In Vivo Magnetic Resonance Imaging of Glucose

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Introduction

Glucose has been a desired target for hyperpolarized ^{13}C MRI due to its ability to report on metabolically active tissues and malignancy. However, the short T_1 of its ^{13}C nuclei [1] ruled out this possibility. Capitalizing on new molecular agent design strategies for the DNP technology which involve using reporter ^{13}C nuclei that are directly bonded to deuterium atoms [2], we show that hyperpolarized glucose imaging is feasible *in vivo*, using a glucose analog which is enriched with both ^{13}C and deuterium in all positions. We show that this strategy allows nonradioactive, noninvasive imaging of glucose.

Material and Methods

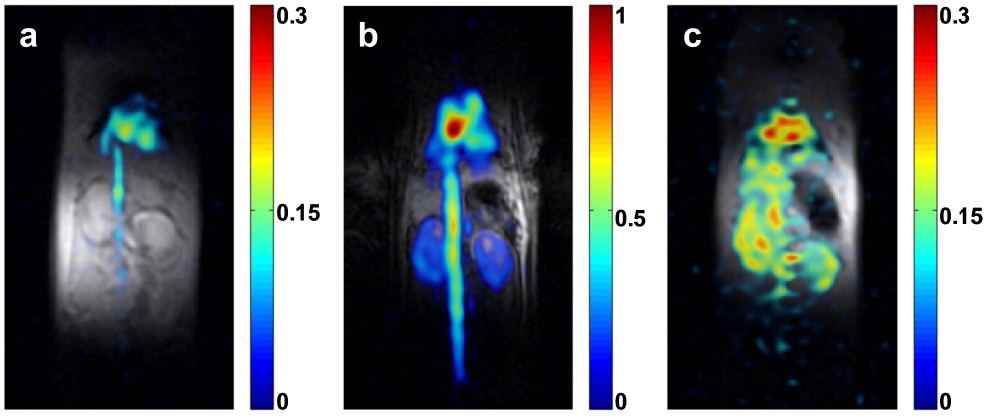
T_1 measurements were performed at 7 T and 11.8 T (Varian, Agilent, Santa Clara CA, USA). A solution containing [$^{13}C_6$, $^{2}H_7$]glucose and trityl radical (OX063, GE Healthcare, London, UK) was hyperpolarized in a dissolution DNP polarizer (Hypersense, Oxford Instruments, Abingdon, UK) at 1.4 K. The hyperpolarized medium was injected to anesthetized male Sprague-Dawley rats, 15-20 s following dissolution. Coronal projection ^{13}C images were recorded with a variable flip angle gradient echo sequence [3] in a 3T clinical MRI scanner (Discovery MR750) equipped with a transmit/receive birdcage ^{13}C RF coil (Morris Instruments, Ottawa, ON, Canada). Proton images were recorded with a custom built ^{1}H surface coil that fit within the ^{13}C coil.

Results

The T_1 of glucose ^{13}C was investigated at 11.8 T and 7 T. In native glucose the T_1 of these nuclei was 1-to-2 s. The deuteration of all of glucose ^{13}C nuclei resulted in a significant elongation of these ^{13}Cs' T_1s. The T_1s of the deuterated glucose ^{13}C ranged between 6-10 s at 11.8T and increased to 8-13 s at 7 T (average increase of 2 s, $P = 6\times10^{-4}$, paired t-test). The T_1 of glucose's deuterated ^{13}Cs were shortened on average by 3.3 s ($P = 1.4\times10^{-3}$, paired t-test) due to the added ^{13}C-^{13}C dipolar interaction in the fully ^{13}C labeled molecule. We note that the fully deuterated and fully ^{13}C labeled [$^{13}C_6$, $^{2}H_7$]glucose has two competing properties, in terms of its potential hyperpolarized imaging signal. On one hand, it is labeled at six positions, all with similar T_1. This property can be utilized to increase the initial hyperpolarized signal sixfold. On the other hand, the T_1s of these ^{13}C nuclei are shorter than any hyperpolarized probe reported to date. *In vivo* imaging (Figure a-c) showed that the 6-fold enhancement of the signal can be realized to form a high SNR image of hyperpolarized glucose, despite the relatively short T_1 of its ^{13}C nuclei.

Figure a-c (64x64 matrix, FOV=20 cm) demonstrate ^{13}C MRI images of rats injected with hyperpolarized [$^{13}C_6$, $^{2}H_7$]glucose. The images were recorded at 8 s (a), 12 s (b), and 20 s (c) from injection start. The dose was administrated over 12 s. Hyperpolarized images (color) are presented overlaid on proton images from the same rat. The color scales represent arbitrary linearly distributed intensity units for the hyperpolarized images. The relative intensities in the three images can be compared based on the corresponding color scale. In Fig. a, the inferior vena cava and the heart are clearly visible with an extremely high signal of the injected hyperpolarized media. In Fig. b, the signal intensity in the main vasculature and the heart is still high, with substantial intensity observed in the kidneys. In Fig. c, signal from the heart is the most intense signal in the image however, signal in the kidneys is clearly observed, as well as signal in other tissues such as the liver.

Discussion Figure (a) illustrates the utility of this imaging approach in catheter angiography, using glucose as a safe, high intensity, injectable agent. In intravenous glucose tolerance tests, which are widely used in detection of diabetes and insulin resistance, a glucose dose of 0.5 g/kg body weight is administered intravenously in a bolus injection. Therefore, it places glucose as one of the safest agents that can be administered intravenously to human subjects. Only about one fourth of this dose was used in the current study. The combination of higher signal intensity and lack of background signal is expected to enable higher contrast and resolution and/or faster magnetic resonance angiography applications which could present an attractive alternative to gadolinium contrast-based MRA or X-ray or CT angiography, particularly for patients with kidney dysfunction. Figure (c) shows a much more intense hyperpolarized glucose signal in the heart than in the vasculature and the kidneys. It may indicate glucose uptake in the myocardium since it is the main tissue that is expected to actively take up glucose under anesthesia.



It is likely that injected [$^{13}C_6$, $^{2}H_7$]glucose is taken up into cells by transport systems similar to those used for FDG uptake. Thus, the imaging method described here, using [$^{13}C_6$, $^{2}H_7$]glucose, may identify the same tissue characteristics identified by FDG-PET, without the ionizing radiation involved in PET examinations.

References [1] M. Harada et al. *Jpn. J. Radiol.* (2010). [2] H. Allouche-Arnon et al. *Contrast Media Mol. IMag.* (2011). [3] G. E. Santyr et al. *Magn. Reson. Med.* (2008). **Acknowledgement** This work was partially funded by BrainWatch Ltd.