Long term effects of recurrent hyperglycemia on hippocampal neurochemistry in developing rats

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INTRODUCTION

Recurrent hyperglycemia (HG, plasma glucose $[Glc]_{plasma}$ > 150 mg/dL) is a common metabolic problem in preterm infants with gestational age below 26 weeks. Acute neurological complications, such as intracranial hemorrhage are associated with hyperglycemia in this population. The long-term effects of recurrent hyperglycemia on the developing brain are not well known. The aim of this pilot study is to investigate long-term effects of recurrent hyperglycemia of graded severity on the neurochemical profile of hippocampus in developing rats using in vivo ^{1}H NMR spectroscopy at 9.4T.

METHODS

All NMR measurements were performed using a Varian INOVA spectrometer interfaced to a 9.4 T magnet, equipped with powerful gradient/shim coils insert (Resonance Research Inc). First and second order shims were adjusted by FASTMAP [1]. Ultra-short echo-time STEAM (TE = 2 ms) combined with outer volume suppression and VAPOR water suppression was used for ^{1}H NMR spectroscopy [2]. Metabolite concentrations were quantified using LCModel with macromolecule spectra included in the database and the unsuppressed water signal was used as an internal reference [3]. Recurrent HG was induced for 2 hours each, twice a day in rat pups from postnatal day (P)3 to P12 by the subcutaneous injection of 30% (moderate HG, $[Glc]_{plasma}$ = 226 ± 12 mg/dL) or 50% dextrose (severe HG, $[Glc]_{plasma}$ = 380 ± 27 mg/dL). In vivo ^{1}H NMR spectra were collected on postnatal day 30 from 7 rat pups.

RESULTS

Spectral quality and the location of VOI are shown in Fig. 1. In addition to seven spectra acquired from hippocampus, three spectra were measured from cerebral cortex. Off all fourteen metabolites and two combined pairs of metabolites consistently quantified from all hippocampal spectra, only ascorbate (Asc), glutamate (Glu), phosphorylethanolamine (PE) and taurine (Tau) indicated a trend for progressive alteration with the severity of HG (Fig 2). A similar trend was also observed in the cerebral cortex for Asc, Glu and Tau.

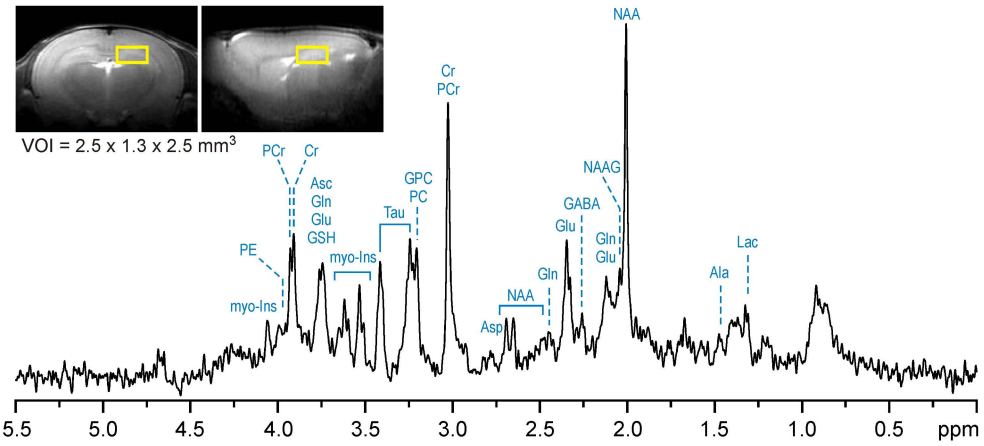

Fig. 1 In vivo ^{1}H NMR spectrum of rat hippocampus on postnatal day 30. STEAM, TE = 2 ms, TR = 5 s, NT = 216, VOI = 8 µL. Processing: Gaussian multiplication (gf = 0.2), FT, zero-order phase correction, no water removal or baseline correction were applied. Inset: RARE images with the location of VOI.

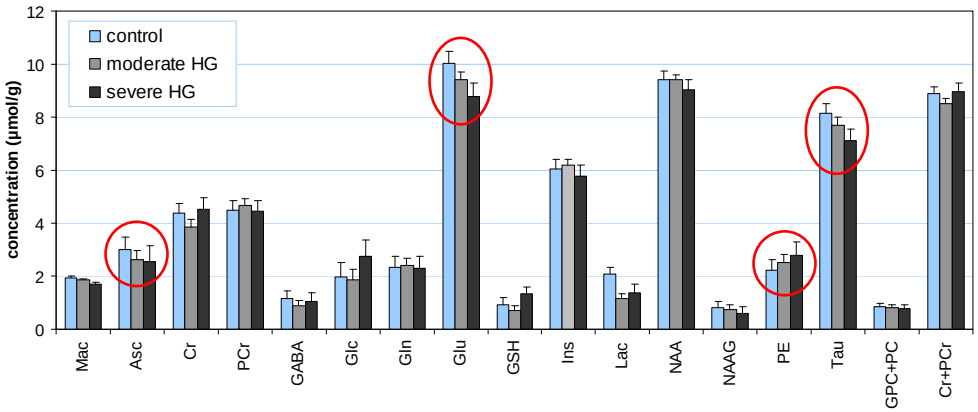

Fig. 2 Changes in the neurochemical profile of rat hippocampus on P30 induced by hyperglycemia episodes during P3 – P13. Error bars: averaged CRLB, n = 1 – 4. Red circles highlight progressive concentration change with the severity of hyperglycemia on P3 – P12.

DISCUSSION

These preliminary data indicate that the recurrent HG may cause long-term alternations in the neurochemical profile of the developing hippocampus. Decreased glutamate has been associated with impaired cognitive function in adult humans. Observed changes in Tau may indicate effects of the recurrent HG on osmoregulation and changes in PE may imply altered myelination. Finally, decrease in Asc may be linked to the oxidative stress. In conclusion, the spectroscopic data suggest that recurrent HG may have a primary role in the cognitive deficits common in preterm infants.

REFERENCES: 1. Gruetter R and Tkac I, *Magn Reson Med* 2000: 43, 319-323; **2.** Tkac I et al., *Magn Reson Med* 1999: 41, 649-656; **3.** Pfeuffer J et al., *J Magn Reson* 1999: 141, 104-120.

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