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HEPATIC ENCEPHALOPATHY: A LOOK AT GLUTAMATE SYSTEM

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ПЕЧЕНОЧНАЯ ЭНЦЕФАЛОПАТИЯ — ВЗГЛЯД НА ГЛУТАМАТНУЮ СИСТЕМУ

Печеночная энцефалопатия — это психоневрологический синдром, который связан с дисфункцией печени и имеет количественно и качественно отличительные черты, зависящие от его тяжести. Он определяет прогноз при остром повреждении печени, в котором до 30 % пациентов подвергаются вклинению мозга из-за отека мозга и внутричерепной гипертензии. При циррозе (хроническая дисфункция печени) это происходит более непредсказуемо, вызывает ряд психоневрологических нарушений, которые включают психомоторную дисфункцию, нарушение памяти, увеличение времени реакции, сенсорные расстройства и плохую концентрацию. При наиболее тяжелых формах у пациентов могут развиться спутанность сознания, ступор, кома и смерть. В минимальном проявлении печеночной энцефалопатии изменения в психической функции незначительны и могут наблюдаться у пациентов без каких-либо явных клинических признаков энцефалопатии. Нейропсихологические особенности минимальной печеночной энцефалопатии приводят к расстройству исполнительной функции. В первую очередь, это затрагивает селективное внимание и быстроту психомоторных ракций, имеющих огромное влияние на связанное со здоровьем качество жизни. Обострение печеночной недостаточности наблюдается у пациентов с хроническими заболеваниями печени. У этих больных течение осложняется такими состояниями, как сепсис, желудочно-кишечные кровотечения (увеличение нагрузки аммиака) или созда-

ние портосистемного анастомоза, что определяет патофизиологические рамки, в которых у пациентов с хроническим «фенотипом» могут регистрироваться отличия от обычного течения острой печеночной недостаточности.

Ключевые слова: печеночная энцефалопатия, острая печеночная недостаточность, глутаматная система.

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HEPATIC ENCEPHALOPATHY: A LOOK AT GLUTAMATE SYSTEM

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome which is associated with liver dysfunction and has quantitatively and qualitatively distinct features relating to its severity. It defines the prognosis in acute liver injury in which up to 30 % of patients succumb from brain herniation due to brain oedema and intracranial hypertension. In cirrhosis (chronic liver dysfunction), it occurs more insidiously causing a range of neuropsychiatric disturbances which include psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities and poor concentration. In its most severe forms, patients may develop confusion, stupor, coma and death. In minimal HE, the changes in mental function are subtle and may be observed in patients with no overt clinical evidence of encephalopathy. The neuropsychological features of minimal HE are suggestive of a disorder of executive functioning. This primarily affects selective attention and psychomotor speed, which has a huge impact on health-related quality of life and has been shown to reduce the ability to drive. Acute-on-chronic liver failure defines a group of patients that have chronic liver disease and in these patients a severe precipitating event such as sepsis, gastrointestinal bleeding (increased ammonia load) or the creation of portosystemic shunting (increased ammonia load) provides a pathophysiologic framework in which the patients with a chronic 'phenotype' can appear clinically indistinct from those with acute liver failure.

Key words: hepatic encephalopathy, acute liver failure, glutamate system

Pathogenesis of Hepatic Encephalopathy

Current evidence suggests that HE is the consequence of a low grade chronic glial edema with subsequent alterations of glioneuronal communication. Different factors, such as ammonia [6], benzodiazepines [7] and inflammatory cytokines can induce or aggravate astrocyte swelling, which results in the activation of osmosignaling cascades, protein modifications, alterations in gene expression and neurotransmission. Among the protein modifications nitration of critical tyrosine residues in glial proteins may play an important role [8]. Several proteins, which are nitrated in response to ammonia, benzodiazepines, hypoosmotic astrocyte swelling or inflammatory cytokines have been identified, inluding glutamine synthetase [9] (GS) and the peripheral type benzodiazepine receptor. The changes in the distribution of this critical enzyme suggests that the glutamate-glutamine cycle may be differentially impaired in hyperammonemic states.

Ammonia

Results of neuropathologic, spectroscopic, and neurochemical studies continue to confirm a major role for ammonia in the pathogenesis of the central nervous system complications of both acute and chronic liver failure. Damage to astrocytes characterized by cell swelling (acute liver failure) or Alzheimer Type II astrocytosis (chronic liver failure)

can be readily reproduced by acute or chronic exposure of these cells in vitro to pathophysiologically relevant concentrations of ammonia. Furthermore, exposure of the brain or cultured astrocytes to ammonia results in similar alterations in expression of genes coding for key astrocytic proteins. Such proteins include the structural glial fibrillary acidic protein, glutamate (Glu) transporters, and peripheral-type (mitochondrial) benzodiazepine receptors. Brain–blood ammonia concentration ratios (normally of the order of 2) are increased up to fourfold in liver failure and arterial blood ammonia concentrations are good predictors of cerebral herniation in patients with acute liver failure. Studies using 1H magnetic resonance spectroscopy in patients with chronic liver failure reveal a positive correlation between the severity of neuropsychiatric symptoms and brain concentrations of the brain ammonia — detoxification product glutamine. Increased intracellular glutamine may be a contributory cause of brain edema in hyperammonemia. Positron emission tomography studies using 13HN3 provide evidence of increased blood–brain ammonia transfer and brain ammonia utilization rates in patients with chronic liver failure. In addition to the use of nonabsorbable disaccharides and antibiotics to reduce gut ammonia production, new approaches to the treatment of hepatic encephalopathy by lowering of brain ammonia include the use of L-ornithine — L-aspartate and mild hypothermia [6].

The Glutamate System

Ammonia-induced depolarization of nerve cells *in vivo* or *in vitro* has been shown to increase the calcium-dependent release of Glu in various brain regions [10]. An obvious direct consequence of this excessive Glu release is overstimulation of the ionotropic Glu receptors, in particular the NMDA receptors. The stimulation is thought to be further enhanced by an increase in extracellular glycine, which is a positive modulator of NMDA receptors [11], and by a loss of GABA-B receptors that negatively modulate Glu release [12].

The critical role of activated NMDA receptors in fulminant hepatic failure (FHF) has been convincingly demonstrated in a study by Vogels et al. [13]. In this study, administration of the competitive NMDA receptor antagonist memantine to rats with acute HE significantly improved the clinical grading of the encephalopathy and EEG activity. Extracellular Glu concentrations returned to control levels. Hyperammonemia also inhibits the cerebral synthesis of kynurenic acid, a wide-spectrum antagonist of ionotropic Glu receptors [14], and the process is believed to exacerbate the neuroexcitatory effects of ammonia.

Glutamine Synthetase

GS in brain is located mainly in astrocytes. One of the primary roles of astrocytes is to protect neurons against excitotoxicity by taking up excess ammonia and Glu and converting it into glutamine via the enzyme GS. Changes in GS expression may reflect changes in astroglial function, which can affect neuronal functions.

Hyperammonemia can be experimentally induced and an adaptive astroglial response to high levels of ammonia and glutamate seems to occur in long-term studies. In hyperammonemic states, astroglial cells can experience morphological changes that may alter different astrocyte functions, such as protein synthesis or neurotransmitters uptake. One of the observed changes is the increase in the GS expression in astrocytes located in glutamatergic areas. The induction of GS expression in these specific areas would balance the

increased ammonia and glutamate uptake and protect against neuronal degeneration, whereas decrease of GS expression in non-glutamatergic areas could disrupt the neuron-glial metabolic interactions as a consequence of hyperammonemia.

Induction of GS has been described in astrocytes in response to the action of Glu on active Glu receptors. The over-stimulation of Glu receptors may also favour nitric oxide (NO) formation by activation of NO synthase (NOS), and NO has been implicated in the pathogenesis of several CNS diseases. Hyperammonemia could induce the formation of inducible NOS in astroglial cells, with the consequent NO formation, deactivation of GS and dawn-regulation of Glu uptake. However, in glutamatergic areas, the distribution of both glial glutamate receptors and glial glutamate transporters parallels the GS location, suggesting a functional coupling between Glu uptake and degradation by Glu transporters and GS to attenuate brain injury in these areas.

In hyperammonemia, the astroglial cells located in proximity to blood-vessels in glutamatergic areas show increased GS protein content in their perivascular processes. Since ammonia freely crosses the blood–brain barrier and astrocytes are responsible for maintaining the blood–brain barrier, the presence of GS in the perivascular processes could produce a rapid glutamine synthesis to be released into blood. It could, therefore, prevent the entry of high amounts of ammonia from circulation to attenuate neurotoxicity. The changes in the distribution of this critical enzyme suggests that the glutamate-glutamine cycle may be differentially impaired in hyperammonemic states [9].

Increased Extracellular Brain Glutamate

Increased extracellular concentrations of brain Glu in Acute Liver Failure (ALF) can result from an increase in Glu release and/or a decrease in Glu removal (uptake) both by neurons and/or astrocytes. Glu can be released from neurons and astrocytes by cell swelling induced mechanisms, reversal of Glu transporters, and/or calcium-dependent mechanisms. In neurons, an increase in Glu release is unlikely to occur because ammonia inhibits glutaminase reducing the amount of Glu available for synaptic release. Furthermore, cytotoxic edema in ALF develops in astrocytes and not neurons, eliminating the possibility of swelling-induced release of Glu from neurons. An inhibition of Glu removal by the high affinity transporters on astrocytes would result in an increase in extracellular brain Glu concentrations. However, it has been demonstrated in vitro that acute application of ammonia potentiates Glu uptake into astrocytes [15]. Ammonia-induced astrocytic swelling may potentially stimulate Glu release from astrocytes; however, this would suggest that increased extracellular brain Glu is the result and not a cause of astrocytic swelling. Interestingly, increased extracellular brain Glu concentrations precede the onset of brain edema in rats with ALF due to hepatic devascularization [11]. Reversal of Glu transporters occurs when high-energy phosphates are depleted. Although ATP levels have been found to be unchanged in ALF, increased lactate production has been demonstrated, suggesting an inhibition of glucose oxidation but this appears to arise late in the development of HE in ALF.

Astrocytes play an important role in synaptic transmission and under normal physiological conditions are capable of releasing Glu in a calcium-dependent manner. There is now increasing evidence that ammonia can stimulate [Ca2C] i leading to stimulation and deregulation of Glu release. Figure 1 represents a hypothesis that may occur during the development of HE and brain edema in ALF. Ammonia enters neurons and inhibits glutaminase resulting in (1) less Glu produced and available for release and (2) disrup-

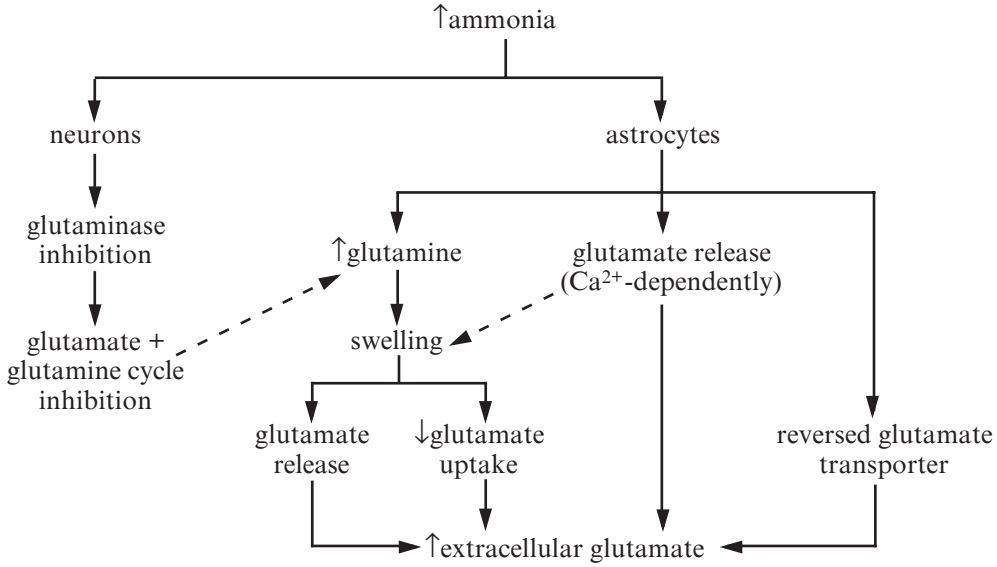

Fig. 1. Diagram demonstrating the possible mechanisms involved in the development of HE and brain edema in ALF

tion of the glutamate-glutamine cycle between astrocytes and neurons. Ammonia also inhibits AMPA receptor activation but does not affect NMDA receptors. Overall, ammonia decreases Glu release from neurons by inhibiting synaptic transmission and decreasing intracellular Glu. Ammonia also enters astrocytes and (1) is detoxified by GS producing glutamine and (2) stimulates Glu release in a calcium-dependent manner leading to increased extracellular Glu. With inhibition of the glutamate-glutamine cycle, glutamine remains "trapped" in the astrocyte resulting in intracellular hypertonicity and cytotoxic swelling. Deregulation of the release of Glu from astrocytes could also be a factor involved in astrocytic swelling. Once the astrocyte is swollen, Glu uptake is inhibited to decrease the ion uptake preventing further swelling. Furthermore, inhibition of Glu uptake and swelling-induced release of Glu may add to the already increased extracellular concentrations of Glu.

Because NMDA receptors are not affected by ammonia as are the AMPA/kainate receptors, this may explain the seizures and hyperexcitability, not uncommonly seen in patients with ALF [16].

Manganese

Amongst the potential neurotoxins implicated in the pathogenesis of HE, manganese emerges as a new candidate. In patients with chronic liver diseases, manganese accumulates in blood and brain leading to pallidal signal hyperintensity on T1-weighted Magnetic Resonance (MR) Imaging. Direct measurements in globus pallidus obtained at autopsy from cirrhotic patients who died in hepatic coma reveal 2 to 7-fold increases of manganese concentration. The intensity of pallidal MR images correlates with blood manganese and with the presence of extrapyramidal symptoms occurring in a majority of cirrhotic patients. Liver transplantation results in normalization of pallidal MR sig-

nals and disappearance of extrapyramidal symptoms whereas transjugular intrahepatic portosystemic shunting induces an increase in pallidal hyperintensity with a concomitant deterioration of neurological dysfunction. These findings suggest that the toxic effects of manganese contribute to extrapyramidal symptoms in patients with chronic liver disease. The mechanisms of manganese neurotoxicity are still speculative, but there is evidence to suggest that manganese deposition in the pallidum may lead to dopaminergic dysfunction. Future studies should be aimed at evaluating the effects of manganese chelation and/or of treatment of the dopaminergic deficit on neurological symptomatology in these patients [17].

The GABA system

The GABA-A–benzodiazepine receptor complex

The first observation of increased GABA-ergic tone in HE of humans consisted of anecdotal reports. The intravenous bolus administration of the central benzodiazepine antagonist flumazenil caused clinical and electrophysiological improvement in patients with FHF or cirrhosis [18]. Such a response occurred in over 50 % of patients with stable HE due to cirrhosis or those with FHF who had received no therapeutic benzodiazepines [19]. The drug displaces ligands that enhance the action of GABA and thus contribute to the manifestations of HE. Ameliorations of HE have also been observed in the rabbit model of galactosamine-induced FHF following pharmacological antagonism of components of the GABA-A/benzodiazepine receptor complex. Similar behavioral and electrophysiological improvements occurred after the administration of the GABA antagonist bicuculline, a chloride channel blocker, and flumazenil [20]. Benzodiazepine antagonist-induced behavioral and electrophysiological ameliorations of HE were also documented in another model of FHF in the rat [21]. Increased GABA-ergic tone in models of HE has also been suggested by increased resistance to the induction of seizures by drugs, e. g. bicuculline [20] and 3-mercaptopropionic acid [22]. The response of individual CNS neurons to GABA-A and central benzodiazepine receptor ligands in HE was also studied. Purkinje neurons in cerebellar slices from rabbits with FHF were shown to be more sensitive to the neuroinhibitory effects of the GABA agonist muscimol and the benzodiazepine agonist flunitrazepam than control neurons. Furthermore, the increased sensitivity of neurons from animals with HE to muscimol could be abolished by a benzodiazepine antagonist, and these agents induced increased spontaneous activity of neurons from animals with HE. They did not increase the spontaneous activity of control neurons [23]. These findings are consistent with enhanced activation of the GABA-A receptor complex in HE. They are also compatible with the concept that a benzodiazepine agonist ligand contributes to increased GABA-ergic tone in HE. Benzodiazepine antagonists cause disinhibition of neurons and a decrease in GABA-ergic tone in HE. These studies complemented the increased sensitivity of patients with cirrhosis to benzodiazepines [24]. The presence of increased levels of central benzodiazepine receptor ligands with agonist properties was supported by rigorous methods (high-performance liquid chromatography and mass spectroscopy) in the brains of animal models of HE25, and humans who had died from FHF due to paracetamol toxicity [25]. Thus, increased brain levels of natural benzodiazepines probably constitute one mechanism for increased GABA-ergic tone in HE. Another mechanism could be increased availability of GABA at GABA-A receptors, largely due to increased cerebral cortical release of GABA. An increased depolarization-induced GABA release was found in cerebral cortical slices [26] and astro-

cytes of rats with thioacetamide-induced FHF [27]. In the same model, the density of cerebrocortical GABA-B receptors that mediate feedback inhibition of GABA release was shown to be only 32 % of the control value [12].

Ammonia may also enhance GABA-ergic neurotransmission as a consequence of direct interaction with the GABA-A receptor complex. Such an effect of ammonia was first demonstrated in cultured neurons. At a GABA concentration of 10-5 M, addition of ammonia (0.2–0.5 mM) induced a concentration-dependent increase in GABA-induced chloride current [28]. Ammonia concentrations that mediated this effect fell within the range causing human precoma-HE [29]. Direct effects of ammonia on the GABA-A/benzodiazepine receptor complex were studied further using radioligand binding assays. Ammonia (0.05–0.5 mM) was shown to increase selective binding of agonist ligands (e. g. muscimol, flunitrazepam) to the GABA-A receptor complex. Higher ammonia concentrations (0.75–2.0 mM) returned ligand binding to control levels. In addition, ammonia and benzodiazepine receptor agonists were found to synergistically enhance the binding of the GABA-agonist muscimol [30]. Thus, ammonia not only directly enhanced the ability of GABA to depress neuronal activity, but could also inhibit CNS function by its synergistic interaction with natural benzodiazepine receptor ligands. The mechanisms underlying the direct actions of ammonia on the GABA-A receptor complex resembles those of the barbiturates [31].

Peripheral benzodiazepine receptors

In the CNS, PBZR are located in the outer mitochondrial membranes of astrocytes [32]. Naturally occurring PBZR ligands have also been identified in the CNS. Peripheral benzodiazepine receptors are thought to exert an indirect control on the GABA-ergic system. Their activation elicits the astrocytic synthesis of pregnenelone-derived neurosteroids, some of which are positive modulators of the GABA-A receptor complex [33].

There is considerable evidence pointing to activation of the PBZR–neurosteroid pathway in HE. Notably, increased densities of PBZR have been reported in the brains of cirrhotic patients who died from HE [34]. Rats with portacaval shunts exhibited increased expression of PBZR messenger ribonucleic acid [35]. In mice with toxin-induced liver failure or hyperammonemia without liver failure, increased ligand binding to PBZR was associated with increased pregnenelone synthesis36, and pretreatment of healthy mice with the PBZR antagonist PK 1195 increased their resistance to subsequent injection of a toxic dose of ammonium acetate [36]. Depending on their concentration, PBZR antagonists and pregnenelone steroids have been shown to either ameliorate or exacerbate ammonia-induced astrocytic swelling in vitro [7; 37].

Summary

In conclusion we have described the current new perspectives in the molecular pathogenesis of HE. The importance of the role of ammonia has been highlighted with respect both to its direct neurotoxicity and on brain swelling through its detoxification to glutamine in the astrocyte, the cell most often implicated in the pathogenesis of HE. In fact one might say that the key to understanding the pathogenesis of HE is the multipurpose approach, including exploring effect of the glutamate system, the GABA system and role of manganese, we believe that research of glutamate system and blood glutamate scavenging may open now new therapeutic options.

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