Localized Detection of Fasting-Induced Changes in Lactate Metabolism By Hyperpolarized ^{13}C MRSI

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Introduction- Fasting induces profound shifts in hepatic metabolism, sustaining cellular respiration in the absence of dietary input. Chiefly, the liver exports large quantities of glucose. In a long fast, gluconeogenesis is the dominant source of this glucose. The kidneys supplement gluconeogenic capacity, exporting increasingly significant amounts as fasting extends, and in diabetes or acidosis[1]. Differential regulation of hepatic and renal components is thought to be important in diabetes, but remains poorly understood due to methodological limitations. While *systemic* investigations of gluconeogenesis are available, routine methods for *localized* data are lacking. HP ^{13}C MRI thus has transformative potential for diabetes research. Lactate is the primary glucose precursor in both organs. HP pyruvate has been more thoroughly studied[2], but handling of circulating lactate is quantitatively more important. Uptake of lactate and pyruvate may be differentially regulated, and gluconeogenesis from them proceeds along theoretically different biochemical pathways. In this study, we investigated localized effects of fasting on metabolism of both HP lactate and pyruvate in rats.

Methods- Seven newly mature rats (13±2wks) were scanned in fed and fasted (24h) states. Each study consisted of back-to-back scans with HP [1-^{13}C]lactate and [1-^{13}C]pyruvate. Recent availability of [1-^{13}C]lactic acid, with improved polarization over salts, facilitated this work[3]. The neat lactic acid however also contained dimers / oligomers with distinct spectral peaks which we suppressed with spectrally selective pre-saturation[4]. For HP lactate studies, localization was by 3D EPSI (15mm isotropic, 30s after infusion, e.g. Fig. 1). For HP pyruvate, signals were localized to two adjacent axial slabs (~20mm thick), designated liver and kidney. Data was reconstructed in SIVIC[5] and loaded into OsiriX[6] for ROI analysis, in DICOM format via SIVIC tools.

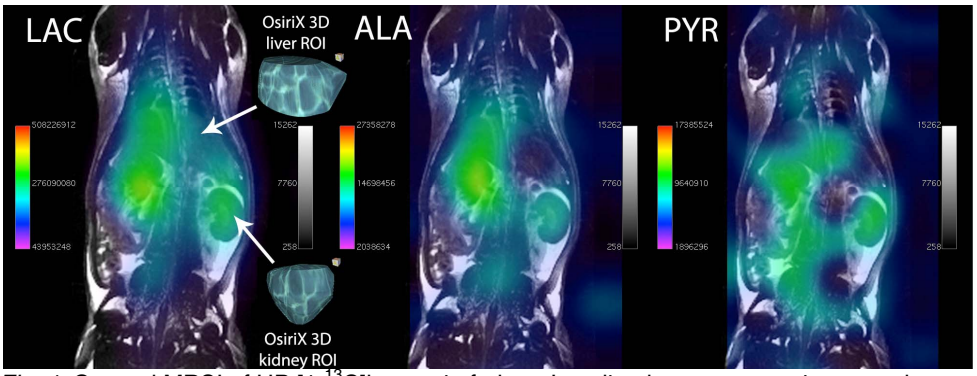

Fig. 1. Coronal MRSI of HP [1-^{13}C]lactate in fed rat. Localized spectra were integrated to produce metabolite images (color) of lactate and HP products alanine and pyruvate, shown overlaid on ^{1}H SSFP anatomic images (grayscale) using OsiriX. Volume renderings of 3D liver and kidney ROI's generated in OsiriX for data analysis are also shown.

Results & Discussion- ***Liver-specific increase of lactate-to-alanine ratio-*** In the HP lactate MRSI data, the hepatic ratio of lactate to alanine was specifically and significantly increased with fasting (liver: +51%, p=0.05; kidney: +27%, p=0.37, Fig. 2A). This result is consistent with increased hepatic uptake of circulating lactate for gluconeogenesis as expected during normal fasting (despite potentially reduced hepatic blood flow during fasting), although the result may also be partially due to lower alanine levels. A lower alanine-to-total carbon signal ratio was detected in the fasted HP pyruvate data, although the effect was smaller (-12%, p=0.01) and not specific to the liver slab. A potential explanation for lower alanine in liver is increased utilization as a gluconeogenic precursor, although alanine is not a significant renal precursor. ***Inactivation of pyruvate dehydrogenase complex (PDC)-*** HP pyruvate slab MRS showed that fasting decreased pyruvate decarboxylation in both liver and kidney. The ratio of bicarbonate to total carbon signal decreased 50% in liver (p=0.03) and 44% in kidney (p=0.01) (Fig. 2B). This is expected since fasting results in high acetyl-CoA, inhibiting PDC[7]. Acetyl-coA likewise stimulates carboxylation of pyruvate via pyruvate carboxylase, the first committed step in gluconeogenesis. PEPCK flux could also yield [^{13}C]bicarbonate[2], but the decrease in bicarbonate with fasting suggests that *in vivo* this signal is linked to PDC activity. ***Summary-*** Although both liver and kidney exhibited the drop in bicarbonate signal with fasting, only liver exhibited the large increase in lactate-to-alanine ratio detected using HP lactate, consistent with the expected local increase in gluconeogenesis in normal fasting. The likely biological explanation is a more rapid shift of liver metabolism toward gluconeogenesis, to be followed by kidney with longer fasting.

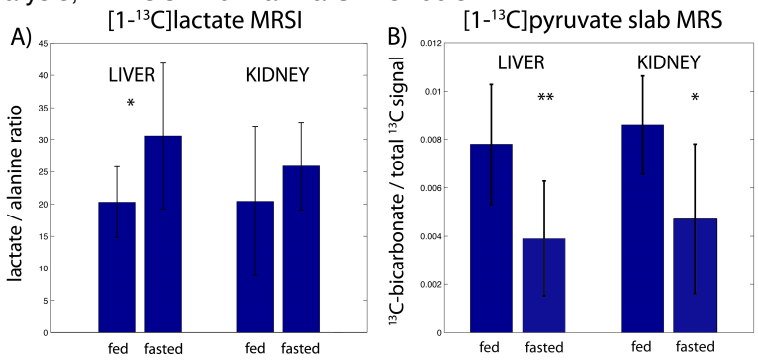

Fig. 2. Bar graphs summarizing key local effects of fasting on HP metabolite ratios in HP lactate (A) and HP pyruvate (B) experiments.

Conclusions- Organ-specific lactate metabolism changes following fasting were detected non-invasively with HP ^{13}C MR.

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