Evidence refuting the Trojan-horse hypothesis of brain swelling in acute liver failure: L-type glutaminase is exclusively neuronal

Y Sharifi, N Shah, D Marsdon, N Davies, F Scaravilli, R Jalan
Hepatology, University College London, London, UK; Neuropathology, Institute of Neurology, Queen Square, London, UK

Introduction Astrocytic swelling is the characteristic feature of hyperammonemia and acute liver failure (ALF) which is thought to result from accumulation of glutamine due to the action of astrocytic glutamine synthetase (GS). It has been suggested that glutamine may not be a benign amino acid and may act as a “Trojan horse” which leads to astrocytic apoptosis as it is metabolised by Glutaminase (GLN) yielding glutamate and ammonia. In vivo proof for this hypothesis is lacking. In health, GLN is mainly neuronal and generates glutamate and GABA. The aims of the study were to define the expression of the ammonia metabolising enzymes, GS and GLN in the brain of ALF animals.

Methods Two groups of CD1 mice were studied, sham: n=6; paracetamol (500 mg/kg IP): n=7. The animals were maintained normothermic and resuscitated with fluid and glucose and sacrificed at 0 h after injection of APAP or before development of coma. Arterial ammonia (COBAS) and frontal cortex brain water (dry weight technique) were measured. The brain sections were stained for GS and K and L-type GLN.

Results Arterial ammonia was significantly higher in the ALF group compared with controls (345±32 vs 132±11 p=0.002) and brain water did not reach significance (53.6±2.3 vs 76.3±2.6 p=0.05). GS protein expression was observed in the astrocytes in the dentate fascia in both groups and was not different but was also seen in the oligodendrocytes only in ALF group. L-type GLN was expressed only in the neurons and not in the astrocytes and was significantly higher in the ALF animals (++++) compared with controls (+). The most marked areas were the striatum and dentate fascia and interestingly the staining was mainly cytoplasmic. K-type GLN was not different between groups and limited to brain capillaries.

Conclusion The results of this study refute the Trojan-horse hypothesis and show for the first time increased protein expression of L-type GLN which is exclusively neuronal. From the pathophysiological perspective, this may function to generate excessive ammonia in the neuron thereby producing neuronal cell death.

Abstract PMO-142 Figure 1