Pathogenesis of Hepatic Encephalopathy and Brain Edema in Acute Liver Failure

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Neuropathologic investigations in acute liver failure (ALF) reveal significant alterations to neuroglia consisting of swelling of astrocytes leading to cytotoxic brain edema and intracranial hypertension as well as activation of microglia indicative of a central neuroinflammatory response. Increased arterial ammonia concentrations in patients with ALF are predictors of patients at risk for the development of brain herniation. Molecular and spectroscopic techniques in ALF reveal alterations in expression of an array of genes coding for neuroglial proteins involved in cell volume regulation and mitochondrial function as well as in the transport of neurotransmitter amino acids and in the synthesis of pro-inflammatory cytokines. Liver-brain pro-inflammatory signaling mechanisms involving transduction of systemically-derived cytokines, ammonia neurotoxicity and exposure to increased brain lactate have been proposed. Mild hypothermia and N-Acetyl cysteine have both hepatoprotective and neuro-protective properties in ALF. Potentially effective anti-inflammatory agents aimed at control of encephalopathy and brain edema in ALF include etanercept and the antibiotic minocycline, a potent inhibitor of microglial activation. Translation of these potentially-interesting findings to the clinic is anxiously awaited. (J Clin Exp Hepatol 2015;5:S96–S103)

Acute liver failure (ALF), also referred to as fulminant hepatic failure, invariably leads to central nervous system dysfunction that may include encephalopathy, seizures and brain edema, a major cause of intracranial hypertension and brain herniation, a leading cause of mortality in ALF. An increase in cerebral blood flow frequently accompanies the onset of brain edema.[1]

Neuropathological assessments of the brain in both human and experimental ALF reveals significant changes to neuroglia in general and to astrocytes and microglia, in particular. Astrocytes in brain sections from patients who died in ALF are swollen[2] as are their mitochondria (Figure 1). Based upon these observations, it is generally assumed that the brain edema that accompanies ALF is primarily, if not exclusively, cytotoxic in nature. Studies in experimental animals with ALF due to toxic liver injury show a similar pattern of changes as well as alterations in expression of genes coding for key astrocytic proteins.[3]

Although gross alterations of the blood-brain barrier (BBB) are not generally a feature of ALF, alterations of cerebrovascular endothelial cell function have occasionally been described.[2,4] On the other hand, material from ALF animals in which edema and encephalopathy were precipitated by infection manifest clear alterations of both BBB function and of expression of BBB tight junction proteins.[5] These latter findings suggest that, in ALF accompanied by significant infection/inflammation, brain edema may comprise both cytotoxic and vasogenic components.

BRAIN METABOLISM IN ACUTE LIVER FAILURE

ALF leads to severe compromise of cerebral metabolism and includes increases of cerebral blood flow, decreases of the cerebral metabolic rate for oxygen (CMRO2) and failure of cerebrovascular autoregulation.[6] These changes have been attributed to a variety of factors including ammonia, glutamine, oxidative/nitrosative stress and pro-inflammatory factors.

Ammonia

A significant positive correlation has been reported between arterial ammonia and the presence of brain

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Abbreviations: ALF: acute liver failure; ATP: adenosine triphosphate; BBB: blood-brain barrier; CCL2: chemokine ligand-2; CMRO2: cerebral metabolic rate for oxygen; CNS: central nervous system; EEG: electroencephalography; GABA: gamma-aminobutyric acid; GFAP: glial fibrillary acidic protein; IgG: immunoglobulin; MRS: magnetic resonance spectroscopy; NAC: N-Acetyl cysteine; NMDA: N-methyl-D-aspartate; SIRS: systemic inflammatory response syndrome; SNATs: several neutral amino acid transport systems; TLP: translocator protein; TNFα: tumor necrosis factor alpha
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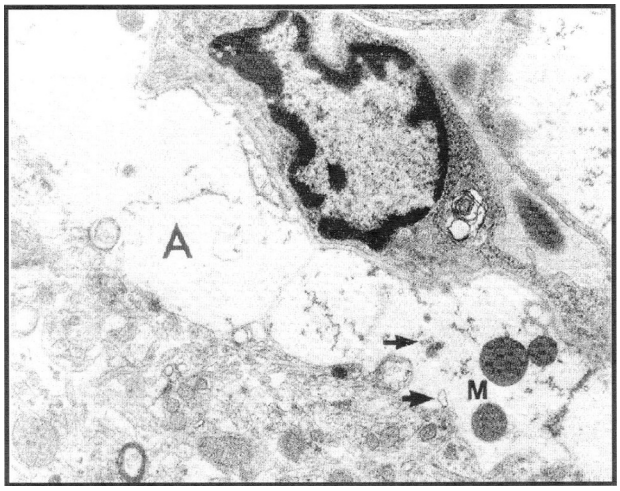

Figure 1 Electron micrograph of frontal cortex from a patient who died in acute liver failure. Note swelling and vacuolation of perivascular astrocyte (A) and mitochondria (M). Endoplasmic reticulum is dilated (arrows). Original magnification ×6000. From reference #2 with permission.

herniation in patients with ALF[7] and arterial ammonia concentrations may be a useful independent predictor of this complication.[8] Brain ammonia removal relies almost exclusively on the synthesis of glutamine, the brain lacking an effective urea cycle. Brain glutamine synthesis from ammonia is an astrocytic responsibility since the enzyme responsible, glutamine synthetase, has a uniquely astrocytic localization.

Ammonia has multiple actions on CNS function that include direct effects of the ammonium ion (NH_4^+) on both excitatory and inhibitory neurotransmission,[9] inhibition of glucose (pyruvate) oxidation[10] and stimulation of glycolysis, altered mitochondrial function[11] and impairment of key cellular transport systems.[9,12]

Glutamine

Brain glutamine concentrations are significantly increased in ALF whether assessed biochemically in autopsy material[13] or by 1H-magnetic resonance spectroscopy (MRS).[14] It was suggested, based upon these findings that the accumulation of glutamine in the brain in ALF was causally related to the encephalopathy and brain edema. Subsequent studies using 1H/13C MRS in an animal model of ALF confirmed the increase in concentrations and in synthesis of glutamine in brain.[15] However, these increases were not significantly correlated with either the severity of encephalopathy or the presence of brain edema in these animals suggesting that increased brain glutamine synthesis *per se* is not a major cause of these neurologic disturbances as had previously been postulated. The subject of the role of glutamine in the pathogenesis of the CNS consequences of hyperammonemic disorders has been the subject of a recent review.[16] In contrast, it has been proposed that the signal that triggers the increase in cerebral blood flow in ALF occurs following the generation of glutamine in the astrocytes.[6] Other mechanisms proposed to explain the role of glutamine in the pathogenesis of encephalopathy and brain edema in hyperammonemia include its transamination to alpha-ketoglutaramate, a neurotoxic metabolite[17] and the suggestion that glutamine, by transport into the astrocyte mitochondrion, acts as a shuttle for the production of ammonia that goes on to lead to mitochondrial energy failure, a hypothesis that has been termed "The Trojan Horse Hypothesis".[18] However direct evidence for a role for these hypotheses in the pathogenesis of the CNS consequences of ALF await further evaluation.

Lactate

Brain energy metabolism has been the subject of intensive investigation using a variety of technical approaches over the last several decades. It is clear that brain concentrations of high energy phosphates such as phosphocreatine and adenosine triphosphate (ATP) are not significantly altered in experimental ALF until the onset of profound coma and isoelectric EEG stages.[19] Similar negative observations have been reported using in vivo brain microdialysis[20] or 1H-MRS.[21] Glucose is the principal energy source for adult mammalian brain and there is increasing evidence to support the notion that brain glucose metabolism is modified early in the progression of the CNS consequences of ALF. Such modifications are not sufficient to result in brain energy failure but have the potential to result in abnormal CNS metabolism and function.

Brain lactate concentrations are increased in a wide range of experimental animal models of ALF resulting from ischemic[19,22] or toxic[23] liver injury as well as in brain microdialysates from ALF patients where increased brain lactate content was found to precede surges in intracranial hypertension.[24] Worsening of neurological status in animal models of ALF is significantly correlated with increases of brain lactate concentrations[15,19] and by increased *de novo* lactate synthesis[15] (Figure 2).

Increases of brain lactate have been shown to be related to intracranial hypertension and a poor outcome in dogs with ALF[25] suggesting a role for increased brain lactate in the pathogenesis of brain edema and, in support of such a notion, exposure of cultured astrocytes to lactate results in significant cell swelling.[26]

NEUROGLIAL FUNCTION IN ACUTE LIVER FAILURE

Astrocytes

Astrocytes play important roles in the maintenance of CNS function by virtue of their interactions with other neural cells (neurons, endothelial cells) and their ability to modulate both excitatory and inhibitory neurotransmission