Noninvasive detection of 2-hydroxyglutarate in gliomas by 1H MR spectroscopy at 7.0 T in vivo

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INTRODUCTION: Mutations in isocitrate dehydrogenase (IDH) 1 and 2 in the majority of WHO grade-2 and -3 gliomas and secondary glioblastomas lead to production of 2-hydroxyglutarate (2HG) [1-3] and are associated with longer life expectancy compared to IDH wild-type tumors [4,5]. There is significant interest in noninvasive measurement of 2HG since this metabolite may provide prognostic information. Several studies were presented at ISMRM 2011 for demonstrating the ^{1}H-MRS feasibility for noninvasive detection of 2HG in gliomas at 3T [6-8]. High-field MRS benefits from the enhanced spectral resolution and the signal gain. Here we present preliminary *in-vivo* MRS 2HG measures at 7T. The performance of short-TE and optimized long-TE PRESS is discussed.

METHODS: An MRS study was carried out in a glioma patient with mutated IDH for comparison of 2HG detection by short-TE (34 ms) and long-TE (92 ms) PRESS at 7T. This 92-ms TE was obtained, with numerical simulations, for maximum 2HG signal amplitude for TE ≥ 34 ms (minimum possible). Experiments were conducted in a Philips whole-body 7T scanner, using a birdcage head transmit RF coil with a 16-channel receive coil. T_2w-FLAIR images were acquired to identify the tumor. PRESS spectra were obtained, using TR = 2.5 s and TE = 34 and 92 ms, from a voxel (2×2×2 cm^3) positioned within the tumor. FIDs were recorded in 16 blocks, each with 4 averages. Spectra were analyzed with LCModel using basis spectra of 20 metabolites which were calculated with published chemical shift and J coupling constants [11,12]. The PRESS volume localization RF and gradient pulses were used in the calculation. The TE = 34 and 92 ms PRESS runs were undertaken with 6.2 and 12 ms 180° RF pulses, respectively (bandwidth = 1.4 kHz for both).

RESULTS AND DISCUSSION: The five J-coupled resonances of 2HG give rise to multiplets at 4.02 (H2), ~2.25 (H4, H4′), 1.98 (H3) and 1.83 (H3′) ppm in 90°-acquisition [9], as shown in **Fig. 1a**. At TE = 34 ms (**Fig. 1a**), the H2 resonance, which is weakly coupled to the H3 and H3′ spins, maintains its signal intensity, but the H4, H4′, H3 and H3′ multiplets are degraded substantially due to the strong coupling effects, and as a result, the 2HG multiplets at 1.8 - 2.3 ppm are not well differentiable from the adjacent multiplets of glutamate (Glu), glutamine (Gln) and GABA, as indicated in sum spectra with and without 2HG. At TE = 92 ms (**Fig. 1b**), the 2HG spins further undergo J evolution, resulting in a negative signal at 2.25 ppm. The adjacent signals of Glu, Gln, and GABA are narrow or reduced, giving improved 2HG selectivity. In *in-vivo* spectra, the multiplets of 2HG, Glu and Gln were clearly discernible at TE = 92 ms (**Fig. 2a**), giving small Cramer-Rao lower bounds (CRLB), compared to TE = 34 ms (**Fig. 2b**). Dependence of LCModel outputs on the baseline function parameter (dkntmn) was investigated (**Fig. 3a**). In the 92 ms data, signal estimates and CRLBs of 2HG, Glu and Gln were essentially independent of the baseline parameter, while the 34 ms data gave substantial variations in the estimates and CRLBs for dkntmn < 0.3. At dkntmn = 0.3, LCModel was run with changing number of signal averages (NSA) (**Fig. 3b**). For TE = 92 ms, the signal estimates were decreased with increasing NSA but became stable for NSA ≥ 30. The CRLBs were decreased with increasing NSA monotonically. However, for TE = 34 ms, metabolite estimates and 2HG CRLB were varied substantially with changing NSA. The correlation coefficients of 2HG to Glu and Gln, returned by LCModel, were smaller in 92 ms data than in 34 ms data (**Fig. 4**). Together these results demonstrate that the optimized long TE method may provide reliable 2HG estimation compared to the short TE method. 2HG measurements with this optimized TE in patient populations are underway.

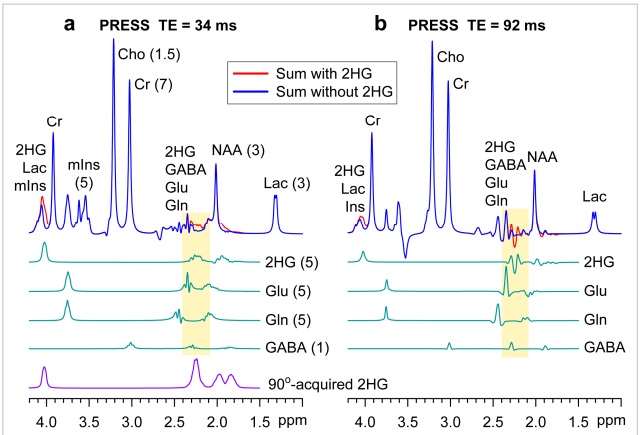

FIG 1. Calculated spectra of metabolites for PRESS TE = 34 and 92 ms at 7T, for concentration ratios shown in brackets. (Upper panel) Sum spectra with (red) and without (blue) 2HG. (Lower panel) Spectra of 2HG, Glu, Gln and GABA. A calculated 90°-acquire 2HG spectrum is shown for comparison. Spectra are broadened to FWHM = 9 Hz.

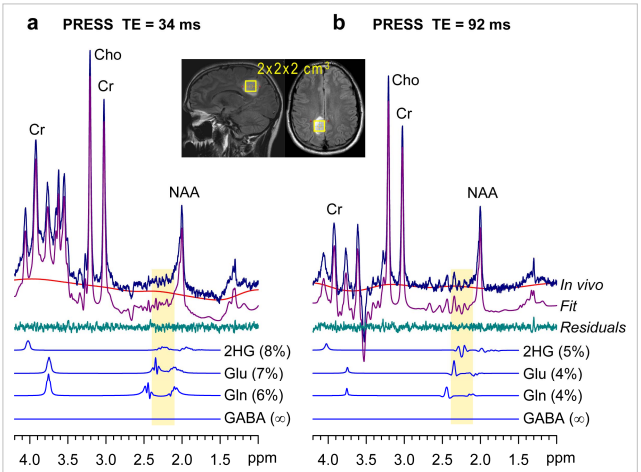

FIG 2. *In-vivo* spectra from IDH-mutated glioma are shown together with LCModel fits, residuals, baseline (red), and spectra of 2HG, Glu, Gln and GABA. Shown in brackets are CRLB. TR = 2.5 s; NSA = 64.

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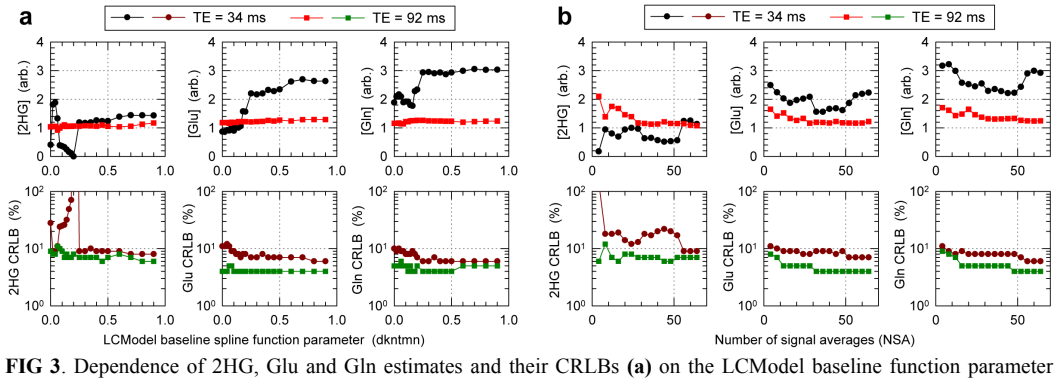

FIG 3. Dependence of 2HG, Glu and Gln estimates and their CRLBs **(a)** on the LCModel baseline function parameter (dkntmn) and **(b)** on number of signal averages (NSA), for the *in-vivo* data shown in Fig. 2.
NSA = 64 for data in (a), and dkntmn = 0.3 for data in (b). LCModel outputs in Fig. 2 were obtained with dkntmn = 0.3.

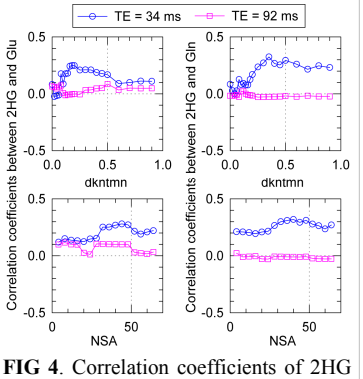

FIG 4. Correlation coefficients of 2HG with respect to Glu (**left**) and Gln (**right**), returned by LCModel.