High Resolution MR Imaging of Brain Lactate using Selective Saturation Transfer

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Introduction: Lactate is an important metabolic biomarker for a variety of neurological disease states, and is now also recognized as an essential substrate of neuronal metabolism [1]. An improved MR method for mapping brain lactate would aid the study of this important metabolite in physiologic and pathologic conditions, and provide a clinically relevant diagnostic tool. ^{13}C and ^{1}H MR spectroscopic (MRS) methods have been used previously to measure brain lactate concentrations but have limited temporal and spatial resolution. The purpose of this study is to investigate whether magnetic coupling between lactate methyl and water protons previously reported in MRS studies [2] and in phantoms [3] can be exploited to generate MRI contrast specific localized lactate accumulations. Our initial findings show that selective radiofrequency saturation of lactate methyl protons results in cumulative saturation of dominant water protons via immobilized macromolecules in both protein phantoms and *in vivo*, increasing the sensitivity of lactate detection *in vivo* as compared to MRS, and enabling high resolution mapping of subtle lactate changes in brain.

Methods: MR imaging experiments were performed at 7T on a Bruker Biospec horizontal bore system. *In vitro* experiments utilized phantoms of varying lactate concentrations combined with 20% heat cross-linked bovine serum albumin (BSA), pH 7.0, temperature 30-35 °C. All *in vivo* experiments were performed in C57 black mice. *In vivo* lactate mapping was investigated in three mouse models: normal mice following i.p. glucose injection, streptozotocin (STZ)-induced diabetic mice, and mice undergoing transient focal middle cerebral artery occlusion (MCAO). Serum glucose levels >300 mg/dl were consistently achieved in mice following peritoneal injection and in diabetic mice. The lactate MR mapping sequence consisted of a train of 10 gaussian saturation pulses (flip angle 30 o, RF power 2 uT, 150 Hx bandwidth, MT module duration 183 ms) applied at offsets of +/- 3.4 ppm (1020 hz) from the bulk water peak, with -1020 hz corresponding to lactate methyl protons. Saturation pulses were then followed by FLASH imaging acquisition (2.4 FOV, matrix 128 x 128, slice thickness 1mm, flip angle 20 o, TR/TE 400/2.2 ms). Identical acquisitions were obtained without the MT prepulse train. The -3.4 ppm images were subtracted from the +3.4 ppm images to create the final subtracted MT images, whereas MT ratio (MTR) images were created by digital division of the +/- 3.4 ppm images into the non-MT image. Specific MT ratios are as described.

Results: Fig. 1 shows indirect imaging of lactate in BSA phantoms via water protons. Image intensity represents the difference image obtained after saturation at +1020 hz and -1020 hz (1020-(-1020)), pH constant at 7.0, temperature 30-35 °C. The graph below shows the MTR [(1020-(-1020))/no MT] in phantoms from 5 to 500 µM, demonstrating micromolar sensitivity for lactate detection *in vitro*. Fig. 2 shows MTR coronal images overlayed on T2-weighted images of mouse brain before (left) and after i.p glucose administration, revealing a global increase in lactate accumulation most pronounced in the basal ganglia. Mean MTR in animals prior to injection was 3.7 +/- 1.2 (n=6); at 90 minutes following glucose administration, mean MTR was 6.0 +/- 0.9. In STZ diabetic animals, mean MTR was 6.2 +/-1.3 (n=4) (data not shown). Fig.3 shows lactate MTR images along-side diffusion-weighted images at 30 min, 4 and 24 hours post occlusion. Note the significant lactate accumulation in the MCA territory during occlusion and preceding the DWI change, with near complete washout of lactate following reperfusion, but a persistent area which becomes a region of stroke extension on DWI at 24 hours.

Discussion and conclusion: Changes in lactate can be readily detected at concentrations at least one to two orders of magnitude lower than MRS and at higher spatial resolution using a simple saturation transfer sequence, allowing for high resolution mapping of lactate change *in vivo*. Further experiments are required to calibrate lactate MTRasym as a function of lactate concentration *in vivo,* which is measured by histological and ^{13}C methods. Extension to humans would allow noninvasive imaging of lactate in normal brain function and disease.

References: 1) Aubert A et. al., (2005) *PNAS* **145**: 16448-53; 2) Luo, Y et. al., (1999) *Magn Reson Med* **41**, 676-85; Swanson, SD (1998) *J Magn Reson* **135**, 248-55

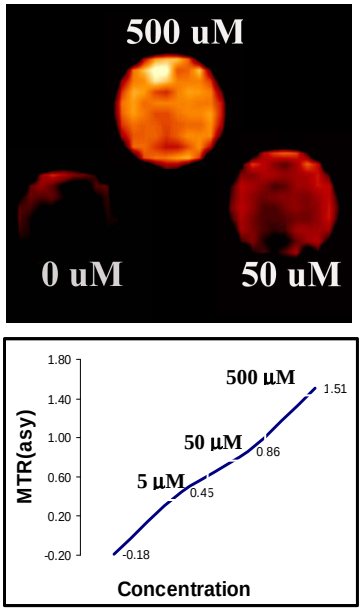

Fig. 1. Lactate detection in BSA phantoms. *In vitro* imaging shows micromolar sensitivity for lactate detection at >30 °C in the presence of protein.

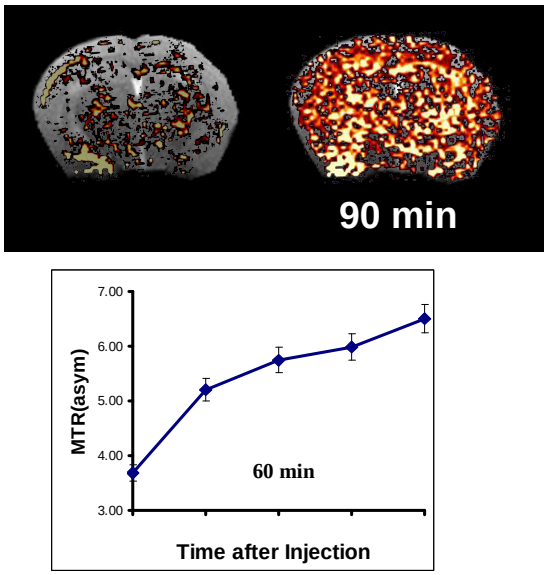

Fig. 2 Lactate detection *in vivo* **following glucose administration**. A global increase in lactate accumulation is seen after serum glucose elevation, most pronounced in the basal ganglia.

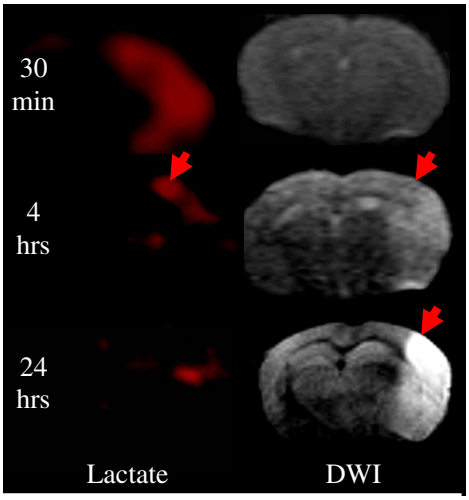

Fig 3. Lactate imaging in experimental stroke. Lactate accumulation proceeds DWI changes in both the hyperacute and subacute stages of focal ischemia.