MRI Monitoring of Progression of Selective White Matter Injury Following a Transient Cerebral Hypoxic-Ischemic Insult in Neonatal Rats

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Introduction

Selective white matter injury is often seen in pre-term infants and is a major cause of cerebral palsy associated with developmental deficits in motor, perceptual, visual or cognitive functions in later life [1]. Recently, a perinatal model of selective white matter injury was produced in 7-day-old rats by exposing them to cerebral hypoxia-ischemia of shorter duration at a slightly lower body temperature [2]. The progression of MR imaging changes after perinatal white matter injury is difficult to follow in sick pre-term infants so the temporal evolution of MR changes are poorly defined. We hypothesized that selective white matter injury would change over time as edema resolves but permanent injury would remain 1 week after the insult.

Material and Methods

Cerebral hypoxia-ischemia or sham procedures were performed in 21 7-day-old rats as described previously [2]. Briefly, the right carotid artery was occluded under isoflurane anesthesia with subsequent exposure to 8% oxygen for 45-50 minutes at a body temperature of approx. 36-37°C (chamber temperature of 34.5 °C). T1, T2, ADC and perfusion maps were acquired at 1h, 24h, or 48h and then again at 7days following hypoxia-ischemia using a 9.4T/21cm MR imaging system [3,4]. T_2 maps were collected from a set of T_2 weighted spin echo images (32 echoes, TR=1200ms, TE=10ms between echoes, FOV=3cm^2, 128×128 matrix) and T_1 maps were acquired with an inversion-recovery Snapshot-FLASH imaging technique (TR=3.55 ms, TE=2.1 ms, increasing time of inversion delays of 234, 503, 831, 1233, 1751, 2480, 3728, 9226 ms). An ADC map was calculated from diffusion weighted images acquired with TR=1200ms, TE= 40ms and b values of 46, 211, 540 and 767 s/mm^2. Perfusion imaging was performed using an arterial spin labeling technique [4] (TR/TE=3.55/2.1 ms, flip angle=12°, average of 32) with an adiabatic inversion pulse in a 1.5G/cm field gradient followed by a TurboFLASH imaging sequence. Control images were also obtained. Cerebral blood flow (CBF, in ml/g/s) was calculated as $CBF=\lambda(1/T_1 + \delta)(Mb_{con}-Mb_{inv})/2\alpha Mb_{con}$. with λ as 0.9 and δ as $0.039s^{-1}$. Measured values included: T_1 of brain; Mb_{con}, the intensity within control images; *Mbinv*, the intensity within images after arterial inversion. Locally developed software was used to measure relaxation times, ADC and CBF within the white matter of the external capsule and gray matter of the parietal cortex or thalamus in the hemispheres contralateral and ipsilateral to the artery occlusion. Tissue damage was also assessed histologically at 7days post hypoxia-ischemia in sections labelled for cell death using TUNEL and sections stained immunohistochemically for myelin basic protein (MBP).

Results and Discussion

At one week post hypoxia-ischemia extensive cortical damage was observed in 3 animals and these animals were excluded from the overall analysis. In the majority of the remaining animals, evidence for permanent selective white matter injury ipsilateral to the occlusion was observed as an increased TUNEL positive cells in white matter and a reduced MBP immunoreactivity. MR imaging changes in both white and gray matter appeared to evolve over time with selective white matter changes being most pronounced at 48 hr. post hypoxia-ischemia.. Thus soon after hypoxia-ischemia, within 1hr of reperfusion, changes in both white (external capsule) and gray matter (parietal cortex) were evident as decreases in ADC and CBF and an increase in T1 and T2 (e.g. figs 1-2). At 24 hr post hypoxia-ischemia, most gray matter MR imaging changes within cortex had recovered whereas white matter changes tended to persist. Indeed, selective ipsilateral reductions in CBF in external capsule were observed at this time point. There was also a tendency for ADC to be increased rather than decreased in the external capsule by 24 hr post-hypoxia-ischemia. At 48 hrs post hypoxia-ischemia there were marked left-right differences in white matter but not gray matter observed in the MR images (Fig.1). Quantitatively, there were significant increases in ADC, T2 and T1 and a decrease in CBF in the external capsule but not in the parietal cortex. By 7days post hypoxia-ischemia, despite histological evidence of cell injury, the changes in the tissue producing these MR changes had recovered and there were no remaining left-right differences in either the ADC, T2, T1 or the perfusion maps.

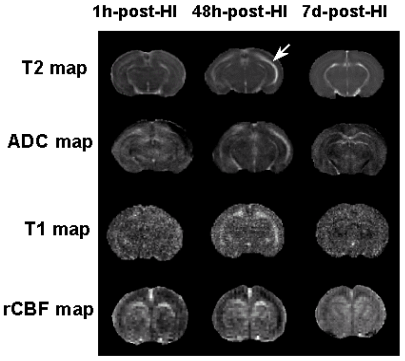

Fig.1. MR image maps of rat brain at various times after cerebral hypoxia-ischemia (HI). White matter changes are apparent in the external capsule (white arrow) at 48 hr post.

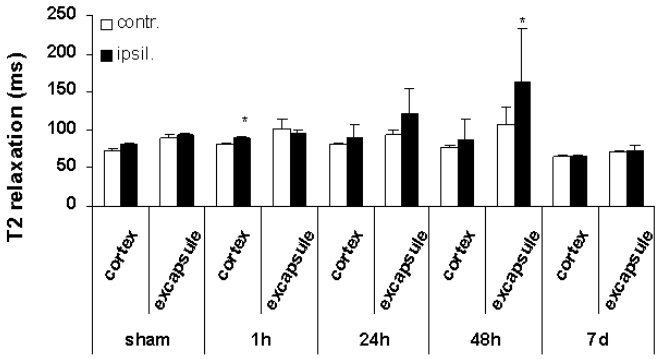

Fig.2. T2 values in sham animals or in rats at various times following unilateral cerebral hypoxia-ischemia. Regions shown: white matter (extermal capsule) and gray matter (parietal cortex) either contralateral (contr.) or ipsilateral (ipsil.) to the carotid artery occlusioin. *P<0.05, compared to contralateral.

Conclusions

Following exposure of neonatal brain to a relatively mild unilateral hypoxia-ischemia, there is selective white matter injury that progresses over time and the evolution of some of these changes can be detected using MR imaging techniques such as ADC, perfusion, T1 and T2. The selective injury detected using MR imaging is maximal at approx. 48 hrs post hypoxia-ischemia and undetectable by 1 week post hypoxia-ischemia despite evidence for histological changes at this time. Increases in ADC appear to be very sensitive and specific for detecting hypoxic-ischemic white matter injury *acutely* but other methods are needed for diagnosing white matter injury in the *sub-acute* stages.

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References

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