Lactate production in human brain tumor; detection by ^{13}C MRS at 3T.

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Introduction:
Highly malignant tumor cells release lactate, therefore, lactate has been postulated as biomarker for malignancy (1). Indeed, lactate is often detected by ^{1}H MRS in brain tumor tissue (2), but its level is very variable and does not appear to be related with the grade of the tumor. The static level of lactate, as it is observed by ^{1}H MRS, is not only determined by cellular production, but also by accumulation in cystic lesions and draining of tumor tissue. For this reason the dynamics of lactate production may be a better marker for malignancy.
Aim: to demonstrate that lactate production can be monitored non-invasively in patients with a high grade brain tumor by localized ^{13}C MRS.

Methods:
A 29 year old patient with histopathologic validated glioblastoma multiforme participated in this study. Before the patient was positioned in the MR scanner (Tim-TRIO, Siemens, Erlangen) an euglycemic clamp was applied by venous infusion of insulin and a variable rate of glucose. Once stable blood plasma glucose levels were established, the patient was positioned in an in-house developed ^{1}H and ^{13}C head coil into the scanner(3). Localized ^{13}C MR spectra were acquired alternating in a tumor and contra lateral voxel (Fig. 1), which were selected on a T2-weighted background image, by adding an Image Selected In vivo Spectroscopy (ISIS) sequence at the ^{1}H channel before acquiring a ^{13}C MR spectrum by Single Channel Distortionless Enhanced Polarization Transfer (SC-DEPT) with broadband WALTZ16 ^{1}H decoupling. The sensitivity of the ^{13}C coil was equal in both voxels as confirmed by a reference measurement of natural abundance ^{13}C in the brain of a healthy volunteer (Fig.2). Six baseline ^{13}C MR spectra were acquired before a 30ml bolus of 100% 1-^{13}C enriched glucose 20% was infused in 10 minutes. During the remainder of the clamp, glucose infusion was adapted to maintain the euglycemic condition (5,8±0.4mmoll^{-1} throughout the entire measurement). Other MRS parameters were; 200us rectangular excitation pulse, TR=2020ms, 72 averages, voxel size 54x32x29 mm, acquisition time 2:26 minutes. ^{13}C MR spectra were analyzed using JMRUI software. After a frequency shift and phase correction the MR spectra were averaged over 10 minutes using a moving window and the integrals of the glucose, glutamate-C4 and lactate peaks were calculated and plotted in time curves.

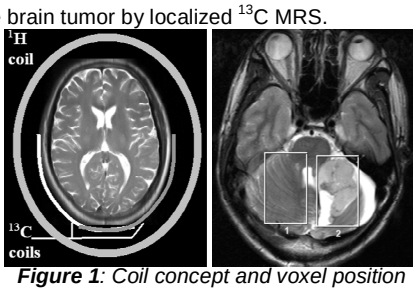

***Figure 1**: Coil concept and voxel position on a T2 weighted background image.*

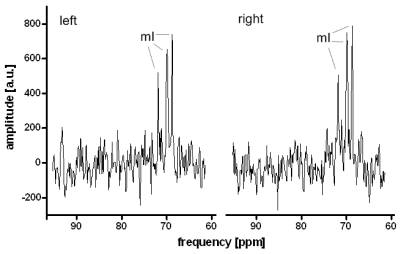

***Figure 2**: reference ^{13}C MR spectra (myo-inositol (ml) region) from voxels positioned at the same location in a healthy volunteer as in the patient; confirming equal sensitivity of the ^{13}C*

Results and discussion:
Approximately 20 minutes after the start of 1-^{13}C glucose infusion a lactate 3-^{13}C signal became visible in ^{13}C MR spectra of the tumor region, whereas in the contra lateral voxel this signal remained in the noise level (Figs. 3,4,5). The ratio of C2 Glx peaks to the C4 Glu peak in the tumor voxel is comparable to this ratio in the contra lateral voxel (0.9), indicating a normal pyruvate carboxylase pathway in both voxels. However, MR spectra of the contra lateral voxel showed a substantial higher SNR for compounds produced in or downstream of the Krebs cycle (e.g. ^{13}C peaks of glutamate and aspartate; Figs 4, 5), reflecting the low level of normal brain tissue in the tumor voxel (~45%) and is in agreement with lower oxidative activity in tumor cells. In contrast, the glucose ^{13}C signals are higher in the tumor voxel. Since the blood brain barrier is defect in the tumor (the tumor is enhancing on post Gd T1 weighted images) this higher glucose amount might reflect leakage of glucose in interstitial and other extracellular spaces.

Conclusion:
We demonstrated for the first time that it is possible to detect the dynamic conversion of glucose into lactate in a human brain tumor. In contrast to tumor tissue normal brain tissue metabolizes glucose down to its end products in the oxidative phosphorylation. Further research of brain tumors with different grades is necessary to assess the value of lactate production in tumor characterization. This may involve more sensitive detection by proton observed carbon edited or other approaches.

References: **1**. Walenta S, Sem. Radiation Oncology 2004;14(3):267-274. **2**. Howe FA, MRM 2003;49(2):223-232. **3**.Klomp DW, NMR Biomed 2007.

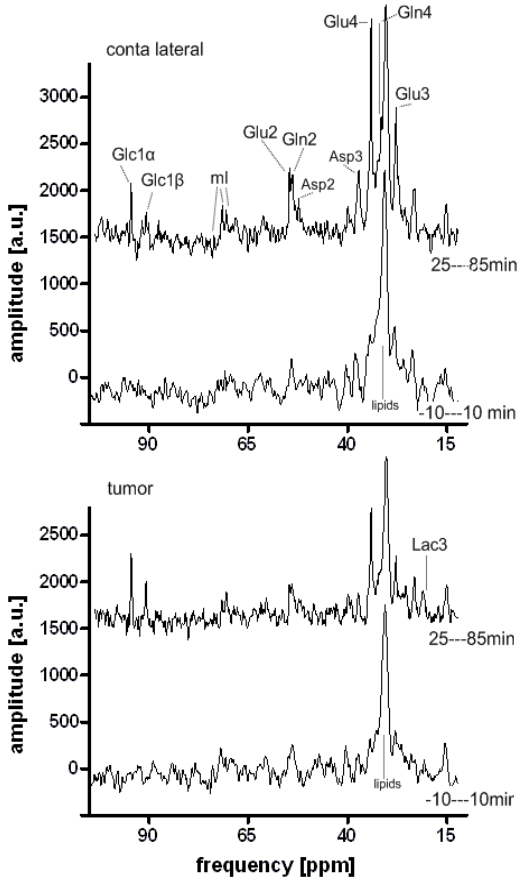

***Figure 5**: Summed ^{13}C MR spectra of baseline and labeled glucose infusion measurement in the tumor and contra lateral voxel. MR spectra are normalized to equal acquisition time.*

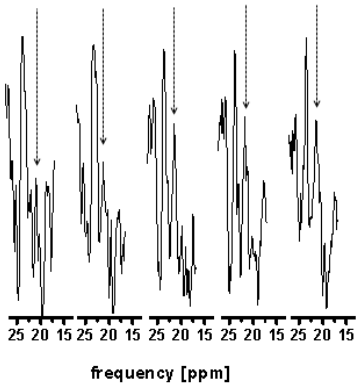

***Figure 3**: **Figure 3**: ^{13}C MR spectra of tumor with a 3-^{13}C lactate signal at 21.2 ppm indicated by the arrow, at time points 27, 37, 47, 62 and 77 minutes from left to right respectively.*

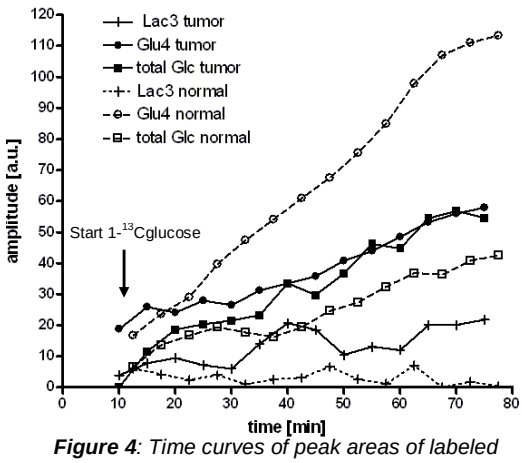

***Figure 4**: Time curves of peak areas of labeled compounds in tumor and contra lateral voxel.*