Exploring human brain oxidative metabolism and neurotransmitter cycling via coupled 13C MRS at 7T

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INTRODUCTION AND PURPOSE:

Abnormalities in neurotransmitter or TCA-cycle metabolism occur in multiple brain disorders. MRS ^{13}C traces acquired during intravenous administration of ^{13}C-labeled substrates can measure brain metabolite production rate[1-3]. However, this approach has required prolonged (90-120 min) infusions inside the MR scanner, which would be difficult to tolerate for patients with these brain disorders. In addition, technical requirements for proton decoupling complicate the application of this technique at high fields. Here we examined the feasibility of infusing ^{13}C-enriched glucose outside the magnet to steady-state followed by ^{13}C MRS at 7T without ^{1}H decoupling.

METHODS:

All procedures were performed following IRB approval and written consent. In adult male human volunteers (n=3), [U-^{13}C]glucose was administered through a peripheral intravenous line for 2 hours (outside the magnet) in a protocol which achieves steady-state plasma glucose ^{13}C enrichment[4]. After discontinuing the infusion, proton-coupled ^{13}C NMR spectra were acquired on a whole-body 7T scanner (Achieva, Phillips Medical Systems) with a quadrature 1H/13C transmit/receive partial volume coil adjacent to the occipital region of the head (Fig. 1A). Four saturation slabs minimized signal contribution from cranial lipids. Non-localized ^{13}C spectra were acquired in blocks averaging 64 acquisitions with TR = 5 s, (5:20 min. per dynamics), BW 7 kHz and 8k points, frequency offset centered on the carbonyl region. The repetition time was set to accommodate for longer relaxation times of ^{13}C carbonyls. Spectra were acquired for 1 hour after cessation of [U-^{13}C]glucose infusion. Non-linear least-squares fitting of the overlapping signals in groups A, B and C (Fig. 1B) were used to determine the C1/C5 ratio of glutamate, as well as the level of enrichment from the S/D45 ratio (Fig. 1B, insert). A baseline (the first 3 data points, Fig. 1C) with identical acquisition parameters was obtained for 16 min prior to glucose administration.

RESULTS AND DISCUSSION:

Figure 1B shows a representative ^{13}C spectrum with detection of individual carbons and associated multiplets (insert) arising from ^{13}C-^{13}C spin-spin coupling in the carbonyls of glutamate, glutamine and aspartate in a healthy human brain at the occipital pole. The sharp, well-resolved spectra (FWHM ~10 Hz) indicate that the long-range J_{CH} coupling is small for the carbonyl/amide carbons, thus justifying the experimental simplification of non-decoupling. The spin-coupled doublet D45 and natural abundance singlet in glutamate C5 were distinctly identified (insert). Based on the area of the singlet, about 17% of acetyl-CoA was derived from [U-^{13}C]glucose after metabolism through pyruvate dehydrogenase in this example. Consistent with this interpretation, a prominent ^{13}C- bicarbonate signal was detected at ~160 ppm. Neither alanine (at ~176.5 ppm) nor lactate (at ~183 ppm) could be detected in these healthy subjects. The glutamate C5/C1 ratio was ~1.35, consistent with ~20% level of anaplerosis. The ^{13}C signals from bicarbonate, glutamate, glutamine and aspartate were stable for at least 60 min (Fig. 1C), indicating relatively slow turnover of the highly enriched whole-body glucose pool in subjects at rest. Although kinetic data were not acquired, ^{13}C MRS of the brain at 7T can provide both metabolic and neurotransmitter cycling information without the need of either ^{13}C infusions inside the MR scanner or proton decoupling.

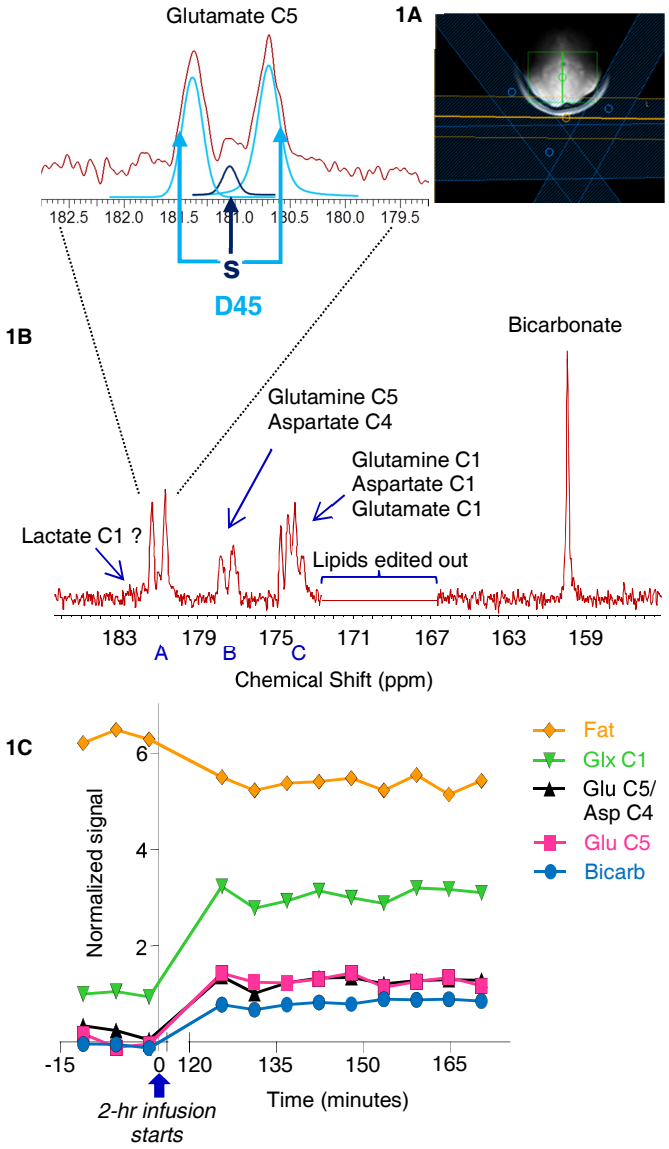

Figure 1: 1A) Proton image of the occipital lobes with saturation slabs placement; 1B) Post-infusion proton-coupled ^{13}C spectrum (carbonyl region) of the occipital lobes of a healthy subject showing detection of infused glucose products; (Zoom-in) Glutamate C5 singlet and doublet fitting; 1C) The time course of ^{13}C signals (normalized to maximum bicarbonate) before infusion and after infusion cessation.

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