Review of: "Deuterium metabolic imaging and hyperpolarized 13C-MRI of the normal human brain at clinical field strength reveals differential cerebral metabolism"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

This article combines two novel magnetic resonance imaging (MRI) techniques, namely, deuterium (^{2}H) metabolic imaging (DMI) and hyperpolarized ^{13}C-MRI (HP-^{13}C MRI) to simultaneously monitor glycolytic and oxidative metabolism in the human brain.

To fully appreciate this work, it is worth briefly reviewing the current state and challenges of MRI. In conventional MRI, the signal of ^{1}H (proton) largely originating from tissue water is imaged to produce high resolution images of soft tissues.^{1}H MRI can deliver exquisite anatomical images but is not particularly useful for metabolic studies. Although other nuclei, in particular, ^{13}C, may offer more information about physiology than^{1}H, in vivo imaging of nuclei other than^{1}H is more challenging due to their low sensitivity (lower gyromagnetic ratio) and much less concentration. Fortunately, recent advances in MR technology make the in vivo detection of ^{13}C as well as other low sensitivity nuclei feasible. Hyperpolarized (HP) ^{13}C NMR/MRI overcomes the low sensitivity problem by creating non-equilibrium^{13}C magnetization, which generates strongly amplified ^{13}C NMR signals. The ^{13}C labeled metabolic tracers are prepolarized and then administered by iv injection. It is important to note that the HP-signal is not persistent but decays by spin lattice (T_1) relaxation, allowing for the in vivo detection of ^{13}C for only a few minutes. Deuterium metabolic imaging involves the administration of deuterium labeled metabolic substrates and the metabolic fate of the tracers are monitored by in vivo deuterium MRI. DMI takes advantage of the short relaxation times of deuterium and compensates for the low sensitivity by applying rapid signal acquisition and scanning.

In this study, both the deuterium and^{13}C MRI data were collected in a 3 T scanner. [6,6'-$^2H_2$]glucose was administered orally at 0.75g/kg (60 g max) dose. Dynamic MR study was performed in one patient to determine the timescale of deuterium incorporation into water, glutamate/glutamine, lactate and lipids at 4.7 ppm, 2.4 ppm1.3 ppm and 0.9 ppm, respectively, The rest of the patients were scanned 1 -2 h after the oral administration of deuterated glucose. Blood glucose measurements indicated normal levels 2 hours after imaging. HP-^{13}C MRI was done immediately after iv injection of HP-[1-^{13}C]pyruvate (0.4 mL/kg, 250 mM). The expected metabolic products were observed with both tracers. The deuterated glucose passed through glycolysis to produce pyruvate (Pyr), which further underwent standard metabolism. Deuterium labeling was observed in lactate (Lac) as a result of Pyr/Lac exchange. The acetyl CoA produced from pyruvate by PDH entered the TCA cycle and the glutamate/glutamine (Glx) pool became labeled via ketoglutarate. Eventually, the ^{2}H label ends up in water as the two carbon units are oxidized in the cycle. The assumption

was made that the ^{2}H lactate reflected cytosolic glycolytic activity while the^{2}H-Glx mirrored mitochondrial oxidative metabolism. Thus, the ^{2}H-Lac/2HGlx ratio was used to index glycolysis against oxidative metabolism. This ratio was around 0.018 over 10 subjects. However, the HP-^{13}C data gave quite different results. Here, the HP-^{13}C-Lac signal was again taken as the measure of glycolytic activity but oxidative metabolism was quantified using ^{13}C-bicarbonate signal. In stark contrast to the DMI results, HP-^{13}C MRI gave a value of 3.7 for the HP-^{13}C-Lac/HP-13C-bicarbonate ratio. In addition, there was no significant correlation between the deuterium and ^{13}C data in subjects who were imaged with both modalities. Thus, according to the DMI data, cerebral metabolism is dominated by oxidative metabolism over glycolysis, whereas the ^{13}C data suggest just the opposite. The authors correctly point out that these seemingly contradictory results are due to differences in administration (oral vs iv), uptake and metabolic processing of the tracers as well as the timing of signal acquisition (hours vs seconds after administration). This last condition is especially important because it essentially means that DMI delivers information on metabolism when it has already reached a quasi-steady state, as evidenced by the relatively slow production of glutamate/glutamine. HP-^{13}C, on the other hand, offers a snapshot of early metabolism when it is dominated by the rapid exchange of the ^{13}C label into preexisting lactate pool. All these explanations sound plausible, however, we would like to offer one more: pyruvate compartmentalization. This is a well documented phenomenon and basically means that the HP-^{13}C-labeled pyruvate and the ^{2}H-labeled pyruvate pool originating from glucose may not be in the same metabolic compartment and therefore, they will not report the same metabolic activity.

In summary, this is a very well written manuscript that reports the application of two emerging MRI techniques, namely deuterium metabolic imaging and hyperpolarized 13C imaging, to monitor metabolism in the normal human brain. The main conclusion of the work is that the metabolic information obtained by deuterium metabolic imaging and hyperpolarized 13C imaging are different but complimentary. Unlike previously reported deuterium imaging of human subjects that were done at ultra-high field that are not used in the clinical practice, the DMI experiments in this work were performed at a clinically relevant field (3 T) demonstrating that the technique is applicable in routine clinical setting.