The pathophysiogical basis of brain swelling of grey vs. white matter in acute liver failure are different: lessons from a study using MARS

C. Zwingmann[1,2], C. Rose[3], S. Sen[4], N. Davies[5], R. F. Butterworth[3], D. Leibfritz[2], L. M. Ytrebo[6], A. Revhaug[7], R. Jalan[8]

[1]Centre de Recherche, Hospital Saint-Luc, Montreal, Quebec, Canada, [2]Department of Organic Chemistry, University of Bremen, Bremen, Bremen, Germany, [3]Neuroscience Research Unit, Hospital Saint-Luc, Montreal, Quebec, Canada, [4]Department of Physics, State University of New York, Buffalo, New York, United States, [5]Institute of Hepatology, University College London, London, United Kingdom, [6]Departament of Anesthesiology and Intensive Care, University Hospital of Northern Norway, Tromso, Norway, [7]University Hospital of Northern Norway, Tromso, Norway, [8]Institute of Hepatology, Royal Free & University College Medical School, London, United Kingdom

Introduction. Encephalopathy in patients with acute liver failure (ALF) is characterised neuropathologically by increased brain water affecting both the grey and white matter (GM and WM). Although water-soluble drugs can be removed by haemofiltration/haemodialysis, morbidity and mortality from intoxication with protein-bound drugs remains high. In an ALF pig model, we have shown that albumin dialysis (Molecular Adsorbents Recirculating System; MARS), a new therapeutic strategy for intoxication from protein-bound drugs [1], prevents a rise in intracranial pressure and reduces swelling in the WM, but not in the GM. This suggests that the pathophysiological basis of the brain swelling (brain edema) in these two areas may be different. The aims of the present study were to perform *ex vivo* high-resolution proton magnetic resonance spectroscopy (^{1}H-NMR) in the GM and WM of pigs with ALF to explore this hypothesis.

Methods: Pigs were randomised into three groups (n=8 in each): (i) sham-operated, (ii) ALF (by portacaval anastomosis (PCA) and subsequent hepatic devascularisation (HAL)) and (iii) ALF + MARS. MARS was performed (without haemodialysis/filtration) between hours 2-6. The experiments were terminated at t=6. The pigs were killed, and the tissue samples were immediately freeze-clampled in liquid nitrogen. Tissue samples were powdered over liquid nitrogen and homogenized in perchloric acid at 0°C. After lyophilization, the samples were redissolved in 0.5 ml D_2O and centrifuged. ^{1}H-NMR spectra were recorded on a Bruker DRX 600 spectrometer. Metabolite concentrations were calculated from ^{1}H-NMR spectra. Brain water was measured from these regions using a specific gravimetric technique.

Results: Over 6 hours, tissue brain water increased in both frontal cortex (GM) and sub-cortical WM ($p<0.05$) in pigs with ALF compared to sham. In the MARS treated animals brain tissue water was reduced in the WM only. Sham vs ALF: An increase in brain water was associated with changes in 8/11 metabolites in WM and 6/11 in GM. However in both GM and WM, only Gln, Phe and Tyr increased, Glu was reduced, and *myo*-inositol and BCAA were unchanged. Different patterns of changes were found for Asp, GABA, NAA, Tau and Trp. ALF vs MARS: MARS resulted in normalisation in 4/6 ALF-induced changed metabolites within the GM and 7/8 metabolites within WM. In both the GM and WM, Phe, Tyr, Glu and Tau were normalised by MARS.

Conclusion: Brain water increases in both frontal cortex (GM) and sub-cortical WM in pigs with ALF. However only 6/11 metabolite changes are similar in each region. This suggests different pathophysiological mechanisms between the GM and WM in HE associated with brain edema. The MARS-induced normalisation of brain water in the WM was paralleled by a normalization of 7/11 metabolites, implicating the importance of this metabolic profile in the pathophysiology of WM edema. The fact that MARS did not reduce GM tissue water, suggests only GABA as an important metabolite in the pathophysiology of GM edema. Our data show, for the first time, a rise in brain (GM and WM) Phe/Tyr in ALF indicating protein breakdown which is normalised with MARS. Since MARS only normalised WM tissue water, this suggests that increases in brain water in WM vs GM are associated with different pathophysiological mechanisms. This may be due to the different cell types found in GM vs WM. Further understanding of these different mechanisms could aid new therapies in HE due to ALF.

References: [1] Sen S et al. Intensive Care Med 2004;30:496-501.