Hepatic Encephalopathy: New Treatments

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Hepatic encephalopathy (HE) is a serious neuropsychiatric syndrome due to acute or chronic liver disease and portosystemic shunting.¹ The clinical symptoms are widely variable, extending from subtle impairment in mental state to coma. Although many factors are believed to be involved in the development and progression of HE such as oxidative stress, neurotransmission changes, neurotoxins, abnormalities in GABA-ergic pathways, and impaired energy metabolism of the brain, most treatments focus on targeting and lowering the accumulation of ammonia as well as targeting inflammation.²

At present, the only drugs that are routinely used in clinical practice are lactulose and rifaximin. Data for the use of the former is poor but still is considered the gold standard. Rifaximin, on the other hand, has been shown to be efficacious for secondary prevention of HE. The areas of primary prevention of HE, treatment of minimal HE, and of a severe acute episode are unmet needs. Here, we will focus on the future horizons regarding the therapies of HE in patients with cirrhosis.

Treatments Targeting Ammonia Production and Removal

Ammonia metabolism is complex and is regulated in multiple organs such as the liver, muscles, kidneys, and brain. Its metabolism is related to three enzyme systems (Figure 1):

1. Urea cycle: This is the key metabolic pathway involved in ammonia detoxification. In liver failure, the reduction in liver cell function reduces its activity.
2. Glutaminase: This enzyme is mainly expressed in the gut and the kidneys and produces ammonia from the breakdown of glutamine.
3. Glutamine synthetase (GS): This enzyme is mainly expressed in the muscle and the liver and becomes active in metabolizing ammonia during liver failure

Some of the most current and emerging treatments for targeting ammonia production and removal are introduced in this section (Table 1).

L-Ornithine and L-Aspartate (LOLA)

L-Ornithine and L-aspartate (LOLA) has the ability to lower blood ammonia because both L-ornithine and L-aspartate are substrates for the urea cycle and can therefore increase urea production.³ It also acts by activating glutamine production through activation of GS in skeletal muscles and perivenous hepatocytes.⁴ Furthermore, although LOLA initially lowers blood ammonia levels even at the end stages of liver disease, its effects in liver failure appear to be temporary, because a rebound effect is observed on cessation of the drug.⁵ Despite this, LOLA is well tolerated and was shown to be superior to placebo.⁶

Ornithine Phenylacetate

Ornithine phenylacetate (OP) acts to reduce ammonia by normalizing gut glutaminase activity and increasing GS activity in peripheral organs, mainly the skeletal muscles and residual hepatocytes. L-Ornithine results in the production of glutamine, and in order to prevent the “rebound effect,” glutamine is conjugated with phenylacetate to form phenylacetylglutamine. This product cannot be metabolized by glutaminase and is therefore harmlessly excreted in the urine. OP successfully prevents increases in arterial ammonia while evidence exists from animal models suggesting a significant decrease in extracellular brain ammonia, preventing intracranial hypertension and improving the mental stage.⁷ OP was shown to reduce ammonia in a pilot study in patients with cirrhosis and gastrointestinal bleeding and is currently in phase 2 clinical trials.⁸

Glycerol Phenylbutyrate (GPB, HPN-100)

GPB acts by providing an alternative pathway for ammonia removal and waste nitrogen excretion in the form of

Abbreviations: GS, glutamine synthetase; HE, hepatic encephalopathy; LOLA, L-ornithine and L-aspartate; OP, ornithine phenylacetate.

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Figure 1 Interorgan ammonia metabolism in (A) healthy and (B) diseased liver.

TABLE 1 Emerging Treatment of Hepatic Encephalopathy

Emerging treatments	Indication	Target	Comments
Probiotics	Cirrhosis	Gut flora	Concern about treating immune-compromised patients
Nutrition protein supplementation and BCAA	Cirrhosis/acute liver failure	Maintain muscle mass/gut ammonia	Caution in ALF
GBP	Cirrhosis	Glutamine	Nitrogen-binding agent
AST-120	Cirrhosis	Gut-derived toxins	
OP	Cirrhosis/acute liver failure	Gut glutaminase activity and GS activity in peripheral organs	
Albumin administration/ dialysis	Cirrhosis	Blood plasma detoxification	Scavenge reactive oxygen Species/removal of toxins
Plasmapheresis	Cirrhosis/acute liver failure	Blood plasma	
Portosystemic shunt occlusion	Cirrhosis/noncirrhotic portosystemic shunting	Gut ammonia	Deleterious in end-stage liver disease

phenylacetyl glutamine. This results in a lowering of blood plasma glutamine and ammonia concentration.⁹

In a randomized, double-blind phase 2b study, GPB reduced HE events in patients with cirrhosis who had previous HE episodes as well as ammonia. Furthermore, its safety profile was similar to placebo, and it has a promising therapeutic potential in HE.⁹

Portosystemic Shunt Occlusion

Large portosystemic shunts, which might arise as a consequence of liver disease, serve to bypass the liver, resulting

in hyperammonemia and HE. Embolization of these shunts leads to resolution of HE in a proportion of patients. However, this procedure is ineffective in advanced cirrhosis and can result in worsening of portal hypertension. Therefore, patients need to be selected carefully.

AST-120

AST-120 involves the use of orally administered microspherical carbon, which exhibits a selective adsorbent profile, adsorbing small molecules including ammonia, lipopolysaccharides, cytokines, and more. A phase 2 trial showed a

TABLE 2 Future Approaches With Potential for Clinical Application

Compound	Potential Indication	Target	Study	Comments
Nonsteroidal Anti-inflammatory	Cirrhosis	glutamate-NO-cGMP pathway	Cauli et al ¹³	Ibuprofen
Minocycline	Acute liver failure	microglial cell activation	Jiang et al ¹⁴	Can cause hepatotoxicity
Phosphodiesterase inhibitors	Cirrhosis	glutamate-NO-cGMP pathway		Sildenafil
THDOC	Cirrhosis	GABA(A) receptor complex		
Fecal microbiota transplantation	Cirrhosis	Gut: enteric bacteria flora	No publication	Trial NCT02255617 at www.clinicaltrials.gov

comparable efficacy to that of lactulose in patients with minimal HE, with fewer side effects. This treatment needs further development.

Nutrition and Branched-Chain Amino Acids

Malnutrition can result in reduced ammonia metabolism by the muscle. As a result, maintaining muscle mass in HE patients will improve the ability to remove ammonia from circulation by its conversion to glutamine, via GS.³ Administration of branched-chain amino acids (BCAAs) can help improve nutrition and may be effective in HE treatment, but more clinical trials are needed.¹⁰

Treatments Targeting Inflammation

Inflammation, which is another important factor in the development and progression of HE, is also targeted by various treatments. The most recent approaches used are as follows (Table 1):

Probiotics

Probiotics act by introducing microorganisms into the body and have been shown to lower blood ammonia and endotoxin levels, decrease inflammation and oxidative stress in hepatocytes, improve HE, and offer secondary protection against further episodes. Probiotics contribute by changing the gut flora, replacing urease-producing species with non-urease-producing species. Better-controlled clinical trials are urgently needed.

Albumin Administration and Dialysis

Albumin can be administered to HE patients because it has antioxidant properties and is able to scavenge reactive oxygen species. Its administration to patients with HE was ineffective in resolving HE severity, but it prolonged survival.¹¹ Albumin

dialysis using Molecular Adsorbent Recirculating System (MARS) improved HE in a controlled clinical trial in patients with severe HE compared with the standard of care.¹²

Future Horizons

There are a few treatments still in the experimental phase, which hold future promise for the therapy of HE (Table 2). It is known that inflammation-associated alterations may contribute to cognitive impairment in HE. As a result, ibuprofen was shown to restore the function of the glutamate–nitric oxide–cyclic guanine monophosphate (cGMP) pathway in cerebral cortex and learning ability in portocaval-shunted rats.¹³ Minocycline reduces microglial cell activation in cerebral insult and results in a reduction of brain edema as well as plasma and cerebrospinal fluid ammonia levels.¹⁰ Furthermore, phosphodiesterase-5 inhibitors such as sildenafil can be beneficial in chronic HE, resulting in increased cGMP levels and improved learning in portocaval-shunted rats. Tetradehydrocorticosterone (THDOC) is a potent selective positive allosteric modulator of the GABA_A receptors, which results in behavioral changes. A study is currently underway (phase 2) investigating whether fecal microbiota transplantation can reverse HE in cirrhotic patients who continue to have breakthrough episodes of HE despite maintenance therapy with lactulose and/or rifaximin. This potential treatment acts by restoring the enteric bacterial flora, reducing the production of ammonia and other neurotoxins.

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