Chemical exchange saturation transfer (CEST) MRI of 2DG and FDG as a tool for molecular imaging of tumors and metastases

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Introduction: Metabolic based molecular imaging is widely used for detecting tumors and metastases [1, 2]. The increased glycolytic rate and glucose avidity of malignant cells (the Warburg effect)[3]) in comparison to normal tissue is the basis of the ability of FDG-PET imaging to accurately differentiate cancer from benign tissue regardless of morphology. 2-deoxy-D-glucose (2DG) and 2-fluoro-2-deoxy-D-glucose (FDG) are two glucose analogues that are taken up by cells through the glucose transporter. They undergo phosphorylation catalyzed by hexokinase but unlike glucose do not undergo further metabolism and thus they accumulate in the cells [4]. Both 2DG and FDG have 4 hydroxyl residues, which are potential candidates for CEST. Very recently Golay et al. [5, 6] reported in scientific meetings CEST measurements of glucose and of 2DG in rat brain and GlucoCEST of tumors [7]. We suggest applying 2DG/FDG CEST-based MRI to develop novel molecular imaging modalities for tumor and metastases detection and follow-up and to better understand tumor metabolism.

Methods: We performed CEST-MRI experiment on implanted xenograph mammary tumors of mice before and following the injection of the glucose analog 2DG. The experiment was performed on a Bruker 7T Biospec scanner. DA3 tumor bearing mice that were allowed to grow for 10-14 days, with an average tumor volume of 5mm^3 were scanned with a surface coil. The mice were anesthetized with 1.5% isoflurane by inhalation; the temperature was monitored and maintained at 37^{o}C. The *in vivo* CEST images were generated as follows: a series of gradient-echo images were collected from a single 5 mm axial slice of rough after presaturation pulse, applied at several frequency offsets from the water, to produce the desired CEST effect [8]. The frequencies (Ω) were used in the range of -4 to +4 ppm relative to the water signal. The signal intensity as a function of irradiation pulse frequency Ω is referred to as the Z-spectrum. Several B_1 powers in the range of 1-10 μT (~40-400 Hz) and durations in the range of 1-5s were tested to obtain the optimal effect. The chemical exchange contrast was measured by Magnetization Transfer asymmetry, MTR_{asym}:

$MTR_{asym}(\Omega) = [M_{CEST}(-\Omega) - M_{CEST}(\Omega)]/M_{CEST}(-\Omega)$

Results and Discussion: We validated that 2DG/FDG glucose analogs can be detected by CEST-NMR/MRI, as a marker of tumor response. The Z spectra of 20mM 2DG6P and FDG solutions showed three peaks at about 1.2, 2.1 and 2.8 ppm, belonging to the hydroxyl protons, (Fig.2). It may be noted that no hydroxyl proton peaks could be observed for the same solutions by ^{1}H NMR single pulse experiment. The MTR_{asym} increased with the B_1 power and for FDG was about 15% for the peak at 1.2 ppm and B_1 power of 200Hz (Fig.2B).

*Preliminary tumor studies by CEST-MRI***:** We performed CEST experiment on DA3 xenograph mammary tumors of mouse, which was i.v. injected with 2DG (20 mg/kg). This dose is only 6% of the approved therapeutic treatment for human and much lower than the LD_{50} i.v. of 2DG in rat which is 8000mg/kg. Initially, for the control experiment, we examined the CEST effect on the same mouse prior to the injection. As it can be seen from Fig.1 the images of the mouse before the 2DG injection, irradiated at frequencies of +1.2 and -1.2 ppm were very similar at the region of the tumor. They differed in the region of the bladder (B). About 30 min following the 2DG injection upon irradiation at a frequency of +1.2 ppm the tumor was darker (see blue cycle) compared to that irradiated at -1.2ppm (A) as well as compared to the images of the control (B). The difference between the images in the region of the tumor after presaturation pulses at ±1.2 ppm reached a value of about 10% and remained constant for more than one hour after the injection. This difference can be ascribes to the trapped 2DG6P.

Conclusions: The results of the present work indicated that 2DG/FDG CEST-based MRI has the potential to detect tumors, tumor response to therapy and tumors metabolism, noninvasively by using MRI.

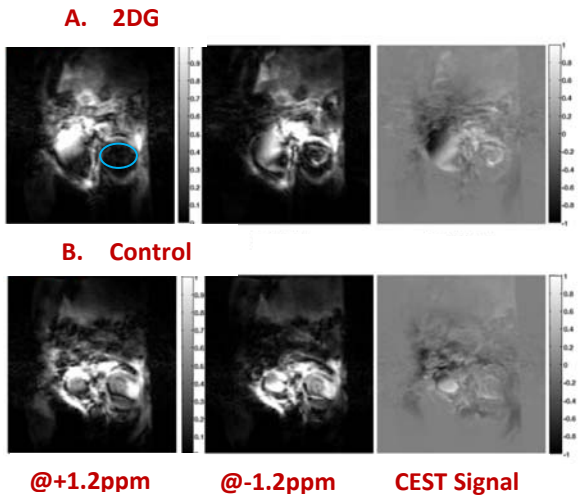

Fig.1: ***In vivo*** images of xenograph mammary tumor of mouse with irradiation at δ=+1.2ppm, δ=-1.2ppm, and the corresponding (A) 2DG chemical-exchange-dependent saturation transfer (2DG-CEST) map and (B) control-CEST map (before injection of 2DG).

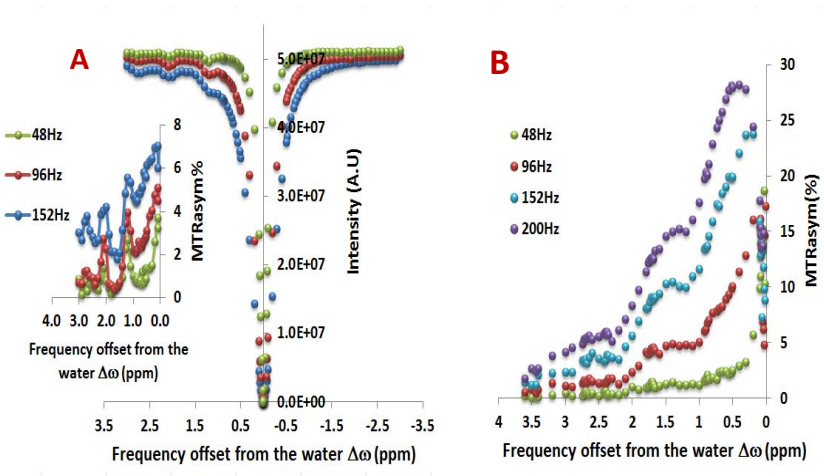

Fig. 2: Z spectra and MTR_{asym} plot of (A) 20mM 2DG6P in D_2O solution (pH=7.1, at T=25^{o}C), (B) 20mM FDG solution (%10 D_2O, 0.01M phosphate buffer, pH=6.3, T=25^{o}C)

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