Rates of change of 1H and 31P MRS cerebral metabolites vs Lactate/NAA in the 48h following global transient global hypoxia-ischaemia in the newborn piglet

N. J. Robertson[1], S. Faulkner[1], A. Bainbridge[2], M. Chandrasekaran[1], D. Kelen[1], S. Thayyil[1], E. Cady[2], X. Golay[3], and G. Raivich[1]
[1]Institute for Women's Health, University College London, London, United Kingdom, [2]Medical Physics and Bioengineering, University College Hospitals, London, United Kingdom, [3]UCL Institute of Neurology, London, United Kingdom

Background: Perinatal asphyxia affects 2-3 per1000 term births in the developed world and is associated with high morbidity and mortality rates. Therapeutic hypothermia is now established as a safe and effective therapy for perinatal asphyxia[1]. Other adjunct therapies are needed, however, as 50% of treated infants still have an adverse outcome and surrogate endpoints are required to speed up clinical trials. A recent meta-analysis demonstrated that the cerebral ^{1}H-MRS lactate/N – acetyl aspartate (Lac/NAA) peak area ratio acquired between 5-14 days after birth is the most sensitive and specific MRI biomarker of long term neurodevelopmental outcome in infants following perinatal asphxyia[2]; lactate/NAA is already used as a translational biomarker in pre-clinical studies and surrogate endpoint in phase II neuroprotection trials. The reciprocal changes in lactate and NAA (increase and decrease respectively) following hypoxia-ischaemia improve the sensitivity to detect neural injury in the sub-acute phase after hypoxia-ischaemia. Further validation of other biomarkers is important for monitoring neuroprotective therapies and refining surrogate endpoints.

Aim: To compare the rates of change of different metabolite peak area ratios vs Lac/NAA following transient global hypoxia-ischaemia in a validated piglet model.

Methods: Twenty-eight Large White male piglets (aged<24 h) underwent transient global hypoxia-ischaemia and serial 1H (white matter (WM) and deep grey matter (DGM)) and ^{31}P MRS (whole brain) data acquisitions. The rate of change (slope) of ^{1}H and ^{31}P metabolite ratios (logarithmic scale) was assessed for each individual animal. Comparative sensitivity to injury was assessed by fitting of WM and DGM metabolite ratios vs WM Lac/NAA.

Results: During the 48h after transient hypoxia-ischaemia WM and DGM Lac/Cr was more sensitive to lower degrees of injury than Lac/NAA, as demonstrated by a steeper slope in the 1st portion of the graph (Fig. 1a). Cho/Cr showed no correlation with Lac/NAA. NAA/Cr demonstrated a reduced sensitivity to mild injury as compared with more severe injuries (with a steeper slope in the 2nd portion of the graph) (Fig 1c). Responding 31P MRS biomarkers exhibited a similar reduced sensitivity to mild injury vs more severe brain damage, ranging from comparatively moderate (Pi/EPP) to very pronounced (NTP/EPP and pH_i) (Fig 2). In other words, when Lac/Cr and Lac/NAA already indicated definite abnormalities, NTP/EPP and pH_i still remained unaffected.

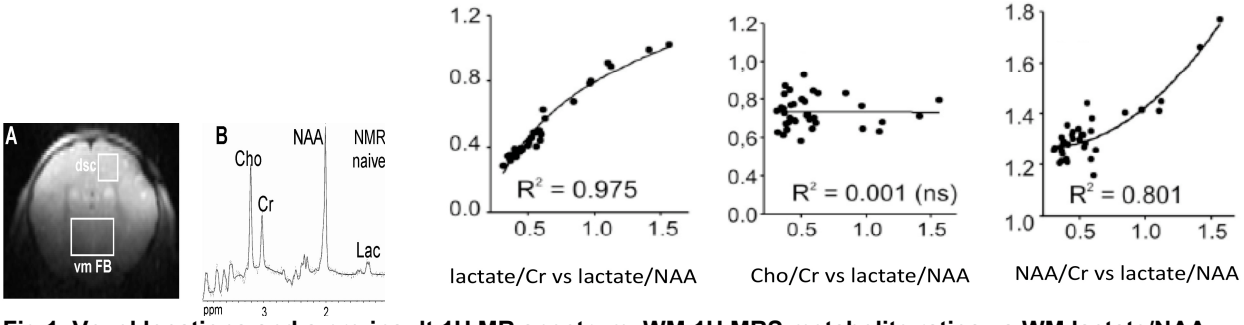

Fig 1. Voxel locations and a pre-insult 1H MR spectrum. WM 1H MRS metabolite ratios vs WM lactate/NAA following hypoxia-ischaemia. dsc - dorsal sub-cortical; vmFB - ventromedial forebrain.

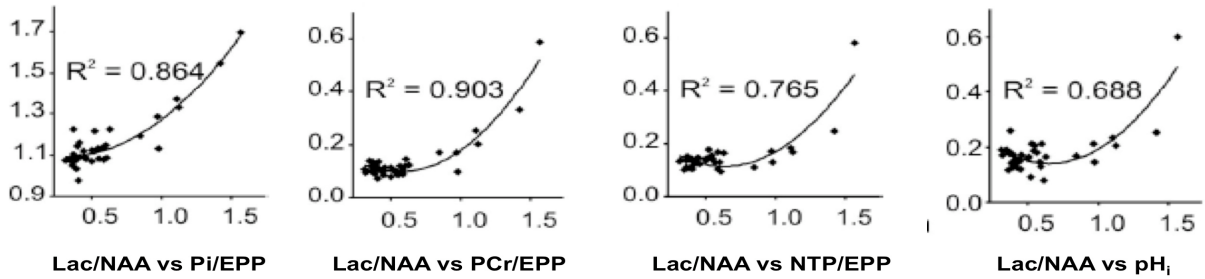

Fig 2. Whole brain 31P MRS metabolite ratios vs WM lactate/NAA

Conclusion: ^{1}H and ^{31}P MRS based biomarkers change at different rates in the 48 h following a transient global hypoxic-ischaemic insult. Compared to Lac/NAA, Lac/Cr changed most rapidly and was most sensitive to lower degrees of injury while NAA/Cr, NTP/EPP and pHi/EPP were least sensitive to injury and responded last. Lac/NAA appears to provide sufficient sensitivity detect moderate to severe brain injury following global hypoxia-ischaemia.

References:

1. Edwards AD et al., BMJ 2010; 340;c363
2. Thayyil et al., Pediatrics 2010;125:E 382-95