

Hepatic encephalopathy and cerebral edema in fulminant liver failure

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RF BUTTERWORTH. Hepatic encephalopathy and cerebral edema in fulminant liver failure. *Can J Gastroenterol* 1993;7(7):547-549. Hepatic encephalopathy and cerebral edema are major complications of fulminant liver failure. Currently available evidence suggests that neurotransmission failure, rather than primary brain energy failure, is responsible for these disorders. Brain ammonia rises to millimolar concentrations in experimental hepatic encephalopathy, and exposure of brain preparations to ammonia results in edema and alterations of excitatory and inhibitory neurotransmission. Specific neurotransmitter systems implicated in the pathogenesis of hepatic encephalopathy in fulminant liver failure include the excitatory amino acids glutamate and aspartate. There is little convincing evidence for a pathogenetic role for the brain gamma-aminobutyric acid (GABA) system in this disorder. While there is some evidence for accumulation of endogenous substances that bind to the GABA-related benzodiazepine receptor in brain in some patients with fulminant liver failure, the pathophysiological relevance of these findings remains to be established. The most rational means of prevention of the cerebral consequences of fulminant liver failure remains the lowering of blood ammonia.

Key Words: Ammonia, Cerebral edema, Fulminant liver failure, Hepatic encephalopathy

Encéphalopathie hépatique et oedème cérébral dans l'insuffisance hépatique fulminante

RÉSUMÉ: L'encéphalopathie hépatique et l'oedème cérébral sont deux complications importantes de l'insuffisance hépatique fulminante. Les résultats disponibles à l'heure actuelle mettent en cause une insuffisance au plan de la neurotransmission plutôt que du fonctionnement énergétique primaire du cerveau. L'ammoniaque cérébral s'élève à des concentrations millimolaires dans l'encéphalopathie hépatique expérimentale et l'exposition de préparations cérébrales à l'ammoniaque donne lieu à de l'oedème et à des altérations de la neurotransmission qu'il s'agisse de stimulation ou d'inhibition. Les systèmes neurotransmetteurs spécifiques en jeu dans la pathogenèse de l'encéphalopathie

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HEPATIC ENCEPHALOPATHY (HE) associated with fulminant liver failure is a clinical syndrome resulting from severe inflammatory and/or necrotic liver disease (of rapid onset). The neurological disorder progresses from altered mental status to coma, generally within hours or days. Death frequently results from brain herniation caused by increased intracranial pressure as a result of massive brain edema.

Available evidence suggests that neurotransmission failure – rather than decreased energy metabolism – is the primary cause of HE in fulminant liver failure. Recent ^1H and ^{31}P magnetic resonance studies have clearly demonstrated that in experimental animal models of fulminant liver failure, high energy phosphates are maintained at normal levels in the brains of severely encephalopathic animals (1).

Pathogenetic mechanisms proposed to explain the central nervous system (CNS) complications of fulminant liver disease include the following: ammonia neurotoxicity, brain amino acid imbalance and the action of 'endogenous' benzodiazepines.

Brain ammonia concentrations are consistently in the 1 to 5 mM range in the brains of experimental animals at coma stages of HE resulting from fulmi-

hépatique liée à l'insuffisance hépatique fulminante incluent les acides aminés excitateurs glutamate et aspartate. Il y a peu de preuves convaincantes à l'effet du rôle pathogène du système de l'acide gamma-aminobutyrique cérébral (AGAB) dans cette maladie. Si quelques indices portent à croire à une accumulation de substances endogènes qui se fixent aux récepteurs de la benzodiazépine liée à l'AGAB au niveau du cerveau chez certains patients atteints d'insuffisance hépatique fulminante, la portée physiopathologique de ces résultats reste à explorer. La mesure préventive la plus rationnelle des séquelles cérébrales de l'insuffisance hépatique fulminante est d'abaisser l'ammoniaque sanguin.

nant liver failure. Brain is devoid of an effective urea cycle so that ammonia removal by brain relies almost exclusively on glutamine synthesis. Glutamine concentrations are significantly increased in autopsied brain samples from patients who died in fulminant liver failure, suggesting exposure to high levels of ammonia; cerebrospinal fluid (CSF) glutamine concentrations correlate well with the severity of neurological impairment in patients with fulminant liver failure. Millimolar concentrations of ammonia (equivalent concentrations to those encountered in brain in fulminant liver failure) affect both inhibitory and excitatory neurotransmission (2). In addition, ischemic liver failure in the rat results in increased brain water content and in parallel increases of brain ammonia, the latter reaching concentrations in excess of 4 mM at coma stages of encephalopathy (3). Addition of 5 mM ammonia to cortical brain slices *in vitro* results in significant swelling. Taken together, these findings suggest a role for ammonia in the pathogenesis of brain edema in fulminant liver failure. Whether edema results from a direct action of ammonia or from the action of an ammonia metabolite such as glutamine remains to be established.

Several studies in the past decade suggest that HE in fulminant liver failure could result from alterations of neuroactive amino acids. In 1982 it was proposed that gut-derived gamma-aminobutyric acid (GABA), by virtue of its decreased removal by the liver and its entry into brain via a permeable blood-brain barrier, might contribute to the neural inhibition characteristic of HE (4). Evidence in favour of this hypothesis was derived from studies in an ex-

perimental animal model of fulminant liver failure derived by treatment with the hepatotoxin galactosamine. However, early findings of alterations of GABA-related enzymes and binding sites observed in galactosamine-induced liver failure were not confirmed by other investigators working either with the same experimental models or with other preparations. Rats with thioacetamide-induced liver failure and HE were found to have unaltered brain GABA receptor affinities and densities (5); similar negative findings were reported in experimental ischemic liver failure. GABA levels are unchanged in autopsied brain tissue from patients with fulminant liver failure (6), and in the CSF and brains of rats with ischemic liver failure (7).

In contrast, there is mounting evidence to suggest that the excitatory amino acids glutamate and aspartate may be modified in HE associated with fulminant liver failure. Using a novel indwelling cisterna magna catheter technique, Swain et al (7) demonstrated increased CSF concentrations of these amino acids in ischemic liver failure in the rat. Brain concentrations of glutamate and aspartate concomitantly decreased as neurological status worsened. Similar changes were observed in thioacetamide-induced liver failure. The loss of these potent neuroexcitatory amino acids in brain in experimental fulminant liver failure affords a possible explanation for the generalized neural inhibition characteristic of this condition. However, the precise mechanism(s) implicated remain to be established.

Benzodiazepines exert their CNS effects by interacting with binding sites on the GABA-benzodiazepine receptor complex. In the 1980s, two reports

demonstrated increased densities of GABA and benzodiazepine binding sites in the brains of animals with galactosamine-induced fulminant liver failure. In 1985, a report described favourable results using the antagonist Ro 15-1788 (flumazenil) in the treatment of a patient with HE resulting from fulminant liver failure (8). It was proposed that the reversal of HE by flumazenil was mediated by the drug preventing the action of 'endogenous benzodiazepines' in the brain of this patient. Following up on this initial report, benzodiazepine receptor antagonists were found to induce a transient decrease in the clinical severity of HE caused by galactosamine-induced liver failure in the rabbit. On the other hand, HE resulting from liver ischemia in both the rat and the rabbit did not respond to benzodiazepine antagonists. Initial findings of beneficial effects of flumazenil in the thioacetamide rat model of fulminant liver failure were not substantiated in a subsequent study (9).

Elevated brain concentrations of benzodiazepines have been described in autopsied brain tissue from approximately 30% of patients with fulminant liver failure resulting from acetaminophen overdose (10). Anecdotal reports and uncontrolled studies in human fulminant liver failure continue to yield conflicting results (8,11,12). The difficulty with any such studies lies in the problems in ensuring the rigorous exclusion of patients previously exposed to benzodiazepine medication.

In conclusion, the precise pathogenetic factors responsible for HE and cerebral edema in fulminant liver failure continue to elude us. New findings of a possible role for ammonia (or one of its metabolites) in brain edema, coupled with the known effects of ammonia on CNS inhibition and excitation, suggest that the most rational means of prevention of the neurological complications of fulminant liver failure remains the lowering of blood ammonia in these patients. The efficacy of benzodiazepine receptor antagonists in the treatment of HE in fulminant liver failure awaits the results of adequately controlled clinical trials.

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