Effect of iron deficiency on developing rat striatum

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INTRODUCTION

Gestational diabetes and intrauterine growth retardation cause fetal brain iron deficiency (ID) [1]. Neonatal ID impairs hippocampus based recognition memory in rat pups and results in concentration changes of multiple metabolites in the developing hippocampus [2]. However, effects of gestational and early postnatal ID on the neurochemical profile of striatum and striatum-dependent behaviors are unknown. The purpose of this study was to investigate effects of ID on metabolite concentrations in developing rat striatum using a completely non-invasive longitudinal study design.

METHODS

All NMR measurements were performed with a Varian INOVA spectrometer interfaced to a 9.4 T magnet, equipped with powerful 2nd-order shim coils (Magnex). First and second order shims were adjusted by FASTMAP [3]. Ultra-short echo-time STEAM (TE = 2 ms) combined with outer volume suppression and VAPOR water suppression was used for localization [4]. Metabolite concentrations were quantified using LCModel with macromolecule spectra included in the database and the unsuppressed water signal was used as an internal reference as in our previous studies [2,5,6]. Fetal and neonatal ID was induced by feeding dams and later pups with a low Fe diet ([Fe] = 3 – 6 mg/kg from gestational day 3 to postnatal day 14 (P14); [Fe] = 10 mg/kg P14 – P28; [Fe] = 40 mg/kg P28 - P37). Control group of rat pups (n = 10) and ID pups (n = 10) were studied longitudinally on P8, P22, and P37. Standard striatum-dependent behavioral tests of bilateral forelimb placing and unilateral vibrissae stimulated forelimb placing were performed on the same days, right before the spectroscopy examination.

RESULTS AND DISCUSSION

Induced ID resulted in anemia (70% reduction of the hematocrit on P22 relative to age matched controls) and a decrease in brain Fe content (30% reduction on P8 relative to age matched controls). Highly resolved in vivo ^{1}H NMR spectra measured from striata (Fig. 1) allowed reliable quantification of 16 brain metabolites (Cramer-Rao lower bounds < 30%). All quantified metabolites changed during postnatal period P8 – P37 and the developmental trajectories were similar in both groups. However, small but highly significant differences between the ID and control groups were observed for multiple metabolites, such as Cr, Glc, Gln, Glu, myo-Ins, Lac, NAA, PCho+GPC, and Tau (Fig. 2). Concentration changes resembled those observed in hippocampus [2], but were delayed by a week. Additional changes in Glc and myo-Ins were observed in the striatum. Biochemical changes indicated effects of ID on energy status (PCr/Cr), substrate utilization (Glc, Lac), neurotransmission (Glu, Tau), glial development and myelination (Gln, myo-Ins, NAA). Changes in the neurochemical profile correlated with delayed performance in striatum-dependent behavioral tests in the ID group.

REFERENCES: **1.** Georgieff MK at al, *J Pediatr* 127: 308 (1995); **2.** Rao R et al, *J Nutr* 133: 3215 (2003); **3.** Gruetter R and Tkac I, *Magn Reson Med* 43, 319 (2000); **4.** Tkac I et al., *Magn Reson Med* 41, 649 (1999); **5.** Tkac I et al, *Magn Reson Med* 50, 24 (2003); **6.** Raman L et al, *Develop Brain Res* 156: 202 (2005).

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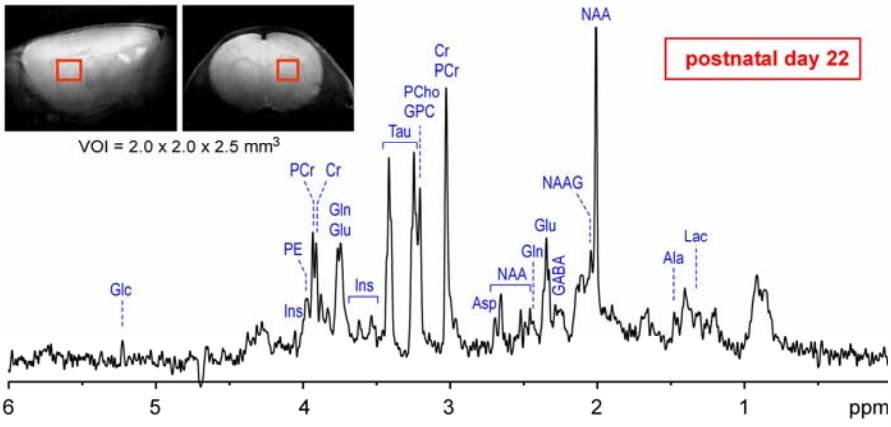

Fig. 1 In vivo ^{1}H NMR spectrum from the developing striatum (P22) of the iron deficient rat measured at 9.4 T. STEAM, TE = 2 ms, TR = 5 s, VOI = 10 µl, NT = 240. Processing: weighted FT and zero-order phase correction. No water removal or baseline correction was applied. Inset: RARE images with the location of the VOI in striatum.

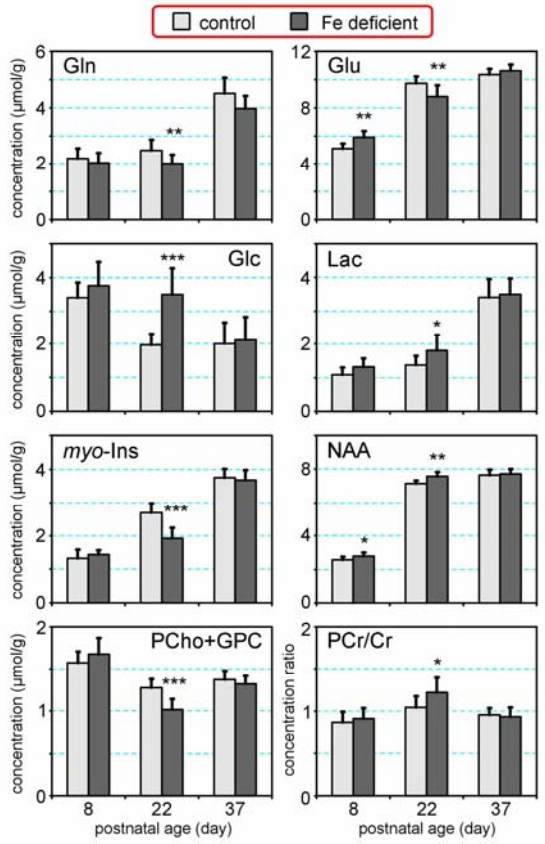

Fig. 2 Effect of iron deficiency on developmental changes of selected metabolite concentrations (means ± SD, n = 10 in each group). * $p < 0.02$, ** $p < 0.005$, *** $p < 0.001$.