Abnormal $^{13}$C Glucose Metabolism in patients with Chronic Hepatic Encephalopathy

Stefan BLUML$^1$, Angel MORENO-TORRES$^1$, Brian ROSS$^2$

$^1$Rudi Schulte Research Institute, Santa Barbara, CA United States; $^2$Huntington Medical Research Institutes, Pasadena, CA United States;

Introduction

Chronic hepatic encephalopathy (CHE) describes a constellation of neurological symptoms and signs associated with liver disease. The pathogenesis of CHE is incompletely understood (1). The cause of increased cerebral glutamine observed in CHE patients with $^1$H MRS is due to excess ammonia delivery to the brain, but several abnormalities detected by $^1$H or $^3$P MRS (2) are unexplained. In animals, an additional effect of increased blood ammonia is inhibition of cerebral glucose metabolism (3). To examine this question directly in human CHE, we administered intravenous $^{1-13}$C glucose to patients and controls and determined cerebral metabolites with $^{13}$C MRS (4,5).

Materials and Methods

Six CHE patients (3m, 3f, 58±6 yrs) and three controls (2m, 1f, 45±18 yrs) were studied with natural abundance and with $^{13}$C MRS after i.v. glucose infusion. 0.2 grams/kg body weight of glucose was infused over 15 min. Experiments were carried out on a GE, Signa 1.5 T system. Before, during and after infusion, spectra were acquired from the occipital brain region with a FID sequence, TR = 1s, 1024 pts, 4 kHz excitation bandwidth and quantified as described in (4).

Results

(i) $^{13}$C patterns of enrichment in CHE were strikingly different from normal (Fig.1). (ii) The kinetics of $^{13}$C glucose appearance in the brain (Fig 2A) and fractional $^{13}$C enrichment of blood glucose were comparable in patients and controls. (iii) $^{13}$C incorporation into Glu$_4$ (Fig 2B), Glu$_2$, Asp$_2$, Asp$_3$ and HCO$_3^-$ and the ratio Glu$/$Glu$_4$ (Fig 2C), all putative markers of TCA-cycle rate, were significantly reduced. ($P<0.01$) in CHE compared to control. (iv) Fractional enrichment ($E%$) of Glutamine (Gln) C$_2$ was decreased ($P<0.03$) and $^{13}$C accumulation into Gln$_{2}$ relative to its substrate Glu$_2$ was increased ($P<0.01$) in CHE (not shown).

Discussion

The lower overall label accumulation in CHE is consistent with a reduced TCA-cycle rate (Fig 3) as less $^{13}$C label reaches α-ketoglutarate (KG), from which less is incorporated into glutamate via fast α-KG/Glu exchange (5). The data also indicate abnormal glutamine synthesis with a potential impact on neurotransmitter Glu/Gln cycling.

Conclusion

$^{13}$C MRS after glucose infusion provides novel insights into the pathophysiology of CHE.

References


Fig. 1: $^{13}$C spectra from (A) control and (B) CHE patient. 155-165 ppm unsubtracted $^{13}$C (60-100 mins); 20-60 ppm difference spectra (80 100 mins).

Fig. 2: Impact of CHE (A) Brain glucose; (B) $^{13}$C isotopic enrichment of glutamate C$_4$ and (C) the ratio GluC$_2$/GluC$_4$ plotted versus time.

Fig. 3: Schema of neurochemical disorder in CHE.

Acknowledgment: This work was supported by the Rudi Schulte Research Institute, Santa Barbara, CA and Cambridge Isotope Laboratories Inc., Andover, MA. FDA IND 56, 510.