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Assessing metabolic differences in rodents on high fat diet using Deuterium Metabolic Imaging

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Objective

Deuterium Metabolic Imaging (DMI) is a novel method to assess metabolism in vivo using 2H MR Spectroscopic Imaging (MRSI) combined with the administration of deuterated substrates, giving great insight into metabolic processes of healthy and diseased brain[1,2], brown adipose tissue[3] and tumor tissue[4]. In this pilot study, we applied 2D DMI following an intravenous injection of deuterated glucose and palmitic acid (PA) to evaluate the differences in liver metabolism of rats on standard and high fat diet at 9.4T.

Methods

DMI measurements were performed on Biospec 94/30 (Bruker Biospin, Germany) MR system with a 2H/1H surface RF coil (Ø=40mm, Rapid, Germany) adjusted for abdominal region. Before the DMI experiments, a conventional MRI was done to optimize the B0 shim.
Following an intravenous bolus injection of [6,6'2H2]glucose (1.95g/kg bw) or palmitate (palmitic acid-d31) (0.0065g/kg bw), a 2-dimensional chemical shift imaging (CSI) sequence (TR=350ms, FA=61.6°, matrix 12x12mm, FOV=50x36mm, Avg=128 (glucose)/192 (PA)) was applied without respiratory gating. Groups of Sprague Dawley rats following a high fat diet (n=3, m=525-640g, age=12 weeks, 60% of calories from pure fat) or standard diet (n=3, m=330-390g, age=12 weeks) were examined for each substrate, respectively. To improve the signal, a saturation slab of 10 mm was placed over the heart. The signal to noise ratio (SNR) of the DMI measurements was enhanced using a Hamming-weighted k-space acquisition mode. Underlying anatomic 1H MR images for DMI were acquired in identical FOV using an axial T1-weighted FLASH sequence (TR=30ms, averages=20, FA=30°, matrix 120x120) under respiratory gating.
The acquired MRS data were pre-processed and analyzed using the Matlab based tool DMIWizard[2]. Spectra were quantified with linear least-squares fitting and the resulting amplitudes translated to concentration according to the 2H natural abundance water peak. The resulting post-injection maps were corrected for the respective physiological baseline signal of glucose or lipids in the liver.

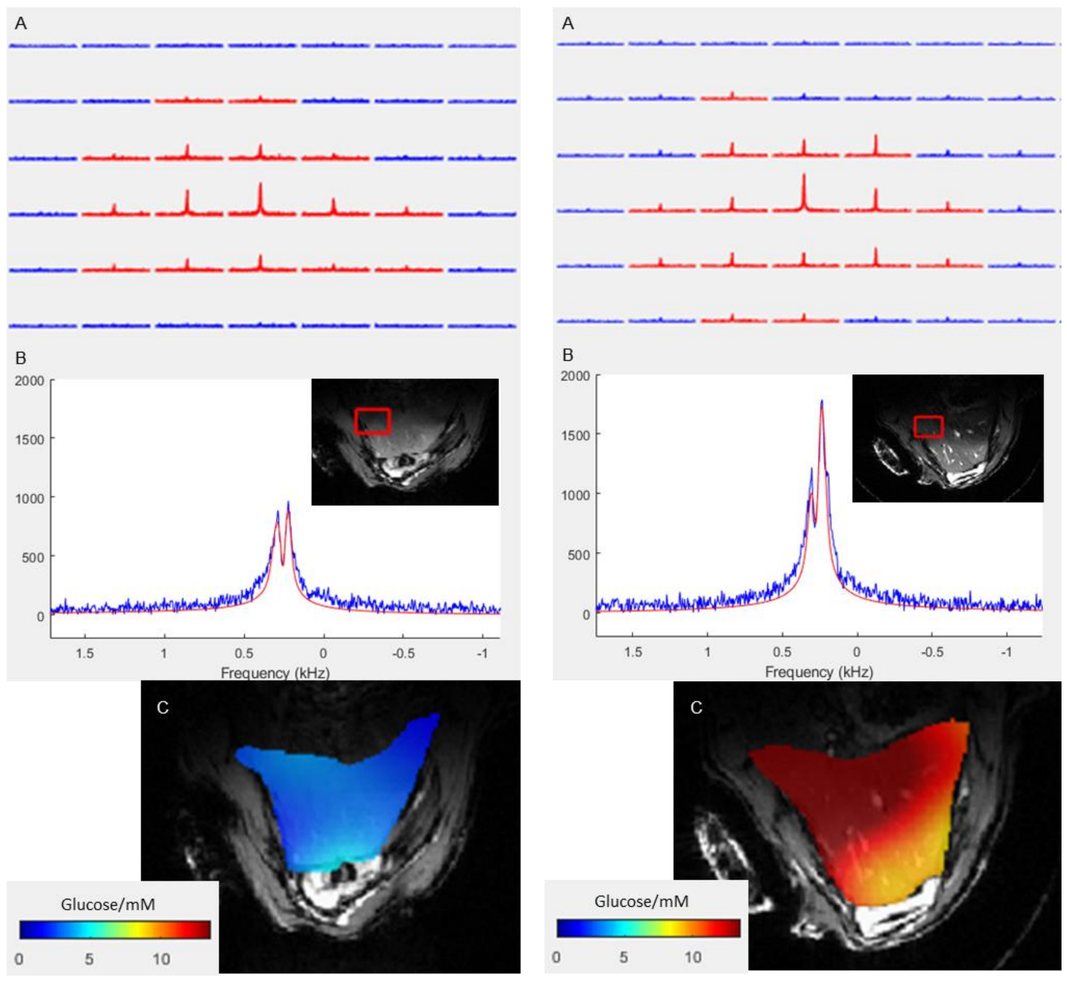

Figure 1: Liver DMI acquired after intravenous glucose administration in animals on HFD (left) and SD. The sections of the matrix maps (A) show the voxels included in the analysis, one of which is shown with spectral fit in (B) as an example. The metabolic maps in (C) clearly demonstrate the lower glucose uptake in HFD rats indicating insulin resistance and an impaired metabolism.

Results and Discussion

Chosen DMI acquisition strategy yielded sufficient SNR and spectral resolution for both infusion protocols in both, SD and HFD rats, in several 2H MRSI voxels co-registered within homogeneous liver parenchyma (Figures 1 and 2).
Quantification of the spectra yielded lower post-infusion glucose levels in rodent livers following a HDF (mean abs. conc. glucose = 5.95 ± 4.77 mM) than with SD (mean abs. conc. glucose = 13.16 ± 6.23 mM). In contrast, the high fat animals had higher levels of palmitic acid uptake (mean abs. conc. PA = 4.03 ± 0.96 mM) after infusion than the SD animals (mean abs. conc. PA = 0.77 ± 1.09 mM). However, the difference between HFD and SD animals is not as high here as after the glucose administration.
The higher glucose levels in livers of SD animals indicate the higher hepatic insulin sensitivity in lean animals, whereas the low glucose levels following injection in livers of HFD animals point toward the insulin resistance, giving evidence of an impaired and slower liver metabolism. The higher hepatic uptake of palmitic acid in HFD animals confirms their phenotype with metabolic disorder. Ingested fats are preferentially stored in ectopic sites of the body.

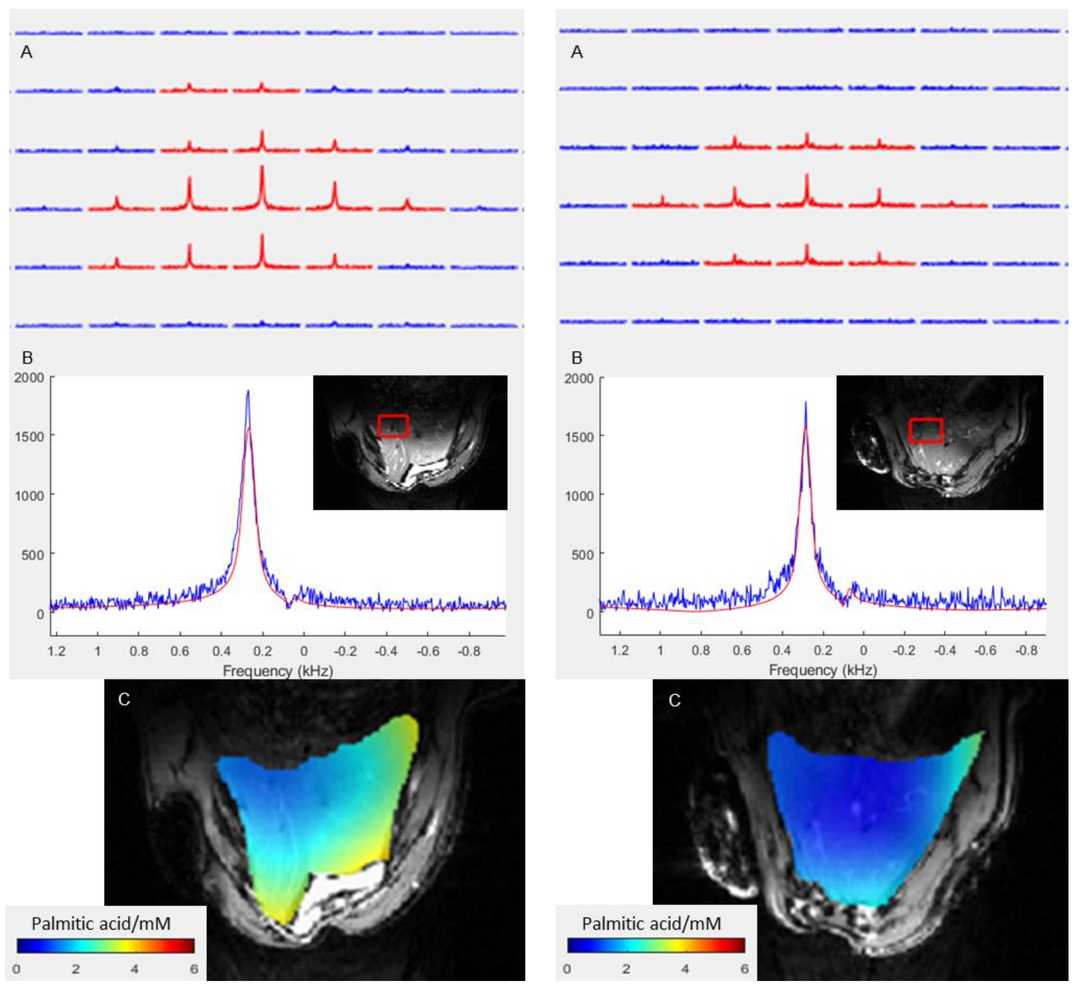

Figure 2: Liver DMI acquired after intravenous administration of palmitic acid in animals on HFD (left) and SD. The section of the matrix maps (A) show the voxels included in the analysis, one of which is shown with spectral fit in (B) as an example. The basal liver fat corrected metabolic map for the rats with fatty liver confirm their metabolic disorder, demonstrating the ectopic fat depots in the liver.

Conclusion

DMI provides a method for visualizing metabolism in vivo making an assessment of differences in metabolically healthy and impaired rodents possible. Thus, DMI holds great potential for the detailed study of metabolic disorders associated with a wide variety of diseases, such as fatty liver disease or diabetes type 2.

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