Hyperpolarized pyruvate allows early detection of lactate in real-time metabolism of acute liver failure rats

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INTRODUCTION

Intracranial hypertension is a severe complication of **acute liver failure (ALF)** secondary to brain edema. The pathogenesis of cerebral edema in ALF is not clear but energy metabolism alterations are involved and genesis of lactate seems to have an important role.

METHODS

Animal Model

ALF animal model was induced in SD-OFA rats by portocaval anastomosis (PCA) and hepatic artery ligation. The metabolism was assessed by ^{13}C-hyperpolarized pyruvate. This study was performed on PCA and ALF rats (n=8/group) repeatedly at 6 and 12 hours after sham or HAL surgery, respectively.

DNP

$^{13}C_1$-pyruvic acid (with 15mM OX63 trityl radical and 1.5mM Dotarem) was hyperpolarized using a HyperSense DNP polarizer for 1 h (≈ 94.1 GHz, 100mW). The sample was subsequently dissolved in a pressurized and heated alkaline buffer ≈ 4 mL, with a resulting polarization of 18±2 % and physiological temperature and pH. Depending on the weight of the rat, 2.5-3.5 mL (0.01mL/g) of the 80 mM hyperpolarized $^{13}C_1$-pyruvate solution was injected into the rat.

Magnetic resonance

^{13}C-Magnetic resonance studies were performed in a 7 T Bruker BioSpec 70/30 USR using a ^{13}C-MR pulse-acquire spectroscopic sequence, acquiring a spectrum every 2 s during 3 min following injection (TR, 2s; excitation flip angle, 5º; sweep width, 150000 Hz; acquired points, 2048; frequency centered on the pyruvate resonance).

AIM

The aim of the study was to follow the dynamic synthesis of brain metabolites using hyperpolarized pyruvate in a model of ALF.

RESULTS

PCA and ALF rats did not show any change in injection time of pyruvate. ALF rats had a significant increase in the ratio of total lactate versus pyruvate compared to PCA rats (ALF at 6h: 0.475±0.070 and at 12h: 0.606±0.156; PCA at 6h: 0.348±0.052 and at 12h: 0.359±0.068; P=0.013) (Figure 1& 2).

Additional MR parameters showed that the rate of lactate production was higher in ALF rats (P<0.001) with significant changes according to the severity of liver failure (6h: 1.41±0.23s^{-1} and 12h: 1.78±0.44s^{-1}, P=0.021) in comparison to PCA rats (6h: 1.06 ± 0.23 s^{-1} and 12h: 1.07 ± 0.17s^{-1}, P=0.900).

There was also an increase in the rate of alanine production independent to the time course (ALF: 0.25±0.10 s^{-1} and PCA: 0.16±0.05s^{-1}, P=0.003). The exponential signal decay term showed an accumulation of lactate in PCA rats (ALF: 29±3s and PCA: 32±1s, P<0.001) and pyruvate (ALF: 18±1s and PCA: 19±1s, P<0.001).

CONCLUSIONS

Magnetic resonance with hyperpolarized pyruvate early detects an increase in lactate in ALF rats, sign of anaerobic metabolism activation. This study also shows for the first time the *in vivo* brain metabolism of ALF rats at nearly real-time. Hyperpolarization may be used to follow the *in vivo* metabolism involved in ALF non-invasively.

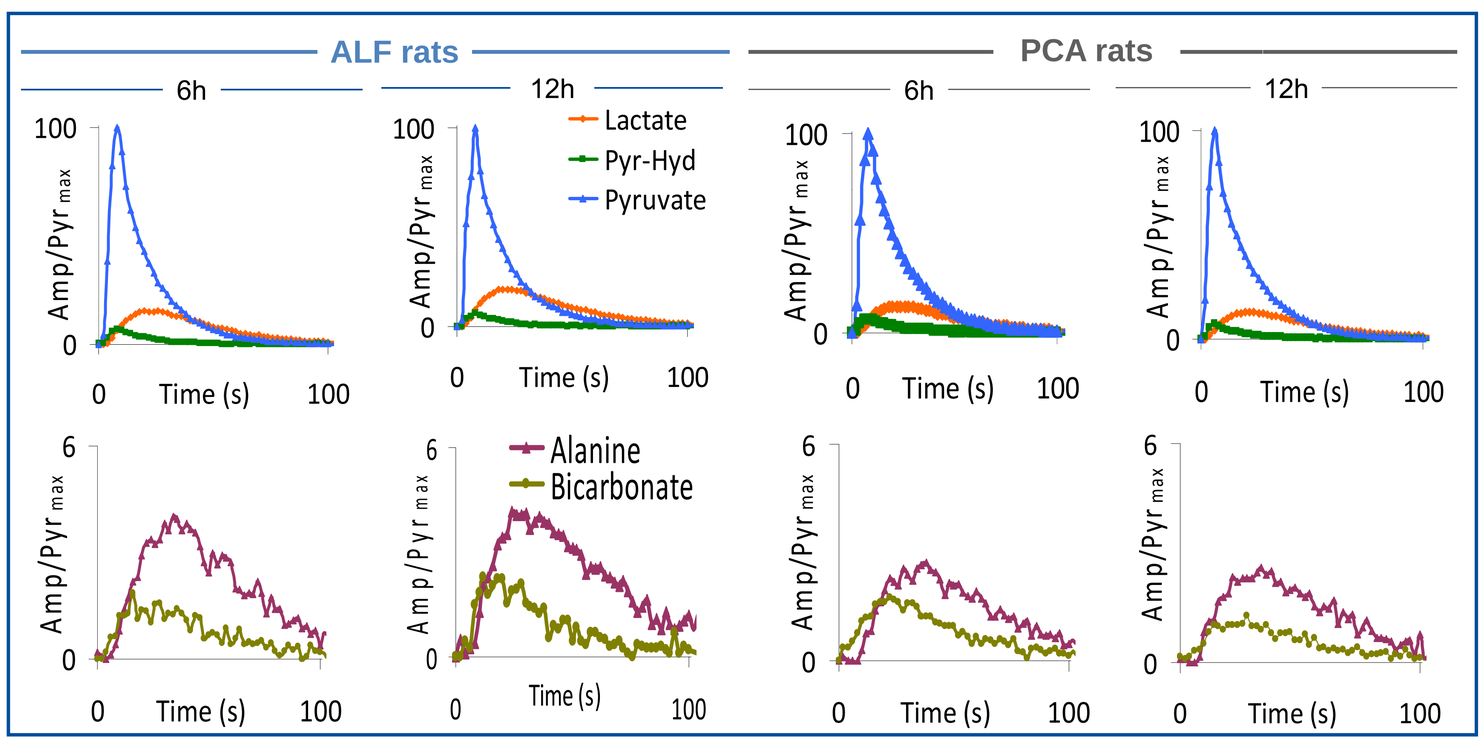

Figure 1 Representative in vivo ^{13}C-spectra of a brain of acute liver failure rat along the disease progression (at 6 and 12 hours after hepatic artery or sham ligation). Peak areas of pyruvate, hydrate pyruvate (Pyr-Hyd), lactate, alanine and bicarbonate normalized to the maximum signal of pyruvate (Amp/Pyr_{max}).

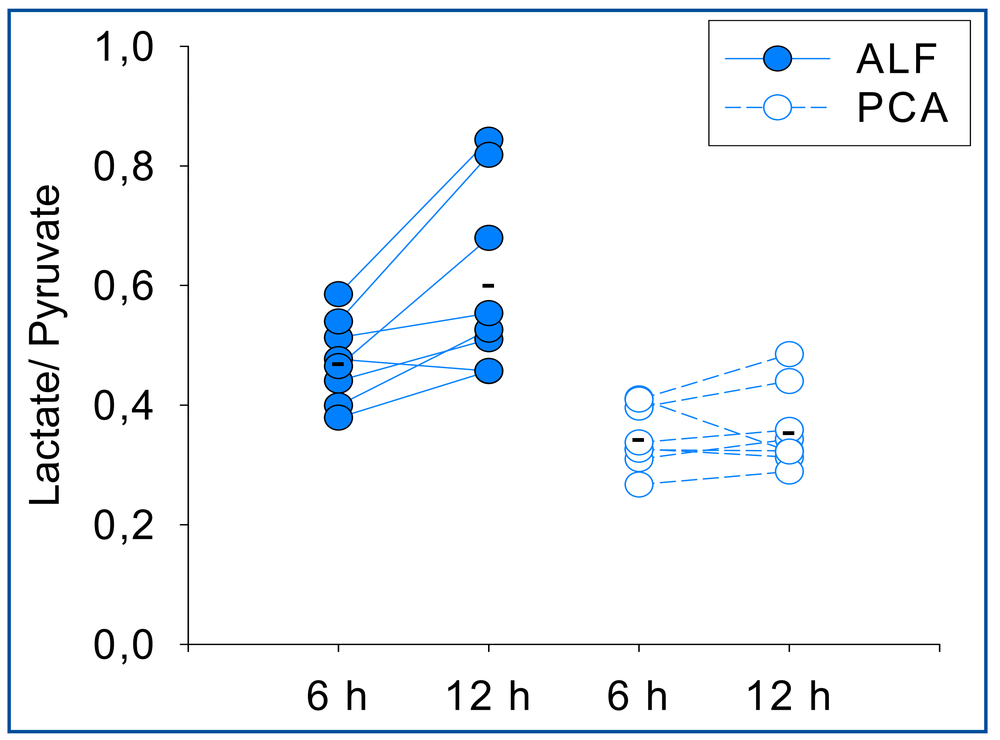

Figure 2 The ratios of the area of lactate versus pyruvate along the disease progression (at 6 and 12 hours after hepatic artery or sham ligation) of ALF rats and PCA rats (the dash shows the mean value of each group).