Deuterium Metabolic Imaging (DMI), a novel method for *in vivo* mapping of glucose metabolism in brain and liver

Henk M. De Feyter, Kevin L. Behar, Zachary A. Corbin, Robert K. Fulbright, Peter B. Brown, Scott McIntyre, Terence W. Nixon, Douglas L. Rothman, Robin A. de Graaf.
Magnetic Resonance Research Center, Yale University, New Haven, Connecticut, USA.

Introduction

Deuterium Metabolic Imaging (DMI) is a novel, noninvasive approach that combines deuterium magnetic resonance spectroscopic imaging (MRSI) with oral intake or intravenous infusion of non-radioactive ^{2}H-labeled substrates to generate 3D metabolic maps. Here we present examples of DMI applications in both animal models and human subjects, using ^{2}H-labeled glucose.

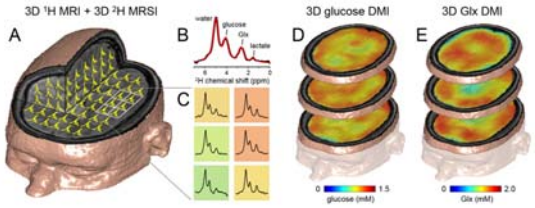

Figure 1. DMI in human brain after oral [6,6'-$^2H_2$]-glucose intake. A) 3D MRI overlaid with ^{2}H MR spectra from a 3D MRSI dataset (9x13x11 matrix) with 20x20x20 mm^3 nominal spatial resolution, acquired between 65 and 90 min after oral [6,6'-$^2H_2$]-glucose administration. B) A typical ^{2}H NMR spectrum from a single MRSI voxel overlaid with a spectral fit (red line) indicating the peaks from water, glucose, Glx and lactate. C) 2x3 grid extracted from the MRSI with data color-coded by the Glx intensity. D) 3D maps of ^{2}H-labeled cerebral glucose and E) Glx levels in mM, extrapolated from the 3D MRSI to the 3D MRI grid. Note the seemingly lower level of Glx in areas corresponding to the ventricles.

Methods

Data were acquired on an 11.7 T or 4 T Magnex magnet interfaced to a Bruker Avance III HD spectrometer, for animal and human studies, respectively. Custom-built radiofrequency (RF) coils were: a four element TX/RX phased-array for ^{2}H RF integrated with a ^{1}H TEM volume coil for human brain studies, a 9 cm diameter ^{2}H surface coil combined with two quadrature ^{1}H coils for MRI and shimming during human liver studies, and a combined ^{2}H/^{1}H volume coil for rat liver studies. [6,6'-$^2H_2$]-glucose was administered orally for human studies, at a dose of 0.75 g/kg of body weight. In rat studies intravenous glucose infusion was applied.
^{2}H MR signal acquisition was achieved with a pulse-acquire sequence extended with 3D phase-encoding gradients during the initial 1.1 ms (animal) or 2.7 ms (human) following excitation.

Results

Figure 1 illustrates DMI data acquisition and processing of a study in a healthy control subject, after oral intake of [6,6'-$^2H_2$]-glucose, with maps of ^{2}H-labeled glucose and glutamate+glutamine (Glx). Figure 2 shows DMI acquisition in rat and human liver following intravenous and oral administration of ^{2}H-labeled glucose, respectively.

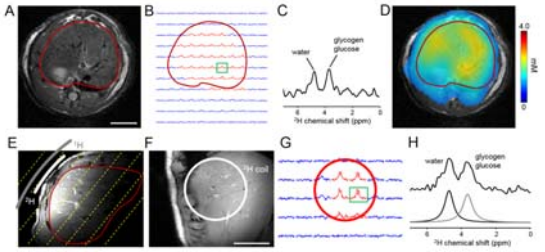

Figure 2. DMI of liver glycogen. A) Respiratory-gated, axial MR image of rat abdomen with the liver delineated in red. B) ^{2}H NMR spectra extracted from a 3D ^{2}H MRSI grid with 4x4x4 mm^3 resolution. Spectra in red have sufficient signal for DMI quantification, whereas spectra in blue were not considered further. C) ^{2}H MR spectrum from the voxel indicated in green (B). D) Color-coded map of 2H-labeled glucosyl units (mM) after 120 min of [6,6'-$^2H_2$]-glucose infusion. E) Axial MR image of liver acquired with the RF coil placed on the lateral side of the human abdomen. RF coils' position and size indicated in grey (^{1}H) and white (^{2}H). Dashed yellow lines emphasize one dimension of the 3D oblique MRSI grid parallel to the ^{2}H surface coil. The red line delineates the liver. F) MR image acquired parallel to the RF coils, with the ^{2}H RF coil (white) superimposed. Scale bar = 50 mm. As with the rat brain data, the ^{2}H surface coil's sensitivity limits DMI data acquisition to positions close to and within the diameter of the coil. G) ^{2}H NMR spectra extracted from a 3D ^{2}H MRSI grid with 25x25x25 mm^3 resolution, 60 min after oral [6,6'-$^2H_2$]-glucose intake. Spectra in red have sufficient signal for quantification, whereas spectra in blue were not considered further. H) ^{2}H MR spectrum from the voxel indicated in green in (G), with the fitted peaks of ^{2}H-labeled glycogen+glucose and water.

Discussion

The use of ^{2}H-labeled substrates is a well-established technique for studying whole body metabolism, detecting the label in blood and tissue samples. DMI combines the administration of ^{2}H-labeled substrates with ^{2}H MRSI to establish a novel MRI-based metabolic imaging technique. We illustrated the feasibility of DMI for human applications in both brain and liver. Ongoing research is focused on improving absolute quantification of DMI, exploring DMI in animal models of disease and patient populations, and investigating other ^{2}H-labeled substrates targeting pathways other than glucose metabolism. DMI is extremely well-suited to be implemented at ultra-high field because of the anticipated increase in signal-to-noise, DMI's very simple RF pulse sequence with very low SAR characteristics, and ^{2}H's low resonance frequency.

Conclusion

DMI is a versatile, robust and easy to implement technique that requires minimal modifications to existing clinical MRI scanners. DMI has great potential to become a widespread method for metabolic imaging in both (pre-)clinical research and the clinic.