Introduction

Background: Mild hypothermia immediately following an hypoxic-ischaemic (HI) insult ameliorated the delayed failure of cerebral energy metabolism observed in a piglet model of human birth-asphyxia. Cerebral water apparent diffusion coefficient (ADC) demonstrated characteristic anatomical patterns of reduction during delayed energy failure in this model: reduced ADC correlating with loss of high-energy phosphorous metabolites.

Purpose: to test, in the newborn piglet, the cerebroprotective efficacy of hypothermia applied with a clinically realistic delay of 2 h following the HI insult, and to investigate the anatomical specificity of cerebroprotection with regional measurements of ADC.

Methods

Animal Model: Eighteen newborn (< 24 h) piglets, mechanically ventilated and anaesthetized, were studied in a 7T Bruker NMR system. In 12 animals, transient cerebral HI was induced by reducing inspired oxygen concentrations to 12% and temporarily occluding both carotid arteries until severe depletion of high energy phosphates was detected by 31P MRS. The animals were then resuscitated by restoring normoxia and releasing the carotid occluders, and observations continued throughout the subsequent 48 hours.

Six animals were maintained at normal body temperature (38.5°C); 6 were cooled to 33.0°C for 24 h starting 2 h after resuscitation and then rewarmed; 6 animals were "sham-operated" controls. Tympanic and rectal temperatures were monitored and maintained using a thermally-regulated water mattress.

Data Acquisition: Cerebral ADC was measured using a stimulated echo diffusion-weighted imaging sequence (TR = 2 s, TE = 34 ms, TM = 200 ms, field of view = 6 cm, slice thickness = 2.5 mm, 128 x 64 image matrix). Diffusion sensitizing gradient pulses of strength 2 and 25 mT.m-1, separation 200 ms and duration 10 ms were applied along the x, y and z axes in turn. Measurements were performed using an elliptical coil (8 x 6 cm) positioned around the cerebral hemispheres.

ADC maps were calculated for each diffusion sensitizing direction and maps of ADC_g were calculated by taking the mean of the x,y and z ADC values. To obtain a more sensitive index of cerebral injury insensitive to anatomical location, cerebrospinal fluid and other extracerebral tissue were segmented from the maps, and the quantity ADC_g was calculated as the mean ADC for all remaining (brain) pixels within the imaging slice.

Results

In the 12 animals subject to the insult, ADC_g values obtained 1-2 h after resuscitation were close to baseline. During the subsequent 48 h, progressive patterns of ADC_g reduction were observed: in some cases commencing in the basal ganglia, in others in the parasagittal cortex, before spreading throughout the entire region of brain visible in the imaging slice.

Fig. 1 shows ADC_g at various times in the experiment for the 3 groups of animals. In the hypothermic group, ADC_g decreased reversibly during the hypothermia. At 46 h after resuscitation, the reduction of ADC_g in the hypothermic group was significantly less (p<0.05) compared with the normothermic group.

Table 1 gives ADC_g and ADC for regions of interest (ROIs) in the basal ganglia and subcortical white matter at baseline and 46 h after resuscitation. No significant changes were seen in the control group.

Discussion

The focal patterns of reduced ADC subsequent to a nominally "global" HI insult, may reflect patterns of injury commonly seen in human infants. The group subject to 24 h of hypothermia at 33°C showed a significantly lower reduction in ADC at 46 h after resuscitation compared with the normothermic group. This suggests that delayed hypothermia ameliorated, or at least delayed, failure of osmoregulation associated with delayed energy failure. The results are encouraging for the clinical application of therapeutic mild hypothermia in neonates suspected of HI cerebral injury.

References


Figure 1 Mean (n=6) global ADC vs time from resuscitation for each experimental group. (**p<0.05 vs baseline; *p<0.05 hypothermic vs normothermic groups)

Table 1: Mean ADC_g (n=6) from basal ganglia (BG) and subcortical white matter (SCWM) ROIs (** p < 0.01 vs baseline, paired t test; units 10⁻⁹ m².s⁻¹)

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<th>BG</th>
<th>SCWM</th>
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<tr>
<td>normothermic</td>
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<tr>
<td>hypo-thermic</td>
<td>0.82(0.09)</td>
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