

1H MRS of Cortical and Subcortical Structures in Mild and Severe Neonatal Hypoxic-ischemic Cerebral Injuries

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INTRODUCTION: Hypoxic-ischemic (HI) cerebral injury is a major cause of brain damage in infants, and is associated with chronic neurological dysfunctions (1). While ¹H MRS has been increasingly used for evaluating acute HI injury in neonates (2-3), little is known about late events of metabolic changes in the brains, which are potentially important in determining and improving the functional consequences of brain lesions. This study employed *in vivo* ¹H MRS to understand the metabolic alterations in cortical and subcortical structures during the recovery period at 3 and 7 days after mild and severe HI injuries to the neonatal brains.

MATERIALS AND METHODS: Animal Preparation: Sprague-Dawley rats (12-16 g, N=11) were divided into 3 groups. In the HI-injured groups, animals underwent unilateral ligation of the left common carotid artery at postnatal day (P) 7 followed by hypoxia at 36-37°C for 1 hour for mild injury (n=3), and 2 hours for severe injury (n=4). Four other rats were untreated and acted as controls.

MR Imaging and Spectroscopy: All MR measurements were acquired utilizing a 7T Bruker scanner. Spin-echo T2WI was performed at 3 days (P10) and/or 7 days (P14) after surgery. MR Imaging and Spectroscopy: All MR measurements were acquired utilizing a 7T Bruker scanner. Spin-echo T2WI was acquired for morphological evaluations and voxel localization for ¹H MRS. After shimming with FASTMAP, ¹H MRS was performed using a PRESS sequence with TR/TE = 2000/11 ms and NEX = 128. A 3x1.5x3 mm³ voxel was placed over the posterior cortex and another 2.5x2.5x2.5 mm³ voxel over the thalamus in each hemisphere (Fig. 1).

Data Analysis: Metabolite ratios were calculated utilizing the Sub-QUEST method in jMRUIv3.0 using simulated metabolites in NMR-SCOPE as prior knowledge. NAA:Cr, Cho:Cr, Glu:Cr, Lac:Cr and Tau:Cr ratios were statistically evaluated using Students' t-tests between contralateral sides of the same group, between different ages of the same group, and between different groups at the same ages. Results were considered significantly different when p<0.05. Cramer-Rao lower bounds were below 20% of estimated amplitudes for most of the metabolites of interests quantitated.

RESULTS: In the T2WIs of mild HI group, a small lesion was identified as hyperintensity in the left cortex at P10 and hypointensity at P14 upon HI-injury at P7 (Fig. 1, open arrows), whereas in the severe HI group, infarcts were observed covering one-fifth to more than half of the left cortex at P10 and P14 (Fig. 1, asterisks). Hyperintensity was also found in the right cortex and left subcortex in 2 severe HI animals at P10, which normalized at P14 (Fig. 1, solid arrows); In ¹H MRS, the metabolite ratios in the normal group were consistent with literature values at the same age (4). In Figs. 2 and 3, relative to the Cr peak, Cho, Glu and Lac increased further in the left cortex of severe HI group than mild HI group at P10. These values then decreased slightly at P14 in both HI groups. Tau also increased on both sides of the cortex at P10 and then drop at P14 for both HI groups. In the left thalamus of the severe HI group, NAA appeared to decrease transiently at P10 and normalize at P14, whereas Cho, Glu, Lac and Tau levels apparently peaked at P10.

DISCUSSION AND CONCLUSION: The higher increase of Glu:Cr in severe than mild HI-injured brains appeared to associate with our previous findings on the increased expression of local glutamine synthetase in severe more than mild HI injuries at the same ages (5-6), indicative of enhanced Glu excitotoxicity in severely HI-injured immature brains. Previous studies also suggested the extracellular overflow of Tau, which might exert neuroprotective actions to neural tissue (7), in company with Glu in the cortex and striatum upon severe neonatal HI insult (8). The transient increase of Cho:Cr in the left cortex at P10 might reflect astrogliosis, cell membrane breakdown and subsequent clearance of debris by macrophages (9), whereas the Lac:Cr level likely reflected the extent of cerebral infarction in the recovery period (2-3). The results of this study may help to investigate potential therapies and the recovery mechanisms upon different severity of neonatal HI insults.

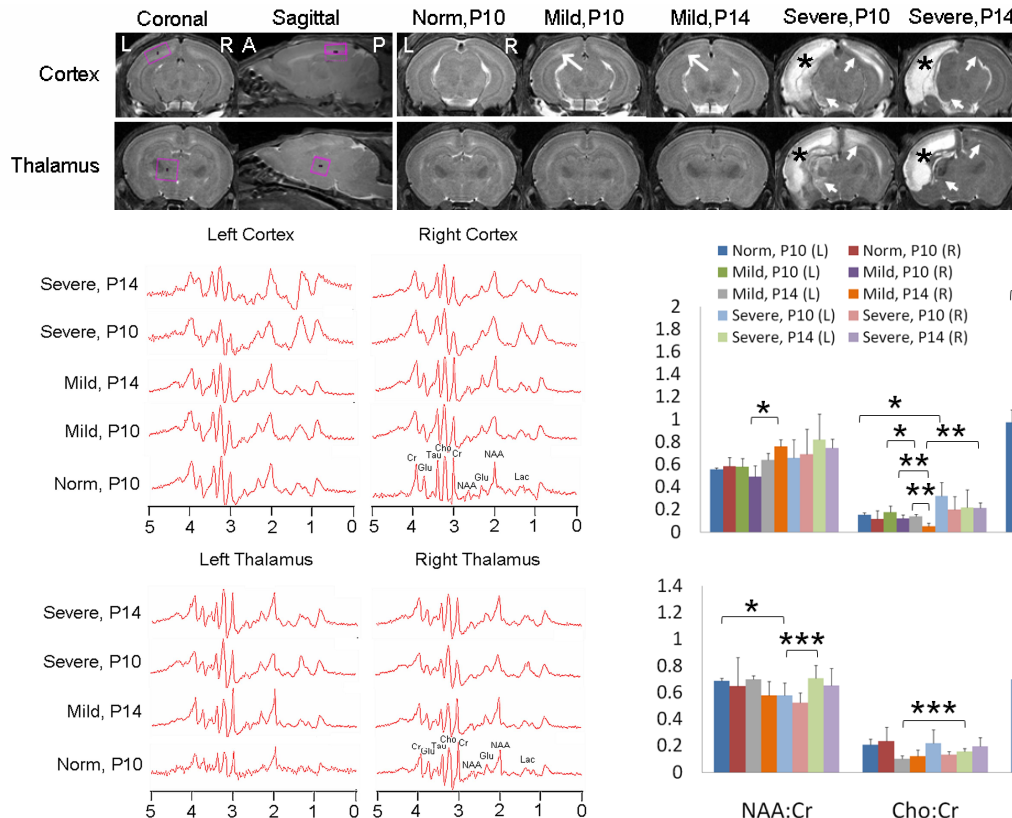


Fig. 1: (Left) Localization of voxels of interests in the cortex and thalamus of the left hemisphere in the coronal and sagittal planes. (Right) T2WIs at the levels of the cortex and the thalamus in normal, and mild and severe HI-injured groups at postnatal days (P) 10 and 14 upon HI-injury at P7.

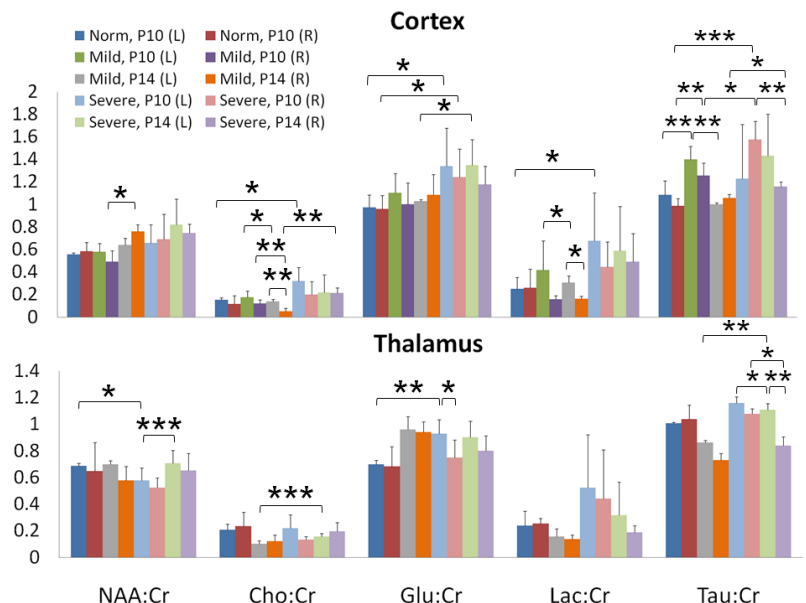


Fig. 2: Averaged MR spectra on both sides of (top) cortex and (bottom) thalamus in normal, and mild and severe HI-injured animals.

Fig. 3: Comparison of metabolite ratios on both sides of (top) cortex and (bottom) thalamus. (*p<0.05; **p<0.01; ***p<0.001) (Unit for Tau:Cr: x2)

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