The Improved Detection of 2-Hydroxyglutarate In Gliomas at 7 T Using High-Bandwidth Adiabatic Refocusing Pulses

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Introduction

The IDH1 and IDH2 genes encode for the enzymes isocitrate dehydrogenase 1 and 2, which catalyze the conversion of isocitrate to alpha-ketoglutarate (α-KG) (1). It has been reported that mutations in these genes occur in up to 80% of a variety of glioma sub-types (2) and lead to the production of 2-hydroxyglutarate (2-HG). The non-invasive detection of 2-HG could thus help physicians with differential diagnosis, tumor classification, and prognostic prediction since the mutation greatly improves prognosis.. Prior MRS studies reported the *in vivo* detection of 2-HG in gliomas at 3T (3) and demonstrated its feasibility at 7T (4). In this study, we used a semi-LASER (5) sequence optimized for minimal chemical shift displacement errors (CSDE) and B_1^+ inhomogeneities, and use sequence timings adjusted to optimum 2-HG detection. In comparison with a PRESS sequence, the semi-LASER sequence has two additional refocusing pulses, providing more freedom to manipulate the strongly coupled spin systems of 2-HG and enabling detection of 2-HG with a reduced CSDE.

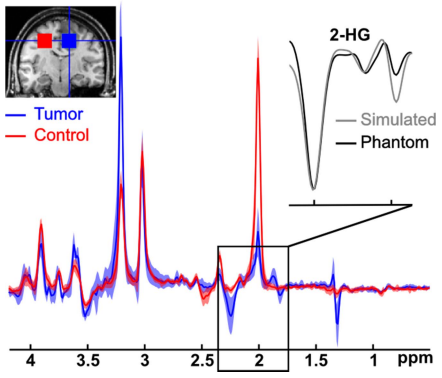

Figure 1. Mean (red and blue) ± standard deviation (shade) of L2 normalized 1H MRS spectra from the tumor and normal brain tissue.

Methods

Five glioma patients with known IDH mutation status were scanned under IRB ethical approval at 7T using a whole body MR system (Siemens, Erlangen) with a Nova Medical 32 channel receive array head-coil. The semi-LASER sequence with VAPOR water suppression and outer volume saturation was modified and optimized for maximum 2-HG signal at TR = 6s and TE = 110 ms (bandwidth of refocusing pulses = 5 kHz). For each patient, spectra were acquired from two voxels (20x20x20 mm^3, 128 transients), one in the tumor and the other in normal brain tissue (Control). Spectra were analyzed with LCModel (6) using basis sets of simulated spectra including 2-HG. An assumed concentration of creatine of 8 μmol/g was used as an internal reference.

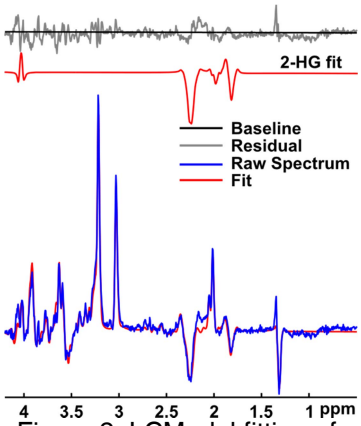

Figure 2. LCModel fitting of spectrum acquired from a tumor voxel.

Results and Discussion

Phantom experiments and density operator simulations of the timing of the semi-LASER sequence were performed at TE 110 ms; one of the multiplets of 2-HG at ~2.25 (H4, H4') had a negative spectral shape (Figure 1). For the *in vivo* results, spectra with good SNR and spectral resolution were consistently obtained from all glioma patients (Figure 1). Due to the negative spectral pattern of 2-HG at a TE of 110 ms, and increased chemical shift dispersion at 7T, the 2-HG signal at 2.25 ppm was clearly discernible in spectra of the tumor voxels whereas no 2-HG signal was observed in the control VOIs (Figure 1). This excellent spectral quality allowed for quantification of the concentration of 2-HG (mean ± SD, 5.92 ± 2.85 μmol/g) in the tumor VOI with a mean CRLB of 15% in only 4 TRs (24 s), whereas in the normal brain tissue the estimated concentration of 2-HG was 0.55 ± 0.32 μmol/g with a mean CRLB of 134% after 11 minutes of acquisition (Figs 2 and 3). The semi-LASER sequence, with a small CSDE and relatively good B_1^+ inhomogeneity insensitivity, was optimized and successfully demonstrated histologically-confirmed 2-HG detection in gliomas at 7T. Whilst a larger sample size is needed to confirm these findings, this pilot study indicates that due to substantial gains in signal-to-noise-ratio and chemical shift dispersion at 7T the proposed acquisitions scheme can offer detection of subtle quantitative changes in 2-HG that may take place during tumour progression or treatment response.

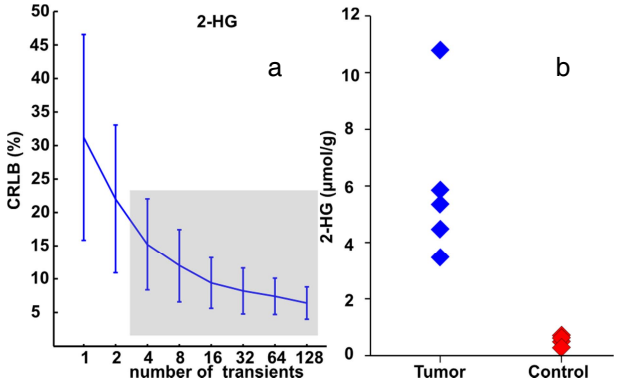

Figure 3. (a) Comparison of CRLBs of 2-HG as a function of the number of transients. (b) Concentrations of 2-HG in tumor and control VOIs.

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References

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