chemical specificity. Spectroscopic imaging of the distribution and chemical fate of HP-[1-^{13}C]-pyruvate may offer powerful insight into changes in tumor metabolism (2). In this work we use a very simple pulse-acquire strategy to explore the temporal dynamics of HP-pyruvate and its chemical fate, and to evaluate the feasibility of dynamic magnetic resonance spectroscopy (MRS) to detect changes in tumor metabolism due to 2DG in murine models of thyroid cancer and glioblastoma.

Methods

All experiments were approved by our Institutional Animal Care and Use Committee, which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. All data was acquired using a 7T Biospec USR70/30 small animal imaging system (Bruker Biospin MRI, Billerica, MA) with four receive channels. All data analysis was performed using Matlab (The Mathworks, Natick, MA).

Dynamic spectra were acquired from cohorts of animals bearing glioblastoma (U87) or anaplastic thyroid carcinoma (ATC). Ten days after implantation of HTH83 cells into the right thyroid lobe, animals with ATC were given sham therapy (N=3) or 2DG (500 mg/kg IP; N=4) and scanned two hours later. Animals bearing U87 (N=5) were scanned 29 days after implantation, then scanned again one day later, one hour after receiving two hourly doses of 2DG (2000 mg/kg by oral gavage). Localizing and anatomic reference scans were collected using the 1H channel of a dual-tuned 13C/1H volume coil. 13C signal was excited using the dual-tuned volume coil and measured using a surface coil. A slice-localized pulse-acquire sequence with a 5kHz spectral bandwidth was acquired every 2s for three minutes, beginning at the same time as injection of 200 uL of 80mM HP sodium pyruvate via tail-vein catheter. The area of peaks corresponding to pyruvate and lactate were calculated to construct time/intensity curves. These curves were normalized by total area for semi-quantitative analysis, and fit to a kinetic model accounting for flux between physical and chemical pools.

Results & Discussion

Dynamic spectroscopy of HP-[1-13C]-pyruvate revealed differences in the rate of conversion of pyruvate into lactate in both groups of treated animals compared to their controls (ATC: P=0.0504; U87: P=0.0796; See Fig 1). Results of this pilot study suggest that kinetic parameters that relate the observed signal to multiple physical and chemical pools can help clarify interpretation of observed changes but will necessitate careful selection of acquisition, reconstruction, and analysis strategies. With both HP-pyruvate and 2DG currently in clinical trial as diagnostic and therapeutic agents, respectively, their synchronized optimization in preclinical models may accelerate translation to improved clinical care.
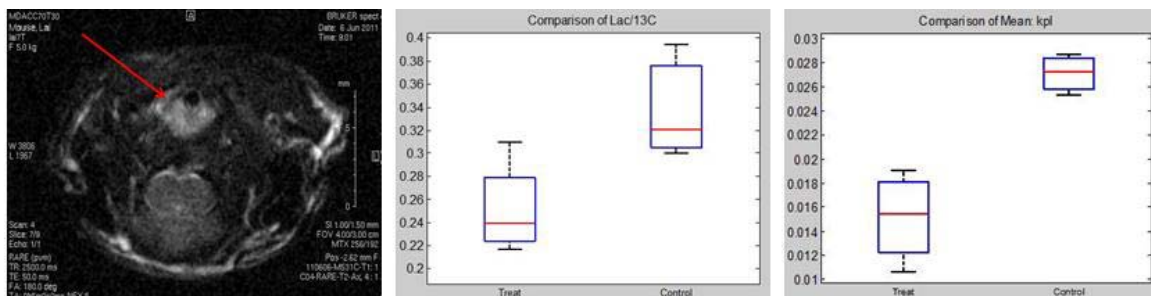

Figure 1: T2-weighted axial image of orthotopic thyroid tumor (left); comparison lactate signal using normalized area under the curve (center, p = 0.0504) and a kinetic model accounting for chemical and physical exchange (right, p < 0.001)

References:
[1] Ardenkjaer-Larsen JH, et al. Proc Natl Acad Sci USA 100(18):10158-63, 2003.
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