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REVIEW

Refining the Ammonia Hypothesis: A Physiology-Driven Approach to the Treatment of Hepatic Encephalopathy

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Abstract

Hepatic encephalopathy (HE) is one of the most important complications of cirrhosis and portal hypertension. Although the etiology is incompletely understood, it has been linked to ammonia directly and indirectly. Our goal is to review for the clinician the mechanisms behind hyperammonemia and the pathogenesis of HE to explain the rationale for its therapy. We reviewed articles collected through a search of MEDLINE/PubMed, Cochrane Database of Systematic Reviews, and Google Scholar between October 1, 1948, and December 8, 2014, and by a manual search of citations within retrieved articles. Search terms included *hepatic encephalopathy, ammonia hypothesis, brain and ammonia, liver failure and ammonia, acute-on-chronic liver failure and ammonia, cirrhosis and ammonia*, *portosytemic shunt*, *ammonia and lactulose, rifaximin, zinc,* and *nutrition*. Ammonia homeostatsis is a multiorgan process involving the liver, brain, kidneys, and muscle as well as the gastrointestinal tract. Indeed, hyperammonemia may be the first clue to poor functional reserves, malnutrition, and impending multiorgan dysfunction. Furthermore, the neuropathology of ammonia is critically linked to states of systemic inflammation and endotoxemia. Given the complex interplay among ammonia, inflammation, and other factors, ammonia levels have questionable utility in the staging of HE. The use of nonabsorbable disaccharides, antibiotics, and probiotics reduces gut ammoniagenesis and, in the case of antibiotics and probiotics, systemic inflammation. Nutritional support preserves urea cycle function and prevents wasting of skeletal muscle, a significant site of ammonia metabolism. Correction of hypokalemia, hypovolemia, and acidosis further assists in the reduction of ammonia production in the kidney. Finally, early and aggressive treatment of infection, avoidance of sedatives, and modification of portosystemic shunts are also helpful in reducing the neurocognitive effects of hyperammonemia. Refining the ammonia hypothesis to account for these other factors instructs a solid foundation for the effective treatment and prevention of hepatic encephalopathy.

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Hepatic encephalopathy (HE) is a morbid and costly complication of cirrhosis that presents as a spectrum from mild inattention to coma.[1,2] It is independently associated with increased mortality and reduced quality of life.[3,4] The etiology of HE is multifactorial and incompletely understood, but it has often been tied to ammonia.

In patients with inborn defects of ammonia metabolism, hyperammonemia is directly linked to a spectrum of neuropathology inclusive of neuropsychiatric disorders, severe brain injury, coma, and death.[5,6] For these patients, interventions to prevent hyperammonemia have proved lifesaving.[6] Patients with cirrhosis can develop similar neurocognitive phenomena in the context of measurably elevated blood ammonia levels, and therapies that demonstrably lower ammonia levels improve symptoms. These correlations underpin the ammonia hypothesis.

This concept of ammonia in the pathogenesis of HE, however, is incomplete. Indeed, the ammonia hypothesis presents a clinical conundrum. On the one hand, although frequently assessed, the clinical utility of ammonia levels is unclear because they rarely correlate with symptoms, let alone outcomes.[7-10] On the other hand, the ammonia hypothesis is a widely accepted premise that leads to frequent assessment of ammonia concentrations in general clinical practice.[11] By refining the ammonia hypothesis to include the substantial contributions of inflammation, endotoxin, and interorgan ammonia trafficking involving the brain, kidney, and muscle,

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ARTICLE HIGHLIGHTS

- Ammonia is an important cause of hepatic encephalopathy (HE), but its levels do not correlate with symptoms, partly because of the additive effect of inflammation.
- The kidney, muscle, brain, and gut all play critical roles in ammonia metabolism.
- Muscle wasting (sarcopenia) is associated with HE.
- Renal injury, hypokalemia, and acidosis can each precipitate HE.
- Standard treatment for HE includes reducing ammonia and bacterial translocation from the gut, nutritional supplementation, and sedative or narcotic avoidance.
- Second-line treatments for HE include probiotics, zinc, closure of portosystemic shunts, and ammonia scavengers, such as glycerol phenylbutyrate.

the true importance of ammonia may be clarified and the clinical power of the hypothesis may increase significantly.

Ammonia is traditionally considered a gut-derived nitrogenous toxin produced by bacterial metabolism of amino acids, primarily glutamine.[1,12,13] Normally, ammonia from the gut is efficiently handled by the liver through 2 main metabolic avenues: the urea cycle (also known as the ornithine cycle) and glutamine synthetase (which converts glutamate to glutamine). Cirrhosis, with its associated hepatocellular dysfunction and portosystemic shunting, reduces the efficiency of these "detoxification" mechanisms. The result is greater systemic distribution of ammonia.[10,14-17] However, although the liver is a critical player in the ammonia story, it is far from the only one.

Herein, we highlight the clinical importance of the multiple organs responsible for ammonia metabolism and the modifying effect of inflammation. We show how a refined ammonia hypothesis informs a complete approach to the patient with HE. This review examines the pathogenesis of HE with a focus on existing and evolving therapeutic targets.

METHODS

A search of the representative literature was performed. Articles were collected through a search of MEDLINE/PubMed, Cochrane Database of Systematic Reviews, and Google Scholar and by a manual search of citations within retrieved articles. Search dates spanned October 1, 1948, to December 8, 2014. Search terms included *hepatic encephalopathy* [MeSH], *ammonia hypothesis, brain and ammonia, liver failure and ammonia, acute-on-chronic liver failure and ammonia, cirrhosis and ammonia*, *portosytemic shunt*, transjugular intrahepatic portosystemic shunt, *portocaval shunt*, *ammonia and lactulose, rifaximin, zinc,* and *nutrition.*

The terminology used to describe HE has changed over time. We use the term *overt HE* to describe an episode of acute disorientation or coma. *Controlled* or *resolved* refers to patients who have recovered from overt HE. *Secondary prophylaxis* describes the use of therapies to prevent another episode of HE. *Covert HE* includes patients who have abnormal psychometric testing without overt confusion.[18]

The Ammonia Hypothesis: The Brain

Multiple organs contribute to absolute ammonia concentrations in the blood, but the symptoms of HE are driven mainly by ammonia's effect on the brain. These effects are mediated by the three critical determinants of HE neuropathology: ammonia, glutamine, and inflammation (Figure 1).[14,19,20]

Astrocytes are the principle brain cells affected in states of hyperammonemia.[20] They are the primary carrier of glutamine synthetase in the brain, which converts ammonia and glutamate to glutamine.[12,21-25] Glutamine plays a significant role in the neurotoxicity of ammonia in HE, contributing to the brain dysfunction associated with hyperammonemia in 2 ways. First, glutamine, generated in the cytosol, is, in turn, actively metabolized by astrocyte mitochondria via glutamine hydrolysis (by the mitochondrial protein phosphate-activated glutaminase), leading to the production of ammonia and the accumulation of reactive oxygen species (ROS). Under physiologic conditions, low intra-astrocyte concentrations of glutamine trigger very low levels of hydrolysis. However, with elevated systemic ammonia concentrations, increased glutamine leads to increased hydrolysis and ammonia production in mitochondria, generating increased ROS.[25] In turn, ROS leads to mitochondrial dysfunction and triggers inflammatory cascades.[12,23,25]

Second, cytosolic glutamine is osmotically active. In the presence of hyperammonemia and

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