Imaging glucose uptake in a preclinical brain tumor model using glucoCEST

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Target audience: Physicians and researchers who are interested in cancer detection, especially in applications and development of biodegradable natural contrast agents for detecting the aggressiveness of brain tumors.

Purpose: Glucose metabolism has an important role in progression of cancers, and overexpression of glucose transporter (GLUT) proteins has been found in numerous cancers, including glioblastoma (1). We and others have shown that D-glucose can be used as a biodegradable contrast agent for cancer detection by employing hydroxyl protons as a natural label for chemical exchange saturation transfer (glucoCEST) in breast tumors and colorectal tumors (2,3). Here, we investigated imaging of gliomas using glucoCEST, which had shown to be problematic for ^{18}FDG PET due to the high background signal of glucose uptake in normal brain.

Method: Animal preparation: Female SCID mice (6-8 weeks; NCI, Frederick, MD) were anesthetized by i.p. injection of ketamine (100 mg/kg) and xylazine (5 mg/kg). Human U87-VEGFVIII cells were implanted (1×10^5 cells/2 µl) by stereotaxic injection into the right caudate/putamen of SCID mice. CEST imaging: Mice were fasted overnight and anesthetized using isoflurane and positioned in a 11.7T horizontal bore Bruker Biospec scanner, and were imaged before, during and after glucose infusion. CEST images were acquired through collection of two sets of saturation images, a water saturation shift referencing (WASSR) set for B_0 mapping, and a CEST data set for characterizing the contrast. For B_0 correction with WASSR images, the saturation parameters were t_{sat}=500 ms, B_1=0.5 uT, TR=1.5 sec with a saturation offset incremented from -1 to +1ppm with respect to water in 0.1ppm steps. For the CEST images: t_{sat}=4 sec, B_1=1.6 uT, offset incremented from -4 to +4 ppm (0.2 ppm steps). The acquisition parameters with a fat suppression pulse were: TR=5.0 sec, effective TE=5 ms, RARE factor=12. Data Analysis: images were processed using custom-written Matlab scripts with CEST contrast quantified by calculating the asymmetry in the magnetization transfer ratio (MTR_{asym}) using $MTR_{asym}=(S^{-\Delta\omega}-S^{\Delta\omega})/S_0$ for hydroxyl protons at $\Delta\omega$ = 0.8-2.2 ppm (glucoCEST contrast). CE-MRI: Following CEST imaging, T1w images of the same slice were acquired before and after bolus injection of 0.1 ml of 0.1 M Gd-DTPA (matrix=128×80). A non-selective saturation recovery gradient echo sequence with TE/TR=1.45/30ms and flip angle=90° was used to suppress effects of water exchange on the measured signal enhancement.

Results and discussion: GlucoCEST contrast increased during glucose infusion (steady state) and highlighted the tumor (Fig. 1a), the location of which was confirmed by MTw and contrast-enhanced (CE) images (Fig. 1a,f). After infusion, the glucoCEST contrast decreased and was comparable to that of pre-infusion. While both brain and tumor glucose uptake was visible, it can be seen from the ΔMTR_{asym} spectra from the ROIs in Fig. 1c that the tumor (Fig. 1d) had a higher ΔMTR_{asym} than contralateral brain (Fig. 1b). Moreover, the dynamic study (Fig. 1e) showed that the ΔMTR_{asym} of the tumor was higher than the brain, starting already during the first 10 mins of infusion even though the time resolution was insufficient to detect points on the rising slope. For rapidly metabolizing tumors, the observed high glucoCEST contrast in the tumor has been attributed to the increased vascular volume in tumors and especially the acidic extravascular and extracellular space (2), but some intracellular contributions may also be present (3).

Conclusion: GlucoCEST imaging of a glioma xenograft model enables, contrary to ^{18}FDG PET, the detection of glucose uptake in brain tumors which can be readily separated from that of normal brain. Together with previous studies in breast tumors (2) and colorectal tumors (3), these results show the potential of glucoCEST imaging as a practical approach for cancer glucose uptake detection. To extend this technique to dynamic measurements of tumor perfusion and metabolism (after stopping infusion), the time resolution needs to be improved, which may be possible by using single-frequency measurements for these broad OH signals.

References: 1. Krzeslak A et al. Pathol Oncol Res. 2012;18:721. 2. Chan KW et al. Magn Reson Med 2012, on-line. 3. Walker-Samuel S, et al. In Proceedings 20th ISMRM, 2012. p. 182.

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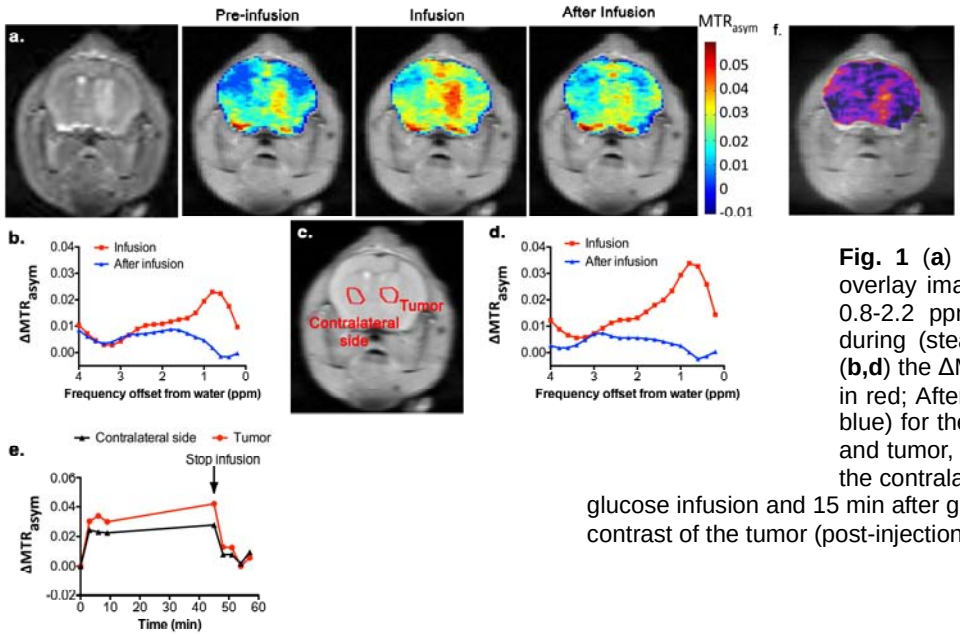

Fig. 1 (**a**) MTw anatomical image and CEST/T2w overlay images showing the glucoCEST contrast at 0.8-2.2 ppm for U87 tumor bearing mice before, during (steady state) and after D-glucose infusion; (**b,d**) the ΔMTR_{asym} (Infusion: (Infusion - pre-infusion) in red; After infusion: (after infusion - pre-infusion) in blue) for the ROIs shown in (**c**) in contralateral brain and tumor, resp. (**e**) Dynamic glucoCEST contrast of the contralateral and tumor during the first 10 min of glucose infusion and 15 min after glucose infusion. (**f**) CE image showing the contrast of the tumor (post-injection-pre-injection).