pH-Weighted Molecular MRI in Brain Tumors

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Target Audience: Researchers interested in new applications of chemical exchange saturation transfer (CEST) MRI and clinicians interested in new molecular imaging methods for isolating regions of proliferating tumor tissue.

Purpose: Glioblastoma multiforme (GBM) is the most common form of primary brain tumor. There remains a clinical need for identifying regions of high proliferation in GBM for biopsy sampling, radiotherapy targeting, and determining treatment efficacy. Extracellular acidosis is a hallmark of tumor proliferation, as is a local increase in uptake of amino acids and other metabolites[1]. CEST MRI is an imaging technique that can provide information about metabolite functional groups such as hydroxyls, amides, and amines by saturating their protons off-resonance from bulk water and measuring the indirect saturation of the bulk water signal following chemical exchange of their protons. CEST MRI has previously been applied to brain tumors, typically through the use of amide proton transfer (APT) imaging, which targets the amide proton on the backbone of endogenous proteins 3.5 ppm upfield from bulk water. In this study, we examined the relationship between pH, metabolite concentration, and CEST signature of glutamine, an amino acid of high relevance in glioma physiology and one of the most highly concentrated amino acids in brain tissue. We hypothesize that elevated CEST contrast in anatomically defined tumor regions will be indicative of extracellular acidosis and increased amino acid concentration, corresponding to a more hospitable environment for tumor proliferation and possibly poor patient prognosis.

Methods: Samples of 25 mM, 50 mM, and 100 mM glutamine were created with pH values ranging from 4.0 to 9.0 in units of 0.2. Additionally, one set of 100 mM glycine samples and one set of 100 mM phenylalanine samples were created for the same pH range. CEST data was acquired for these samples from -5 ppm to +5 ppm in units of 0.2 ppm, at 1.5 T, 3.0 T and 7.0 T. Serial single-slice CEST data was acquired for 15 glioblastoma patients undergoing radiochemotherapy. Multi-slice CEST data was acquired in 3 glioblastoma patients who also underwent PET imaging with ^{18}F-FDOPA, an amino acid analog tracer. Additionally, CEST data was acquired for a low-grade glioma patient and used to identify targets for biopsy. Finally, this CEST technique was implemented in a mouse glioma model at 7.0 T. CEST contrast was obtained in all cases by calculating the asymmetry between 3.0 ppm and -3.0 ppm, and dividing by a CEST image with no saturation pulse.

Results: Our results showed an approximately sigmoidal relationship between CEST contrast and pH within a range of 5.0-8.0 pH units. CEST contrast increased with both decreasing pH and increasing amino acid concentration, and the three amino acids imaged produced similar CEST signatures within a physiologically relevant range (6.0-7.0 pH units) at 3.0 T (Fig. 1). Clinically, the area of acidic tissue as measured by CEST appeared to trend with enhancing tumor volume three months after treatment (Fig. 2). CEST also identified regions of low pH that appeared similar to regions of high ^{18}F-FDOPA uptake (Fig. 3). In a low-grade glioma patient, two tumor regions with elevated CEST signal were shown to contain tumor on biopsy, while a region not showing elevated CEST signal did not contain tumor on biopsy (Fig. 4). CEST imaging in a mouse glioma model showed a core of low-pH tissue near the location of tumor implantation that was confirmed on histological analysis (data not shown).

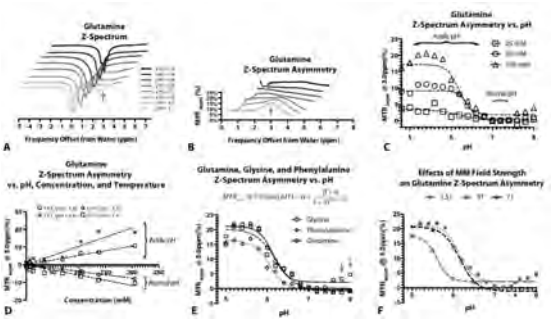

Fig. 1. CEST data from amino acid phantom studies. A) Z-spectra of 100 mM glutamine at varying pH at 3T. B) CEST asymmetry at 3.0 ppm as calculated from the data in (A). C) CEST asymmetry as a function of pH for 25, 50, and 100 mM glutamine. D) CEST asymmetry at in varying conditions. E) CEST asymmetry for three amino acids at 100 mM. F) CEST asymmetry as a function of pH at different field strength.

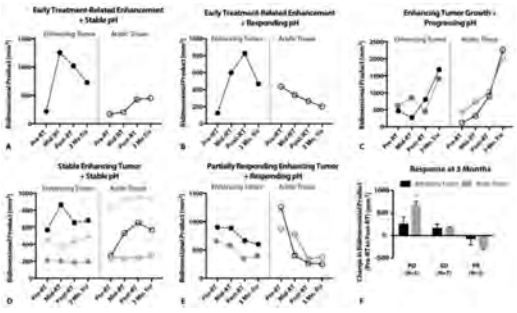

Fig. 2. Comparison of low-pH tumor area and contrast-enhancing tumor area for GBM patients showing progressive disease (PD), stable disease (SD), and partial response (PR).

Discussion: CEST MRI provides molecular information about imaging targets that cannot be obtained with standard anatomical imaging techniques. CEST targeted to the amino acid amine group has advantages in brain tumor imaging over more standard APT imaging in terms of imaging time and the strong dependence of the signal on extracellular pH. This CEST technique appears to non-invasively provide similar contrast as ^{18}F-FDOPA uptake, which may indicate the dependence of the CEST signal on amino acid concentration as well as pH. CEST was able to identify regions of actively proliferating tumor prior to biopsy; additional biopsy targeting using pre-surgical CEST imaging is warranted in future patients.

Conclusion: This study provides evidence that CEST targeted to amino acid amine protons may provide a pH-weighted biomarker in human gliomas.

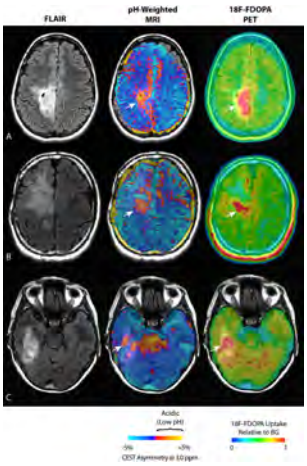

Fig. 3. MRI and PET data for three GBM patients. pH-weighted CEST MRI appears to identify similar lesions as ^{18}F-FDOPA PET.

References:
1) Harris RJ, Neuro Oncol, 2012.
2) Jones CK, Magn Reson Med, 2006.

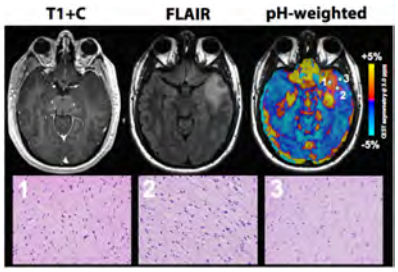

Fig. 4. MRI data for a low-grade glioma patient prior to CEST-targeted biopsy. Panels 1-3 show histology data from biopsy samples taken from locations 1-3 on the pH-weighted image. Biopsy samples 1 and 2 (low pH) contained tumor, while biopsy sample 3 (high pH) did not.