High Resolution MR Imaging of Brain Lactate using Selective Saturation Transfer

C. Lascola¹², T. Venkatraman¹, S. Snodgress¹, and H. Wang³
¹Radiology, Duke University Medical Center, Durham, North Carolina, United States; ²Brain Imaging and Analysis Center, Durham, North Carolina, United States; ³Anesthesiology, Duke University Medical Center, Durham, North Carolina, United States

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. ¹³C and ¹H 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 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.

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 alongside 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, 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 MTR asym as a function of lactate concentration in vivo, which is measured by histological and ¹³C methods. Extension to humans would allow noninvasive imaging of lactate in normal brain function and disease.


![Fig. 1. Lactate detection in BSA phantoms. In vitro imaging shows micromolar sensitivity for lactate detection at >30 °C in the presence of protein.](image1)

![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.](image2)

![Fig. 3. Lactate imaging in experimental stroke. Lactate accumulation proceeds DWI changes in both the hyperacute and subacute stages of focal ischemia.](image3)