Dynamic MRS of hyperpolarized 1-^{13}C pyruvate in brain tumor afflicted mice treated with temozolomide

Teresa Delgado-Goñi[1,2], Eva Monteagudo[3], Miquel E. Cabañas[3], Carles Arús[1,2], and Silvia Lope-Piedrafita[3]

[1]*Department de Bioquímica i Biologia Molecular, Unitat de Bioquímica de Biociències, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Barcelona, Spain,* [2]*Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Cerdanyola del Vallès, Barcelona, Spain,* [3]*Servei de RMN, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Barcelona, Spain*

Introduction: Hyperpolarized [1-^{13}C] pyruvate has been proved to be a promising tool in oncology, where lactate/pyruvate measured ratios have been shown to correlate with disease progression and response to therapy.[1] Most preclinical studies have focused in subcutaneous lymphoma or prostate tumors, but less work has been performed in brain tumors, especially in mice.

Aim: To evaluate the detection of response to therapy in a well characterized mouse brain glioma model using hyperpolarized [1-^{13}C] pyruvate.

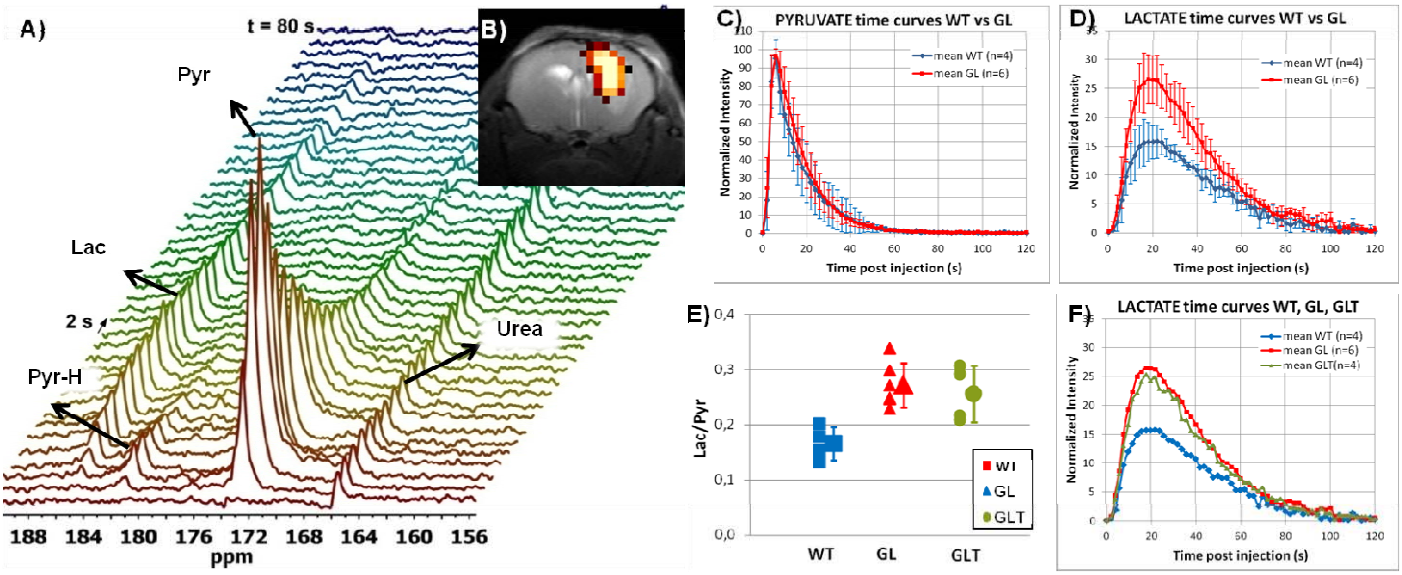
Methods:

Animal Model: fourteen C57BL6 female mice (18-22g) were used in this work. Four mice were used as controls (WT), and the remaining animals harbored a GL261 brain glioblastoma induced as described in [2]. Four of the glioma-bearing mice were treated with temozolomide as in [3]. Mice underwent ^{13}C MRS on day 18±1 post-inoculation.

Magnetic resonance (MR): A sample of [1-^{13}C] pyruvic acid, 15 mM OX63 trityl radical and 1.5 mM Dotarem was hyperpolarized using a HyperSense DNP polarizer for approximately 1 h (≈ 94.1 GHz, 100 mW). The sample was subsequently dissolved in a pressurized and heated alkaline buffer (≈ 4 mL), with a resulting polarization of 18±2% and physiological temperature and pH. Mice were injected through the tail vein 0.01mL/g of the 80 mM hyperpolarized [1-^{13}C] pyruvate solution. ^{13}C-magnetic resonance spectroscopy studies were performed in a 7T Bruker BioSpec 70/30 USR with a ^{1}H/^{13}C surface coil placed on top of the mouse head. ^{13}C-pulse-acquisition spectra were acquired over 3 min after the beginning of the injection (TR, 2s; excitation flip angle, 5º; sweep width, 150kHz; acquired points, 2048; frequency centered on the pyruvate resonance). Spectra were analyzed using AMARES algorithm as implemented in jMRUI software package. Quantitative peak areas were plotted against time.

Results:

Time course ^{13}C spectra following hyperpolarized pyruvate injection (Fig. A) were acquired from WT, treated (GLT) and untreated glioblastoma-bearing (GL) mouse brains. Increased lactate signal from within the tumor region was observed by ^{13}C chemical shift imaging (B). Comparing WT vs GL mice, no-significant differences were observed in the pyruvate time curves of the fitted spectra (Fig. C), however significant differences ($p<0.05$) were detected in the lactate signals from 12s to 50s post-injection (Fig. D). We did not see statistical differences between GL and GLT mice neither in the lactate time curves (Fig F, mean standard deviation error bars not plotted for a cleaner curve visualization) nor in the mean Lac/Pyr ratios (Fig. E) (Lac/Pyr WT: 0.17±0.03, GL: 0.27±0.04, and GLT: 0.26±0.05). Nevertheless, Lac/Pyr ratios of the individual GLT mice seemed to have two separate patterns, one with increased ratios and the other with smaller values, which could indicate different behavior with respect to therapy response variability in the evaluated mice.



Conclusion: Our experimental protocol using ^{13}C MRS with hyperpolarized [1-^{13}C] pyruvate was able to discriminate between WT from GL mice but was not able to detect differences between temozolomide treated and untreated mice. Longitudinal studies, where Lac/Pyr ratios can be normalized to individual initial time points, may be necessary to fully corroborate our preliminary results.

References: [1] Day, *et al*., *Nat Med*. 2007, 13: 1382; [2] Simões *et al*. *NMR Biomed*. 2008, 21: 251. [3] Delgado, *et al.* Proc ISMRM 2010, 18: 2787.