The molecular pathogenesis of hepatic encephalopathy

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Abstract

Hepatic encephalopathy (HE) incorporates a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction with a potential for full reversibility. Distinct syndromes are identified in acute liver failure and cirrhosis. Rapid deterioration in consciousness level and increased intracranial pressure that may result in brain herniation and death are a feature of acute liver failure whereas manifestations of HE in cirrhosis include psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration and in severe forms, coma. For over a 100 years ammonia has been considered central to its pathogenesis. In the brain, the astrocyte is the main site for ammonia detoxification, during the conversion of glutamate to glutamine. An increased ammonia level raises the amount of glutamine within astrocytes, causing an osmotic imbalance resulting in cell swelling and ultimately brain edema. The present review focuses upon the molecular mechanisms involved in the pathogenesis of HE. Therapy of HE is directed primarily at reducing ammonia generation and increasing its detoxification.

Keywords: Hepatic encephalopathy; Ammonia; Cirrhosis; Acute liver failure; Hypothermia

1. Background

Hepatic encephalopathy (HE) continues to be a major clinical problem. In subjects with acute liver failure, patients can succumb to a neurologic death, with brain edema and intracranial hypertension. In patients with cirrhosis (chronic liver disease), a wide spectrum of symptoms are summarised under the term HE. These neuropsychiatric abnormalities range from minor sleep disturbances, through discernable altered brain function, overt psychiatric/neurological symptoms to deep coma. However, recent studies have suggested that patients with cirrhosis can develop cerebral changes that are indistinct from that observed in acute liver failure suggesting that the underlying pathogenic mechanisms in the development of this syndrome are likely to be similar (Jalan, Dabos, Redhead, Lee, & Hayes, 1997). Although, there have been a number of hypotheses such as the ‘GABA hypothesis’, the ‘false neurotransmitter hypothesis’ and the ‘manganese hypothesis’ to explain the pathogenesis of HE, ammonia (NH₃, or ammonium (NH₄⁺)) has consistently been shown to be the important factor over a century (Fig. 2). In this review we will focus upon the role of ammonia in the pathogenesis of this syndrome.

2. Pathogenesis of hepatic encephalopathy

In 1893, members of Pavlov’s group in St. Petersburg described ‘the meat intoxication syndrome’. They described a causal relationship whereby the shunting of blood from the portal vein into the vena cava (by-passing the liver), resulted in the liver not being able to
The cell that is central in the pathogenesis of hepatic encephalopathy is the astrocyte. (a) Pathogenic mechanisms of hepatic encephalopathy in both acute liver failure and in cirrhosis are likely to be similar (ALF: acute liver failure; ICP: intracranial pressure; HE: hepatic encephalopathy). (b) Electron micrograph of the brain from a patient dying from acute liver failure showing a swollen astrocyte (A) (M: mitochondria). (c) Histopathology of the brain from a patient dying from cirrhosis showing evidence of type II astrocytosis (Alz) and a normal neuron (n) (from Kato, Hughes, Keays, & Williams, 1992).

metabolise ammonia into urea leading to ammonia accumulation in the blood. In dogs, they observed a rise in arterial blood ammonia levels after the main protein meal that was associated with behavioral disturbances (Nencki, Pawlow, & Zaleski, 1896). Over 50 years later the same observations of elevated arterial ammonia levels and behavioral alterations were made in human patients with cirrhosis of the liver. Lockwood, Yap, and Wong (1991) provided the first direct evidence in patients linking ammonia to the pathogenesis of HE using positron emission tomography with $^{13}$N ammonia as tracer. They showed that the rate of uptake of ammonia into the brain of patients with HE was significantly higher than in healthy volunteers and that arterial concentrations of ammonia may increase the uptake of ammonia in the brain through an increase in the permeability of the blood–brain barrier to ammonia. Recent studies have shown that an arterial ammonia levels of $>150 \mu$mol/l in patients with acute liver failure predicts a greater likelihood of dying from brain herniation. It has been estimated, from studies in experimental animals, that brain ammonia flux in acute liver failure may be up to 45-fold higher than normal (Dejong, Deutz, & Soeters, 1993).

2.1. Neuropathology

Both in cirrhosis and also in acute liver failure, the neurons and the blood–brain barrier are anatomically normal. HE in cirrhosis is characterised
Fig. 2. Schematic representation of the various factors involved in the pathogenesis of hepatic encephalopathy. The figure illustrates that a combination of liver dysfunction and portacaval shunting contributes to the development of hepatic encephalopathy. The blood-brain barrier is anatomically normal but functional derangements have been demonstrated. The various neurotoxins and neurotransmitters defects that have been implicated in the pathogenesis of hepatic encephalopathy are illustrated. The inset shows the major mechanisms through which ammonia may produce neurotoxicity.
neuropathologically by Alzheimer type II astrocytosis (Fig. 1). In acute liver failure the astrocytes appear swollen (Fig. 1). Astrocytes occupy about one third of the cortical volume and form a barrier segregating neurons from the external environment. Astrocytes are the site of ammonia detoxification in the brain and eliminate ammonia by the synthesis of glutamine through amidation of glutamate by glutamine synthetase. The finding that similar changes can be induced experimentally in astrocytes in culture following exposure to ammonia suggests that HE is primarily due to dysfunction of these cells with neuronal dysfunction occurring secondarily (Nencki et al., 1896). Astrocytes maintain and regulate the extracellular environment and influence neuronal excitability and neurotransmission (Norenberg, 1977).

2.2. The ‘ammonia–glutamine–brain oedema hypothesis’

This hypothesis suggests that the accumulation of glutamine in the astrocytes induced by hyperammonemia produces osmotic stress and causes the astrocytes to swell (Fig. 3). This hypothesis has been explored in several animal models. Infusion of ammonia into portacaval shunted rats produces an increase in brain glutamine; brain water and the animals become comatose. This hypothesis has been explored almost in its entirety in humans. Haussinger et al. (1994) demonstrated a disturbance in cell volume homeostasis and astrocyte swelling using proton magnetic resonance spectroscopy. They showed a depletion of myo-inositol, which correlated with an increase in the glutamine/glutamate peak (Fig. 3). This finding has since been confirmed by a number of investigators. Cordoba et al. (2001) performed proton magnetic resonance spectroscopy and magnetisation transfer ratio, which is a measure of brain water, in 24 patients. This was repeated in a subgroup of 11 after liver transplantation. They demonstrated a reduced magnetisation transfer ratio and increase in the glutamine/glutamate signal which correlated with deterioration in neuropsychological function. This suggests that hyperammonemia results in an increase in brain water, which alters neuropsychological function. These changes normalised after liver transplantation. We have recently confirmed that induction of hyperammonemia in cirrhosis produces an increase in brain glutamine, which results in an increase in brain water and a deterioration in neuropsychological function (Jalan et al., 2001).

The swelling of astrocytes activates extracellular regulated protein kinases, elevates intracellular calcium concentration, upregulates the expression of...
peripheral benzodiazepine receptors, affects multiple ion channels and amino acid transport, induces endosomal alkalization which affects receptor densities and neurotransmitter processing, induces deposition of glycogen and inhibition of glycogenolysis and increases the synthesis of neurosteroids which are potent modulators of neuronal γ-aminobutyric acid (GABA) receptor activity. These mechanisms induce changes in multiple neurotransmitter systems that produce the neuropsychiatric disturbances.

2.3. Direct ammonia related neurotoxicity

Ammonia in concentrations that are reported in the brain in experimental liver failure impairs postsynaptic inhibition in cerebral cortex, brainstem, and spinal cord preparations by blocking chloride extrusion from the postsynaptic neuron thereby rendering the inhibitory neurotransmitter ineffective. Similar concentrations of ammonia also inhibit excitatory neurotransmission by a direct postsynaptic action.

In millimolar concentrations, ammonia has the potential to cause cerebral energy failure through inhibition of α-ketoglutarate dehydrogenase, a rate-limiting tricarboxylic acid cycle enzyme. Moreover, liver failure results in increased brain concentrations of lactate and CSF lactate concentrations are increased in direct correlation with deterioration of neurological function. Increased CSF lactate has also been reported in cirrhotic patients with HE (Yao et al., 1987). Increased lactate production most likely results from decreased entry of pyruvate into the tricarboxylic acid cycle following ammonia-induced inhibition of α-ketoglutarate dehydrogenase. Administration of ammonium salts to portacaval-shunted rats results in coma and decreased brain ATP content. However, this energy deficit is only apparent at the coma-stages but animals with severe encephalopathy prior to the coma stage do not manifest significant reductions in brain ATP content.

2.4. Altered gene expression in liver failure

During liver failure and consequent hyperammonemia, the brain responds rapidly by altering the expression of genes that code for various proteins whose role is critical to CNS function including the maintenance of cell volume and neurotransmission. Brain extracts from animals with experimental acute liver failure show that the expression of several genes was altered. Not surprisingly the genes that show alterations in expression in acute liver failure are those that code for proteins involved in astrocytic function. These genes include the astrocytic glutamate transporter (GLT-1), the astrocytic structural protein, glial fibrillary acidic protein, the “peripheral-type” benzodiazepine receptor and aquaporin IV, a protein implicated in astrocytic water channels (Desjardins, Bélanger, & Butterworth, 2001). The pathophysiologic consequences of this altered gene expression are unclear and needs to be studied in suitable knock-out models.

3. Treatment of hepatic encephalopathy

3.1. Hepatic encephalopathy in cirrhosis

Patients with HE fall into two groups. First, are those patients who have episodes of encephalopathy and are relatively well between attacks. These patients usually have a precipitating event such as dietary protein loading, gastrointestinal bleeding, exacerbation of the underlying liver disease, sepsis, dehydration, hypokalemia, hypoxia, use of sedatives, and constipation. Second, are patients with spontaneous encephalopathy. Management of HE therefore involves the detection and treatment of the precipitating events, the treatment of HE itself and the treatment of the underlying liver disease.

The major strategy for the therapy of HE is directed at ammonia reduction, which can be attained either by decreasing its absorption/production or increasing its removal. Traditionally, the gut has been thought to be the major site of ammonia production and current strategies are directed at methods of reducing ammonia absorption/production from the gut. The mainstay of treatment is dietary protein restriction, which should only be used short-term to avoid deleterious nutritional consequences. In practice, the most widely used agents are the orally administered non-absorbable disaccharides such as lactulose and lactitol which act by ensuring bowel movement, by affecting bacterial metabolism including ammonia production and absorption of ammonia. Antibiotics such as neomycin, tetracyclin, metronidazole and vancomycin are used with a view to reducing the bacterial flora and consequent ammoniagenesis from
breakdown of urea and other proteins. Newer agents such as sodium benzoate and L-ornithine L-aspartate are aimed at metabolic removal of ammonia. The use of the former agent is based upon the hypothesis that benzoate combines with ammoniagenic amino acids such as glycine and that of L-ornithine L-aspartate on the notion that it may provide substrate to the liver for enhancing the urea cycle and also substrate for ammonia detoxification in the muscle. Current evidence for the use of the different strategies has been recently reviewed (Ferenci, Herneth, & Steindl, 1996).

3.2. Acute liver failure

The management of HE in acute liver failure is a lot more unsatisfactory. Without liver transplantation, a mortality rate of 90% is expected in those patients with acute liver failure who have increased intracranial pressure and fulfill criteria for poor prognosis. Present treatment modalities are confined to the use of 20% mannitol, which reduces brain edema by inducing osmotic diuresis, barbiturates which produce cerebral vasoconstriction and removal of fluid by haemofiltration.

Several studies in animal models of acute liver failure set the stage for the clinical application of moderate hypothermia in man (Traber, DalCanto, Ganger, & Blei, 1989). Although the number of patients treated with hypothermia for increased intracranial pressure is limited, data clearly show that moderate hypothermia is a safe and effective method of treatment of increased intracranial pressure that is unresponsive to other medical therapies and can be used as a successful bridge to liver transplantation. Although the exact mechanisms by which hypothermia reduces intracranial pressure in acute liver failure is unclear, it has been shown to reduce arterial ammonia and its extraction by the brain and reducing cerebral blood flow and restoring its autoregulation (Jalan, Olde Damink, Lee, & Hayes, 1999).

4. Conclusions

Although we know that ammonia is critical to the pathogenesis of HE, there is no direct correlation between the measured concentration of ammonia and the severity of HE, which can occur with normal concentrations of ammonia. Additional factors may therefore be important. We know from studies in a large cohort of patients with acute liver failure that the systemic inflammatory response syndrome (SIRS), whether or not precipitated by infection, increases the severity of cerebral oedema in acute liver failure, causing progression of HE and conferring a poorer prognosis. Astrocytes belong to the macrophage lineage and therefore have the potential repertoire of cytokine responses. They contain most cytokines and have the ability to synthesise interleukin-1β (IL-1β) in response to peripheral inflammation (Licinio & Wong, 1997), which may induce soluble mediators such as nitric oxide, superoxide and prostaglandins, which make the brain more susceptible to the effects of hyperammonemia. Newer therapeutic approaches are likely to evolve through better understanding of the molecular basis of HE and how ammonia interacts with other factors to produce HE.

References


