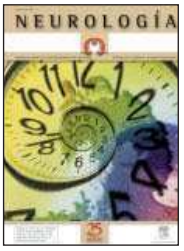
Neurología. 2010;**25(4)**:239-247

NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW ARTICLE

Molecular aspects of hepatic encephalopathy

A.L. Márquez-Aguirre [a], A.A. Canales-Aguirre [a], U. Gómez-Pinedo [b] and F.J. Gálvez-Gastélum [c,*]

[a] *Unidad de Biotecnología Médica y Farmacéutica, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, CIATEJ, Guadalajara, Mexico*
[b] *Laboratorio de Morfología Celular, Unidad Mixta CIPF-UVEG, CIBERNED, Valencia, Spain*
[c] *Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Mexico*

Received on 5th December 2009; accepted on 21st December 2009

KEYWORDS
Hepatic encephalopathy;
Ammonia;
Manganese;
Neurotoxins;
Oxidative stress

Abstract
Introduction: Liver fibrosis and its end stage, cirrhosis, is an enormous worldwide health problem. Hepatic encephalopathy (HE) or portal-systemic encephalopathy continues to be a major clinical problem of long-term cirrhosis. In this review we emphasise the molecular basis of HE and the involvement of oxidative stress in the development of this disease.
Background: Several studies suggest that the pathogenesis of HE could be multifactorial and have different factors implicated, such as alterations in blood brain barrier, substances such as ammonia and manganese, and disorders in the neurotransmission of dopamine, glutamate and GABA.
Development: HE is a severe complication of both acute and chronic liver failure. Neuropathologically, it is characterized by astrocyte changes known as Alzheimer type II astrocytosis. In addition, astrocytes manifest altered expression of astrocyte-specific proteins, such as, glial fibrillary acidic protein, glutamine synthetase, monoamine oxidase and peripheral type benzodiazepine receptors.
Conclusions: HE is a complex neuropsychiatric syndrome associated with liver failure. These alterations are products of increases in oxidative stress in brain due to neurotoxin activity. The main strategy for HE treatment is directed at ammonia reduction, which can be achieved either by decreasing its absorption/production or increasing its removal.

* Corresponding author.
E-mail: galvez_gastelum_@hotmail.com (F.J. Gálvez-Gastélum).

PALABRAS CLAVE
Encefalopatía hepática;
Amonio;
Manganeso;
Neurotoxinas;
Estrés oxidativo

Aspectos moleculares de la encefalopatía hepática

Resumen
Introducción: La fibrosis hepática y su etapa final, la cirrosis, representan un enorme problema de salud mundial. La encefalopatía hepática (EH) o encefalopatía portosistémica es una afección clínica de la cirrosis a largo plazo. En esta revisión se destacan las bases moleculares de la EH, así como el papel del estrés oxidativo en el desarrollo de esta enfermedad.
Fuentes: Diversos estudios señalan que la EH es de origen multifactorial, las alteraciones en la barrera hematoencefálica, sustancias como el amonio y el manganeso, así como alteraciones en la neurotransmisión de dopamina, glutamato y GABA, se han implicado en la patogenia de esta enfermedad.
Desarrollo: La EH es una complicación severa de la insuficiencia hepática tanto aguda como crónica. Neuropatológicamente, se caracteriza por cambios astrocitarios conocidos como astrocitosis Alzheimer tipo II y por la expresión alterada de proteínas específicas de astrocito, como la proteína acídica fibrilar glial, la glutamina sintetasa, los inhibidores de la monoaminooxidasa y los receptores periféricos tipo benzodiacepina.
Conclusiones: La EH es un síndrome neuropsiquiátrico complejo asociado a una falla hepática. Estas alteraciones son producto de un incremento de estrés oxidativo en el cerebro como consecuencia de la acción de neurotoxinas. La principal estrategia para el tratamiento de la EH se dirige a la reducción del amonio, ya sea por la disminución de su absorción/producción o promoviendo su eliminación.

Introduction

Hepatic fibrosis and its final stage, cirrhosis, represent an enormous health problem worldwide. In Mexico it is the second leading cause of death for productive-age people[1]. This disease is the result of a healing response to chronic liver injury from a variety of causes, including infections by hepatitis B virus (HBV), hepatitis C virus (HCV), chronic alcohol abuse and cholestasis induced by prolonged biliary obstruction[2,3]. The molecular pathophysiology of liver cirrhosis is characterised by increased, altered deposition of extracellular matrix proteins, mainly collagen of types I, III and IV. The excessive deposition of this fibrous tissue in the subendothelial space or Disse space decreases the blood flow exchange between hepatocytes and sinusoidal blood (fig. 1). The effects of this fibrous tissue deposition on the liver cause not only the metabolic characteristics of advanced liver disease, but also an impact on distant organs, including the brain[4-6]. These conditions induce various complications such as oesophageal varices, splenomegaly, ascites, cholestasis, portal hypertension and hepatic encephalopathy (HE)[5-10]. HE or portosystemic encephalopathy is a serious clinical problem in long-term cirrhosis. One of the main characteristics observed in this disease is motor deficit, which includes rigidity, asterixis and deficient muscle coordination[11]. In clinical practice, HE is classified into four categories, with increasingly advanced deterioration of mental status in each category (table 1). It is also classified into three main types according to its origin or cause: the first, type A, is associated with an acute hepatic lesion, type B is related to portosystemic shunting, and type C is associated with cirrhosis and portal hypertension with portosystemic shunting[12]. Additionally, a subclinical stage of HE has been described, whose prevalence is estimated to vary between 14% in patients with Child-Pugh A cirrhosis and 45% in patients with Child-Pugh B/C cirrhosis, according to the Child-Pugh classification[13-15]. The objective of this review was to analyse the information that has led to clarifying the pathophysiology of hepatic encephalopathy, with special emphasis on the molecular aspects involved in the development of this disease.

Pathogenesis of hepatic encephalopathy

The pathogenesis of HE involves the action of neurotoxins such as ammonia and manganese, as well as various phenomena that include alterations in neurotransmission, blood-brain barrier permeability and energy metabolism (fig. 2). Although HE pathogenesis is complex and not yet fully understood, numerous animal models have been used to study the development of this disease. Additionally, the advent of modern cell and molecular biology techniques, as well as the use of imaging techniques in neurophysiology, has allowed considerable progress in understanding HE pathogenesis[16].

Neuropathology

Astrocytes occupy about one-third of the volume of the cerebral cortex and form a segregation barrier for the neurons from the external environment. They are involved

Table 1 Clinical grades of hepatic encephalopathy

Grade 1	Lack of awareness, euphoria or anxiety, and reduced attention span
Grade 2	Lethargy, apathy, minimal disorientation of time and space, personality changes and inappropriate behaviour
Grade 3	Drowsiness, confusion and disorientation
Grade 4	Coma

in several processes essential for brain function, they maintain and regulate the extracellular environment, they participate in free radical scavenging, metal retention, immune response modulation and inflammation, and they influence neuronal excitability and neurotransmission[11,17,18]. These cells present different morphological changes. Type II Alzheimer astrocytosis appears during hepatic cirrhosis and astrocytes acquire a semblance of inflated cells during acute liver failure[51]. It has been documented that in HE, astrocytes present an altered expression of astrocyte-specific proteins such as glial fibrillary acidic protein (GFAP), enzymes such as glutamine synthetase (GS), monoamine oxidase (MAO) inhibitors and peripheral benzodiazepine receptors (PBR)[19].

Role of astrocytes

Among the different types of cells in the central nervous system (CNS), astrocytes are an important source of extracellular proteins and adhesion molecules. These play a central role in the formation of the glial scar after injury in

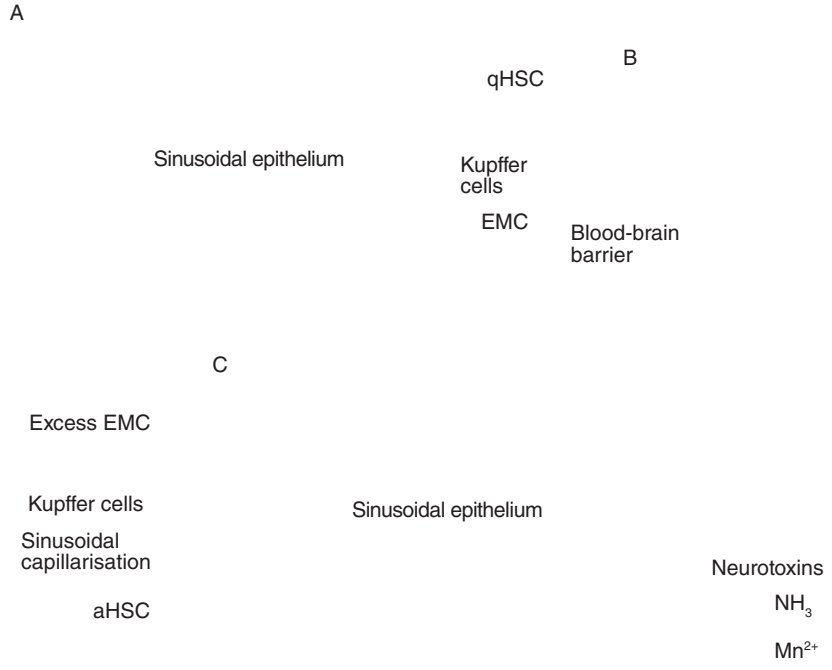


Figure 1 Molecular pathophysiology of hepatic fibrosis.
A: a graph showing the architecture of the Disse space in a normal liver where substances (neurotoxins) that can damage brain cells can be removed.
B: changes in hepatic architecture begin with a hepatocyte lesion resulting in the recruitment and stimulation of inflammatory cells in the liver, such as Kupffer cells. Factors released by these inflammatory cells transform hepatic stellate cells (HSC) into a myofibroblast-like phenotype. The activated HSC proliferate and secrete large amounts of extracellular matrix proteins. Subsequently, sinusoidal endothelial cells lose their fenestrations, thereby producing increased blood flow resistance in the hepatic sinusoids.
C: the loss of normal tissue architecture contributes to the deterioration of organ function which culminates in penetration of neurotoxins (ammonia and manganese) into the brain and causes oxidative stress and cell death.
EMC: extracellular matrix components; aHSC: activated hepatic stellate cells; qHSC: quiescent hepatic stellate cells.

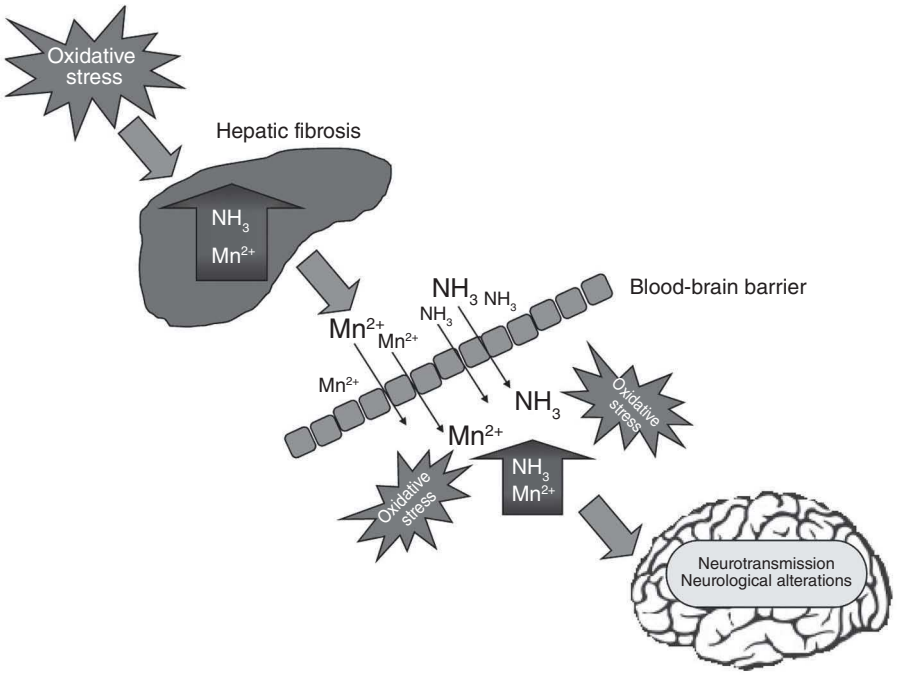


Figure 2 Alterations in the development of hepatic encephalopathy. Normal brain function depends on many aspects of normal liver functioning. Although the brain is protected from neurotoxic substances by the blood brain barrier (characteristic of blood vessels in the brain, which prevents many blood compounds from passing into brain tissue), some neurotoxins can penetrate this barrier after an injury to the liver such as cirrhosis. This liver disease induces an increase of neurotoxic substances such as ammonia and manganese, which in turn induce oxidative stress when they cross the blood-brain barrier and cause damages in neurotransmission, breakdown of energy synthesis and, ultimately, cell death.

numerous types of lesions to preserve the integrity of the tissue and limit the area of injury, in a process called reactive astrogliosis. The glial scar formed around the lesion attempts to protect the healthy CNS tissue from secondary injuries; however, at the same time, it inhibits a possible axonal regeneration after the lesion[20].

Role of neurons

In contrast to the morphological changes described for astrocytes, neurons do not present changes in cellular architecture during HE. In histopathological studies of brains from patients with chronic liver damage, neurons are observed in normal conditions and quantities. In addition, some markers of neuronal integrity such as N-acetylaspartate do not change in these patients. Studies in HE animal models provide compelling evidence that these neuronal death mechanisms are similar to those observed in ischemia. These mechanisms include NMDA receptor-mediated excitotoxicity, oxidative/nitrosative stress, lactic acidosis and the presence of proinflammatory cytokines[21].

Neurotoxins

Ammonia. Ammonia (NH3) is the key neurotoxin implicated in HE pathogenesis. In recent years, there has been significant progress in defining its involvement in the genesis of cerebral oedema during fulminant hepatic failure[13,22,23]. The use of ammonia infusions in rats has shown that cerebral oedema and intracranial hypertension can be experimentally induced and that this phenomenon can be inhibited by administering methoxamine sulfate, a GS inhibitor. This has led to the concept that CNS-derived glutamine participates in ammonia detoxification by producing an osmotic gradient across the blood brain barrier, which leads to cerebral oedema and swelling of astrocytes[11,22]. The structural and neurochemical changes in the brain as a result of exposure to ammonia have been the subject of intense research. Ammonia induces astroglial changes that contribute to cell swelling by increasing intracellular glutamine, which causes alterations in the blood brain barrier affecting glutamatergic neurotransmission and increasing the expression of neuronal nitric oxide synthase[22].

Manganese. Manganese (Mn^{2+}) is a neurotoxic metal. Chronic exposure to it produces neurological alterations such as rigidity, tremor and impaired gait[5]. Both deficiency and excess of Mn can have profound effects on the CNS. Industrial or experimental exposure to Mn^{2+} has been associated with affective and psychiatric disorders[24]. A higher content of Mn^{2+} has been found in the basal ganglia of cirrhotic patients than in non-cirrhotic, and it has been correlated with extrapyramidal symptoms. *In vitro* studies indicate that Mn^{2+} inhibits mitochondrial oxidative phosphorylation, while intracerebral administration of Mn^{2+}

increases lactate and decreases ATP concentrations. At present, the cell compartmentalization of Mn^{2+} accumulation is not fully understood. Some investigators have reported that glial cells possess a transport mechanism with high Mn^{2+}affinity, capable of accumulating this metal in up to 200 times the extracellular concentration and with intracellular concentrations of 50-75 μmol. Additional studies have revealed that 60-70% of the Mn^{2+} accumulated is captured by mitochondria, while the rest is located in the cytoplasm[18,25]. Manganese is a transition element that can have different oxidation states (including Mn^{2+}, Mn^{3+} and Mn^{7+}). The transition from Mn^{2+} to trivalent Mn^{3+} leads to an increased oxidative capacity of the metal that can cause production of reactive oxygen species (ROS), lipoperoxidation and/or damage to the cellular membrane[25]. The mechanism of Mn^{2+} neurotoxicity is not fully understood, although it has been proposed that a dopaminergic dysfunction in the basal ganglia could be a possible cause[5,22]. Finally, it has been reported that Mn^{2+} stimulates dopamine autoxidation (DA) in dopaminergic neurons, a process accompanied by increased formation of quinones and bound proteins: cysteine-DA and cysteine-dihydroxyphenylacetic acid (DOPAC)[26,27].

Oxidative stress

Although to date there is little evidence of direct involvement of oxidative stress in patients with HE, several studies indicate that oxidative stress plays a key role in HE pathogenesis. Although it has been documented that the factors involved in HE pathogenesis are capable of generating free radicals and reducing antioxidant capacity in the CNS, the exact involvement of ROS generated by neurotoxins such as ammonia is not entirely clear. Recently, Kosenko et al.[28] and Hilgier et al.[29] have shown that the infusion of ammonium into the corpus striatum of rats results in the production of hydroxyl radicals. Kosenko et al.[30,31] also reported a significant decrease in the activity of antioxidant enzymes such as glutathione peroxidase, manganese-superoxide dismutase (SOD-Mn) and catalase, as well as increased lipid peroxidation and reduced glutathione (GSH). In addition, Warskulat et al.[32] observed that the expression of heme oxygenase-1 (HO-1) decreased in rats treated with ammonia, a common phenomenon under conditions of oxidative stress. Positive effects have been observed in the experimental treatment of HE with antioxidants (ascorbate, alphatocopherol, deferoxamine, butylated hydroxyanisole, dimethyl sulphoxide and dimethylurea)[33,34]. Negru et al.[35] identified high levels of free radicals in conjunction with decreased antioxidant capacity due to alcoholic liver disease in patients with HE. The most significant evidence of the involvement of oxidative stress in ammonia neurotoxicity has been derived from studies with cell cultures. Cultured astrocytes have been shown to be highly susceptible to oxidative stress, particularly with mitochondrial affectation. Although it is known that oxidation of lipids, proteins and nucleic acids affects cell structure and function, the precise consequences of oxidative stress in HE/hyperammonemia are not completely known. However, it is known that oxidative stress is associated with astrocyte swelling, a major component of cerebral oedema in fulminant hepatic failure (FHF), as well as with the induction of mitochondrial permeability transition (MPT), a phenomenon related to the lack of mitochondrial energy. It is therefore likely that other alterations in a state of hyperammonemia are related to oxidative stress. Both oxidative stress and nitrosative stress can cause MPT. It is important to point out that recent studies demonstrate the induction of MPT by Mn^{2+} in cultured astrocytes in a concentration-dependent manner, and that both the SOD and vitamin E offer partial protection in this phenomenon, thus indicating a possible role of oxidative stress in Mn^{2+}-induced MPT. The selective vulnerability of astrocytes to Mn^{2+} is not clear[36], although, as noted previously, the presence of transporters with high affinity for Mn^{2+} in astrocytes, as well as an elevated capacity to accumulate Mn^{2++}, may explain astrocyte susceptibility to Mn^{2+} toxicity.

Neurotransmission dysfunction

Dopaminergic

The mechanism of DA reduction in HE has been considered as the cause of the accumulation of false neurotransmitters. Increased DA conversion in patients with encephalopathy increases the concentration of the aromatic amino acids phenylalanine and tyrosine in the brain, both of which are precursors of the neurotransmitter DA. Additionally, it has been reported that Mn^{2+} alters dopaminergic transmission through an increase in DA conversion[5].

Glutamatergic

Glutamate is an amino acid and one of the amino acid neurotransmitters in the brain with an excitatory effect. It basically consists of a central carbon atom bound to a carboxyl group (COOH) and an amine group (NH3). Cerebral glutamate is derived solely from endogenous sources; mainly from ketoglutarate, a product of the Krebs cycle[37]. Neuronal glutamate acts as a neurotransmitter for communication between neurons, which can be excitatory or inhibitory. The excitatory action of glutamate in the brain and spinal cord of mammals has been known since the fifties[37], but not until the late seventies was it recognized that glutamate is the major excitatory transmitter in the nervous system of vertebrates[38].

GABAergic

Gamma-aminobutyric acid (GABA) is the predominant inhibitory neurotransmitter in the CNS of mammals. The alteration of GABAergic neurotransmission is implicated in the pathophysiology of various neurological and neuropsychiatric diseases such as epilepsy, schizophrenia, neurodegenerative disorders, sleep disorders and hepatic encephalopathy. GABAergic neurotransmission is mediated by GABA, which activates the postsynaptic $GABA_A$ receptor complex (GRC), a specific ligand of chloride-selective ion channels. The channel opens after activation, allowing

Table 2 Drugs used in the treatment of hepatic encephalopathy

N-acetylcysteine	Restores glutathione stores
Sodium benzoate	Enhances ammonia excretion
Indometacin	Normalises intracranial pressure
Carnitine	Improves mitochondrial function and reduces free radical production by mitochondria
Lactulose	Decreases ammonia absorption after intestinal pH change (osmotic cathartics)
Neomycin	Inhibits the growth of urease-producing bacteria and decreases the amount of ammonia produced in the gastrointestinal tract
Rifaximin	Nonabsorbable oral antibiotic that decreases the serum concentration of ammonia

chloride to enter and inhibit the postsynaptic neuron. The alteration of GABAergic neurotransmission in HE was proposed more than two decades ago[39].

Treatment of hepatic encephalopathy

Recent advances in the treatment of HE have focused on the modification of metabolic imbalances. The main strategy in HE treatment is aimed at reducing ammonia, which can be achieved by reducing overall production / absorption or increasing its elimination. Traditionally, it is known that the gastric cavity is the main site of ammonia production, so current strategies are directed towards methods of reducing the production / absorption of ammonia in the intestine. The priority of treatment has focused on restricting protein in the diet (table 2). In practice, the most commonly used agents are non-absorbable disaccharides such as lactulose and lactitol. These act by promoting bowel movements, thus affecting bacterial metabolism, including the production and absorption of ammonia[11,22,23]. Antibiotics such as neomycin, tetracycline, metronidazole and vancomycin are used to reduce the bacterial flora and thus ammonia production as a result of the degradation of urea and other proteins. New agents such as sodium benzoate and L-ornithine L-aspartate (LOLA) are aimed at the metabolic elimination of ammonia. For over 25 years, non-absorbable disaccharides have been the main treatment used. However, these non-absorbable disaccharides have been used as treatment without an adequate evidence base. In a systematic review of 22 randomized trials on the use of lactulose/lactitol for hepatic encephalopathy, Bodils Als-Nielsen et al.[40] concluded that there is insufficient evidence to recommend or discourage their use.

Experimental models of hepatic encephalopathy

In a suitable model for HE study, the experimental animals should exhibit the typical symptoms of liver disease in addition to presenting neurological changes such as the presence of type II Alzheimer astrocytes. The following section describes some of the models used in HE study.

Surgical models

These models do not fully meet the criteria outlined previously for an HE animal model. In one of the surgical models, the blood is shunted from the portal vein directly to the caudal vena cava, thus bypassing the liver. This has the major disadvantages that it can only be reversed by transplantation and that the type of coma is different from that observed in patients. A more appropriate surgical model is the one using complete devascularization of the liver by a permanent portocaval bypass in the hepatic artery. This procedure is irreversible, so temporary ligation of the hepatic artery is the most appropriate surgical model for the study of HE[41].

Models of hepatotoxicity

It has been reported that there is a correlation between brain concentrations of aromatic amino acids and experimental hepatic encephalopathy induced by carbon tetrachloride (CCl_4, 1ml/kg, 3 times a week for 10 weeks). The brain concentrations of aromatic amino acids, especially tyrosine (Tyr) and phenylalanine (Phe), in rats with hepatic encephalopathy were increased with respect to controls. The increase of Tyr and Phe in the brain, caused by hyperammonemia, as well as elevated blood Phe and Tyr values, could be fundamental in the development of hepatic encephalopathy[42]. The model of liver damage induced by treatment with thioacetamide (TAA) presents astrocytic inflammation and changes similar to those observed in the brains of patients with HE[43]. However, although TAA-induced HE affects the cerebral glutamatergic system, differences in experimental design (such as the number of administrations or the drug dose) have yielded different results[44].

Surgical and chemical combination

The combination of surgical and chemical models has been used successfully in each of the three existing types of HE. The proposed models for type A HE (associated with acute liver failure) include treatment with hepatotoxic drugs, partial or total devascularization and partial or total hepatectomy. To date there is no good model for the study of chronic HE. Perhaps the most effective and most used is

the portocaval shunt, but this is only a good model for type B HE. Other type B models carry out partial ligation of the portal vein to simulate the portosystemic shunt. Finally, the models proposed for type C chronic HE (in conjunction with cirrhosis and portal hypertension) require the use of hepatotoxins, such as intoxication by CCl_4 or TAA or, failing that, bile duct obstruction. While it is true that biliary tract ligation can induce HE by itself, exposure to neurotoxins (such as Mn^{2+}), together with liver damage (by hepatotoxins or surgical methods), is the method that best simulates HE pathogenesis[45].

Intravenous injection of galactosamine hydrochloride

Although in this model the animals show effects similar to acute severe hepatic encephalopathy, there are many objections to its use. Different types of responses have been reported among the animal species used; in addition, the drug is costly and there are difficulties in generating hepatic encephalopathy[46].

Chronic and systemic exposure to endotoxins

It has been reported that plasma concentrations of gut-derived endotoxin (lipopolysaccharides) are often elevated in patients with cirrhosis, and they are thought to contribute to HE establishment. This type of experimental model was developed to mimic the "leaky gut" syndrome, that is, the translocation of endotoxins from the bloodstream in cirrhotic patients[47].

New therapeutic strategies in HE

Hepatic encephalopathy is a significant cause of morbidity and mortality in patients with advanced chronic liver disease. Current treatments have side effects, besides a high cost and incomplete efficacy. The most useful therapy in HE should include the healing of liver failure, since signs of cerebral oedema disappear rapidly when there is an improvement of the liver in patients with acute liver failure and HE[48]. Although different therapeutic procedures for HE have been used, many of them are complementary and include the manipulation of intestinal amino acid production to change the bacteria in the colon by administering high doses of urease in bacteria (*Lactobacillus acidophilus*), as well as the use of drugs acting on the urea cycle to improve HE in a manner similar to the administration of lactulose and some diets enriched with branched chain amino acids. Liver transplantation is obviously the most aggressive treatment to improve liver failure manifestations, but in some chronic cases there is no improvement in neurological signs or recovery is only partial[48]. Moreover, although chronic antibiotic administration has proven effective in HE treatment, serious adverse effects have been reported with the use of neomycin or metronidazole. Some researchers have examined the use of rifaximin, a nonabsorbable derivative of rifamycin with a broad spectrum of activity against gram-positive and aerobic and anaerobic gram-negative bacteria, for HE treatment. Rifaximin appears to offer greater benefits in terms of safety, efficacy and tolerability profile than lactulose and possibly neomycin[49]. A quaternary ammonium L-acyl-carnitine compound has also been proposed as a powerful, low-cost, safe alternative treatment for patients with cirrhosis and HE[50]. A study carried out by Galvez-Gastelum et al. evaluated the effects of gene therapy with adenoviral vectors containing human cDNA with urokinase-type plasminogen activator and metalloprotease 8 (Ad-huPA and Ad-MMP8, respectively) in hepatic fibrosis and HE-induced symptoms (Mn^{2+} accumulation and DA metabolism). Their study used Wistar rats which, after bile duct ligation (BDL), received 1 mg/ml of $MnCl_2$ in their drinking water (BDL/Mn^2). Subsequently, encephalopathic and cirrhotic animals were treated with the therapeutic vectors. It was found that animals with BDL/Mn^2 presented motor alterations such as trembling, muscle rigidity and gait disturbance; these symptoms decreased significantly after gene therapy with Ad-huPA and Ad-MMP8. In addition, it was found that liver fibrosis decreased after treatment and dopamine concentrations in the brain (corpus striatum) increased compared with rats suffering encephalopathy without therapy. Untreated cirrhotic animals presented an abnormal morphology of the cellular elements (gliosis) of the corpus striatum and substantia nigra, where the expression of glial fibrillary acidic protein (GFAP) had increased and that of tyrosine hydroxylase (TH) had decreased. These anomalies decreased with Ad-huPA and Ad-MMP8. The treatment was therefore effective in reversing experimental fibrosis and hepatic encephalopathy (unpublished data).

Conclusions

Hepatic encephalopathy is a complex neuropsychiatric syndrome associated with fulminant hepatic failure, chronic parenchymal liver disease or portosystemic shunt. Its symptoms vary from subtle changes in mentality and motor deficits, such as rigidity, asterixis (shaking, tremor) and poor muscle coordination, as well as alterations of physiological circadian cycles and complete loss of consciousness (hepatic coma). Although HE pathogenesis is complex and not yet fully understood, numerous animal models for the study of HE have been developed. The results of previous studies indicate that HE pathogenesis may be multifactorial, involving various factors such as blood-brain barrier alterations, substances such as ammonia and manganese, and neurotransmission of dopamine, glutamate and GABA. These changes are the result of neurotoxin-mediated oxidative stress in the brain. Therapies for HE treatment have focused on modifying metabolic disturbances in HE (neurotransmission), as they relate to the hypothesis of ammonia. The main strategy for HE treatment is aimed at reducing ammonia, either by decreasing its absorption or increasing its elimination. Traditionally, it has been thought that the intestine is the major site of ammonia production, so current strategies are directed towards methods of reducing the absorption / production of ammonia in the intestine.

Conflict of interests

The authors declare no conflict of interests.

References

1. Social Security Online. Available at: http://www.ssa.gov.
2. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005;115:209-18.
3. Rodriguez-Hernandez H, Jacobo-Karam JS, Castañón-Santillán Mdel C, et al. [Survival in patients with liver cirrhosis at the Durango, IMSS Regional General Hospital]. Gac Med Mex. 2002;138:325-30.
4. Butterworth RF. Hepatic encephalopathy-a serious complication of alcoholic liver disease. Alcohol Res Health. 2003;27:143-5.
5. Montes S, Alcaraz-Zubeldia M, Muriel P, Ríos C. Striatal manganese accumulation induces changes in dopamine metabolism in the cirrhotic rat. Brain Res. 2001;891:123-9.
6. Salgado S, Garcia J, Vera J, et al. Liver cirrhosis is reverted by urokinase-type plasminogen activator gene therapy. Mol Ther. 2000;2:545-51.
7. Henderson NC, Iredale JP. Liver fibrosis: cellular mechanisms of progression and resolution. Clin Sci (Lond). 2007;112:265-80.
8. Lotersztajn S, Julien B, Teixeira-Clerc F, Grenard P, Mallat A. Hepatic fibrosis: molecular mechanisms and drug targets. Annu Rev Pharmacol Toxicol. 2005;45:605-28.
9. Garcia-Moreno LM, Conejo NM, González-Pardo H, et al. Evaluation of two experimental models of hepatic encephalopathy in rats. Braz J Med Biol Res. 2005;38:127-32.
10. SIler-López F, Sandoval A, Salgado S, et al. Treatment with human metalloproteinase-8 gene delivery ameliorates experimental rat liver cirrhosis. Gastroenterology. 2004; 126:1122-33.
11. Jalan R, Shawcross D, Davies N. The molecular pathogenesis of hepatic encephalopathy. IJBCB. 2003;1471:1-7.
12. Méndez M, Méndez-López M, López L, et al. Spatial memory alterations in three models of hepatic encephalopathy. Behav Brain Res. 2008;188:32-40.
13. Córdoba J, Mínguez B. Hepatic encephalopathy. Sem Liver Dis. 2008;28:70-80.
14. Groeneweg M, Moerland W, Quero JC, et al. Screening of subclinical hepatic encephalopathy. J Hepatol. 2000;32:748-53.
15. Clasificación de Child-Pugh. Available at: http://www.hepatitis.cl/child-pugh.htm.
16. Haussinger D, Schliess F, Kircheis G. Pathogenesis of hepatic encephalopathy. J Gastroenterol Hepatol. 2002;17:S256-9.
17. Brusilow S. Hyperammonemic encephalopathy. Medicine. 2002;81:240-9.
18. Chun-Jung C, Su-Lan L. Oxidative stress involves in astrocytes alterations induced by manganese. Exp Neurol. 2002;175:216-25.
19. Hazell A. Astrocytes and manganese neurotoxicity. Neurochem Int. 2002;41:271-7.
20. Su-Jin Y, Kim M, Kim S, et al. Induction of TGF-β-inducible gene-h3 (βig-h3) by TGF-,1 in astrocytes: implications for astrocyte response to brain injury. Mol Brain Res. 2002;107:57-64.
21. Butterworth RF. Neuronal cell death in hepatic encephalopathy. Metab Brain Dis. 2007;22:309-20.
22. Ong J, Mullen D. Hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2001;13:3325-34.
23. Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. Lancet. 2005;365:431-3.
24. Sassine MP, Mergler D, Bowler R, Hudnell HK. Manganese accentuates adverse mental health effects associated with alcohol use disorders. Biol Psychiatry. 2002;51:909-21.
25. Hazell A, Butterworth R. Hepatic encephalopathy: an update of pathophysiologic mechanism. Proc Soc Exp Biol Med. 1999;222:99-112.
26. Ramesh G, Ghosh D, Gunasekar P. Activation of early signaling transcription factor, NF-kB following low level manganese exposure. Toxicol Lett. 2002;136:151-8.
27. Erikson K, Dobson AW, Dorman DC, Aschner M. Manganese exposure and induced oxidative stress in the rat brain. Sci Tot Env. 2004;334:409-16.
28. Kosenko E, Venediktova N, Kaminsky Y, et al. Sources of oxygen radicals in brain in acute ammonia intoxication in vivo. Brain Res. 2003;981:193-200.
29. Hilgier W, Anderzhanova E, Oja SS, et al. Taurine reduces ammonia- and N-methyl-D-aspartate-induced accumulation of cyclic GMP and hydroxyl radicals in microdialysates of the rat striatum. Eur J Pharmacol. 2003;468:21-5.
30. Kosenko E, Kaminski Y, Lopata O, et al. Blocking NMDA receptors prevents the oxidative stress induced by acute ammonia intoxication. Free Radic Biol Med. 1999;26:1369-74.
31. Kosenko E, Kaminsky Y, Kaminsky A, et al. Superoxide production and antioxidant enzymes in ammonia intoxication in rats. Free Radic Res. 1997;27:637-44.
32. Warskulat U, Görg B, Bidmon HJ, et al. Ammonia-induced heme oxygenase-1 expression in cultured rat astrocytes and rat brain in vivo. Glia. 2002;40:324-36.
33. Song G, Dhodda VK, Blei AT, et al. GeneChip analysis shows altered mRNA expression of transcripts of neurotransmitter and signal transduction pathways in the cerebral cortex of portacaval shunted rats. J Neurosci Res. 2002;68:730-7.
34. Ryter SW, Choi AM. Heme oxygenase-1: molecular mechanisms of gene expression in oxygen-related stress. Antioxid Redox Signal. 2002;4:625-32.
35. Negru T, Ghiea V, Pasarica D. Oxidative injury and other metabolic disorders in hepatic encephalopathy. Rom J Physiol. 1999;36:29-36.
36. Norenberg MD, Jayakumar AR, Rama Rao KV. Oxidative stress in the pathogenesis of hepatic encephalopathy. Metab Brain Dis. 2004;19:313-29.
37. Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. J Nutr. 2000;130:S1007-15.
38. Mark LP, Prost RW, Ulmer JL, et al. Pictorial review of glutamate excitotoxicity: fundamental concepts for neuroimaging. Am J Neuroradiol. 2001;22:1813-24.
39. Ahboucha S, Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at GABA from the molecular standpoint. Metab Brain Dis. 2004;19:331-43.
40. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. BMJ. 2004;328:1046.
41. Giges B, Dein HL, Sborov VM, et al. Experimental hepatic coma. Surg Gynecol Obstet. 1953;97:763-8.
42. Yamamoto HA. Brain phenylalanine and tyrosine levels and hepatic encephalopathy induced by CCl 4 in rats. Toxicology. 1990;61:241-7.
43. Matsushita M, Yamamoto T, Gemba H. The role of astrocytes in the development of hepatic encephalopathy. Neurosci Res. 1999;34:271-80.
44. Hilgier W, Olson JE. Brain ion and amino acid contents during edema development in hepatic encephalopathy. J Neurochem. 1994;62:197-204.
45. Montes S, Alcaraz-Zubeldia M, Muriel P, Rios C. Role of manganese accumulation in increased brain glutamine of the cirrhotic rat. Neurochem Res. 2003;28:911-7.
46. Blitzer BL, Waggoner JG, Jones EA, et al. A model of fulminant hepatic failure in the rabbit. Gastroenterology. 1978;74: 664-71.

47. Lindros KO, Jarvelainen HA. Chronic systemic endotoxin exposure: an animal model in experimental hepatic encephalopathy. Metab Brain Dis. 2005;20:393-8.
48. Antoni M. Hepatic encephalopathy: from pathophysiology to treatment. Digestion. 2006;73:86-93.
49. De Melo RT, Charneski L, Hilas O. Rifaximib for the treatment of hepatic encephalopathy. Am J Health Syst Pharm. 2008;65:818-22.
50. Shores NJ, Keeffe EB. Is oral L-acyl-carnitine an effective therapy for hepatic encephalpathy? Review of the literature. Dig Dis Sci. 2008;53:2330-3.
51. Camacho-Muñoz B, Hernández-Ramos FJ, Ortega-Martínez de Victoria L. Enfermedad de Creutzfeldt-Jakob y encefalopatía hepática: coexistencia en la misma paciente. Rev Neurol. 2001;33:540-4.