Editing Cancer Biomarker, 2-hydroxyglutarate, with a Novel Proton Magnetic Resonance Spectroscopy

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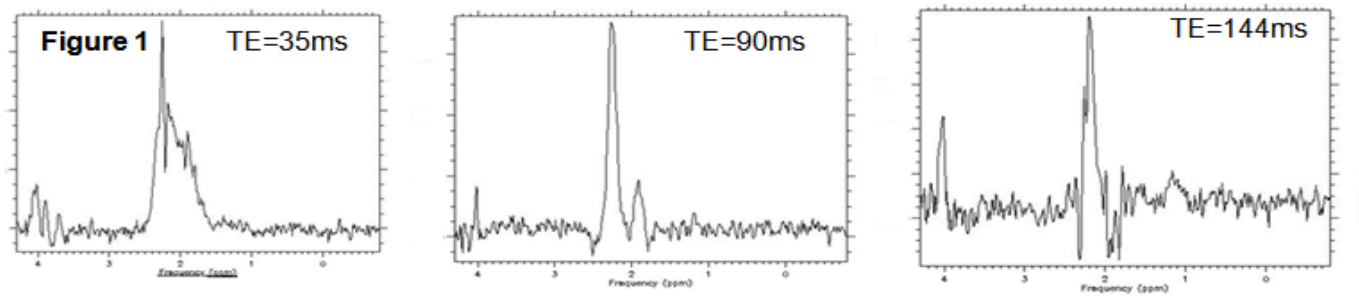
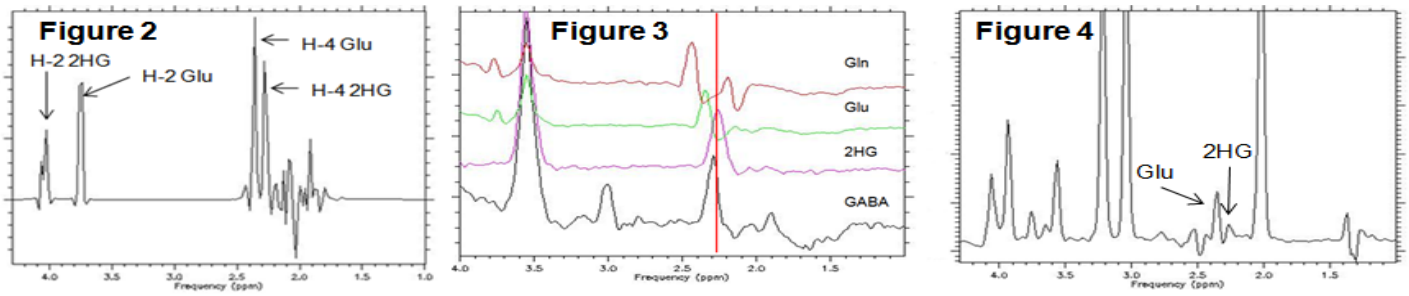
Background: The mutations of cytosolic isocitrate dehydrogenase 1 and 2 enzymes (IDH1 and IDH2) are a common occurrence in several tumor cells including 70% in low grade gliomas and secondary glioblastoma multiforme (GBM), in 20-45% of angioimmunoblastic T-cell lymphoma and in 10% in acute myeloid leukemia (AML) (1). These mutated IDH1/2 enzymes metabolize α-ketoglutarate (in the TCA cycle) to form D-2-hydroxyglutarate (D-2HG) in high concentration. This new oncometablite has been shown to reflect the diagnosis and classifications of IDH mutations in brain cancer patients. Proton MRS is a modality that holds great interest due to its ability to quantify the metabolite levels in both normal and diseased brains including N-acetylaspartate, a neuronal marker, myo-inositol, a marker for glia activation and glutamate, an important neurotransmitter. However, direct measurement of the 2HG resonance using proton MRS in the brain is difficult due to the strong overlapping of GABA, glutamate and glutamine resonances. The goal of this study is to introduce a reliable and simple proton magnetic resonance spectroscopy, a TE-averaged point-resolved spectroscopy approach to quantify 2HG in cancer patients.

Description of the Approach and Results: *High field proton MRS spectra of 2HG:* Single voxel proton MRS spectra of 2HG (0.2M solution, pH=6.5) were examined. Spectra were acquired at several echo times (short, intermediate and long) to assess the relationship of J-coupling using the GE 3T probe-p pulse sequence timing. Figure 1 demonstrates that the short echo time broad overlapping 2HG resonances centered at 2ppm result in pseudo singlet with increasing echo times, thus a potential candidate for metabolite editing using TE-averaged approach for high quality, quantifiable 2HG resonance suitable for human studies.



Optimization of TE-averaged PRESS data acquisition: GAMMA (2) spectral simulation library embedded within the VeSPA software project (3) was used to determine how spin systems of 2HG and glutamate, metabolite observed in cancer, behave with the components and timing relationship of the TE-averaged GE PRESS pulse sequence. Using a hard pulse approximation and published 2HG coupling constants (4), we obtained data acquisition parameters for TE-averaged PRESS with starting TE of 35ms and ending at 75ms. These parameters give unobstructed H-4 resonance of 2HG at 2.28ppm which is well separated from the edited glutamate H-4 resonance (2.35ppm) (Figure 2). Four sets of *in vitro* TE-averaged spectra of glutamate, glutamine, GABA and a mixture of GE liquid braino (5) with 0.01M of 2HG (0.1M of glycine was added to all solutions for internal chemical shift reference) were acquired on a 3T MR scanner (Figure 3 and 4). Figure 4 shows H4 resonance of 2HG is clearly resolved from H4 glutamate and the underlying aspartyl group of NAA.



Conclusions: We provide a simple non-invasive direct measurement of 2HG suitable for human subjects. Cancer subjects with proven mutated IDH enzymes scanning are currently in progress.

References and Acknowledgements: 1). Parsons D, et al. 2008;321(5897):1807-1812. 2). S.A. Smith et.al., J. Magn. Reson, Ser. A 106, 75-105, 1994. 3). B.J. Soher et al. ISMRM Stockholm, Sweden. 2011 p.3169. 4). Choi C, et al., Nature Medicine, 2012, 18(4), 624-630. 5) Schirmer T. et al., NMR in Biomed, 2000, 13, 28-36. The author (NS) thank NIH/NIDA for financial support and Whittier Foundation (BDR).