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The Ammonia Hypothesis of Hepatic Encephalopathy should be Revisited

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Hepatic Encephalopathy (HE) is a neurological complication of the brain following liver damage that was classically thought of being a functional decline in neuronal activity due to metabolic disturbances [1]. Acute liver failure as well as chronic liver diseases can cause HE, with the progression of HE correlating to the severity of liver damage [2]. Initially there are disturbances in cognition, that then progress to disruptions in motor control, and finally global suppression of neural circuits, which can lead to coma. The first factor identified as a causal link and a treatment point for HE was ammonia. However, recent research has begun to elucidate strong support for other pathological processes in this disorder as well. Due to these varying ideas on the progression of HE, this editorial will discuss why the ammonia hypothesis of HE pathogenesis is supported by current research as well as some strong counterpoints that refute this hypothesis.

Ammonia is normally cleared from the body via the urea cycle metabolic pathway in the liver and subsequent excretion via the kidneys. However, after liver damage, this metabolic process is impaired leading to an increase in serum levels of ammonia. In animal models of HE it has been demonstrated that levels of ammonia are elevated into the low millimolar range when animals are approaching severe neurological decline [2]. Also, patients who have HE have significantly elevated levels of ammonia and increased ammonia metabolism as determined by Positron Emission Tomography of $^{13}NH_3$ [3]. Ammonia has been shown to disrupt paracellular and transcellular transport across the Blood-Brain Barrier (BBB) as well as to increase BBB leakage and increase vasogenic cerebral edema [4]. However, due to this increase in BBB leakage, ammonia has the secondary effect of crossing the permeable BBB where it is metabolized by astrocytes in the process of converting glutamate into glutamine [5]. As glutamine levels increase, there is a concomitant increase in osmotic pressure that draws water into the cell, leading to swelling of astrocytes and cytotoxic cerebral edema [2]. Besides the changes that lead to the production of cerebral edema, ammonia has the capability to influence neurotransmission. Electrophysiology studies have determined that pathogenically relevant levels of ammonia, around 1 mM, are able to inhibit excitatory glutamatergic neurotransmission [6]. This can lead to suppression of neural circuits and is thought to lead to the generation of cognitive decline. However, this concentration is typically only found during end stage HE and thus studies using lower doses of ammonia may be more relevant. One study using lower concentrations of ammonia, around 0.1 to 0.5 mM, found that ammonia is able to potentiate the effect of γ-Aminobutyric Acid (GABA) by increasing its affinity for the $GABA_A$ receptor by stabilizing the $GABA_A$ receptor complex [7]. This increased affinity of GABA for its receptor leads to increased GABA activity, which has been associated with HE pathogenesis and leads to decreased motor activity and reduced consciousness [8]. One other potential effect that ammonia may have is its ability to disrupt cerebral energy metabolism, which is a pathological state present in patients who have HE [9,10]. However, with the current research that has been performed, it is difficult to ascertain whether this decrease of cerebral energy metabolism is a primary mechanism driving pathogenesis or if it happens to be a secondary effect of the other pathological processes that occur in this disorder. Thus, ammonia is able to contribute to HE pathogenesis by increasing cerebral edema, reducing excitatory neurotransmission, increasing inhibitory GABAergic tone, and possibly by disrupting cerebral energy metabolism.

The other side of this hypothesis is that ammonia is not involved or is only playing a secondary role in HE pathogenesis. Support for this is demonstrated in clinical studies that have used ammonia-reducing therapies, such as lactulose, that are effective only in chronic cases of HE with little to no effect on patients with HE derived from acute liver failure [11]. Interestingly, it has also been reported that in cirrhotic patients who have minimal hepatic encephalopathy that levels of ammonia are not increased significantly compared to asymptomatic cirrhotic patients [12]. Furthermore, neurotoxicity from ammonia does not replicate some of the minor symptoms present in HE such as sleep abnormalities and subtle personality changes [8]. In addition to this, methods used to remove ammonia from the circulation in HE patients, such as hemodialysis, are able to lower circulating ammonia in patients, but the therapeutic effects that are generated on neurological symptoms are variable demonstrating that removing ammonia from the serum does not always lead to improved neurological states in patients with HE [13]. Animal models of acute ammonia intoxication have demonstrated that ammonia toxicity typically leads to a lethargic preconvulsive state that progresses to seizures and finally to coma [14]. While during the progression of HE development of lethargy and coma is obvious, seizures do not occur very often. To add to this, administration of ammonium acetate does not lead to the same EEG changes that are found in HE patients that have chronic liver disease [15]. This was also found to be replicated in electrophysiology studies in rabbits where inducing ammonia neurotoxicity did not have the same effects on evoked potentials as rabbits who had undergone the galactosamine model of liver failure [14]. The authors of this study concluded that ammonia toxicity models were not adequate to assess the electrophysiological changes that occur during HE. Another confounding factor of the ammonia neurotoxicity models is that they often use levels of ammonia that are substantially higher than those

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typically observed in patients who have HE and due to this the results that are generated are difficult to translate to clinical cases of HE. Thus, it appears that ammonia does not correlate well with EEG modulations, electrophysiological changes, and cognitive and sleep problems that take place during HE and adds extra symptomologies such as seizure activity which suggests that ammonia toxicity cannot be the only causal factor in the development of HE.

While it appears that ammonia does play a part in HE pathogenesis, the studies conducted clinically and using animal models have demonstrated that other elements must be involved with HE progression to explain pathogenesis not accounted for by ammonia toxicity. As it stands, ammonia seems to play a significant role in chronic liver disease states while playing a small role during acute liver failure and minimal hepatic encephalopathy. Future studies will need to find ways to isolate these pathological processes in various acute and chronic liver damage models to fully identify the pathological effects of ammonia. In conclusion, ammonia does play a role in HE progression but due to its lack of involvement in some aspects of HE progression, there is the need to investigate its interplay with other pathological processes to help develop better therapeutic treatments options for HE.

References

1. Cash WJ, McConville P, McDermott E, McCormick PA, Callender ME, et al. (2010) Current concepts in the assessment and treatment of hepatic encephalopathy. QJM 103: 9-16.

2. Hazell AS, Butterworth RF (1999) Hepatic encephalopathy: An update of pathophysiologic mechanisms. Proc Soc Exp Biol Med 222: 99-112.

3. Lockwood AH, Yap EW, Wong WH (1991) Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab 11: 337-341.

4. Skowrońska M, Albrecht J (2012) Alterations of blood brain barrier function in hyperammonemia: an overview. Neurotox Res 21: 236-244.

5. Chen Y, Swanson RA (2003) Astrocytes and brain injury. J Cereb Blood Flow Metab 23: 137-149.

6. Fan P, Lavoie J, Lé NL, Szerb JC, Butterworth RF (1990) Neurochemical and electrophysiological studies on the inhibitory effect of ammonium ions on synaptic transmission in slices of rat hippocampus: evidence for a postsynaptic action. Neuroscience 37: 327-334.

7. Takahashi K, Kameda H, Kataoka M, Sanjou K, Harata N, et al. (1993) Ammonia potentiates GABAA response in dissociated rat cortical neurons. Neurosci Lett 151: 51-54.

8. Jones EA, Weissenborn K (1999) Neurology and the liver. Edited by Hughes RA PG. London, BMJ Books 240-277.

9. Cooper AJ, Plum F (1987) Biochemistry and physiology of brain ammonia. Physiol Rev 67: 440-519.

10. McCandless DW, Schenker S (1981) Effect of acute ammonia intoxication on energy stores in the cerebral reticular activating system. Exp Brain Res 44: 325-330.

11. Mpabanzi L, Jalan R (2012) Neurological complications of acute liver failure: pathophysiological basis of current management and emerging therapies. Neurochem Int 60: 736-742.

12. Shawcross DL, Wright G, Olde Damink SW, Jalan R (2007) Role of ammonia and inflammation in minimal hepatic encephalopathy. Metab Brain Dis 22: 125-138.

13. Opolon P (1980) Large-pore hemodialysis in fulminant hepatic failure. Edited by Brunner G. SF. Berlin, Springer Verlag 141-146.

14. Pappas SC, Ferenci P, Schafer DF, Jones EA (1984) Visual evoked potentials in a rabbit model of hepatic encephalopathy. II. Comparison of hyperammonemic encephalopathy, postictal coma, and coma induced by synergistic neurotoxins. Gastroenterology 86: 546-551.

15. Cohn R, Castell DO (1966) The effect of acute hyperammoniemia on the electroencephalogram. J Lab Clin Med 68: 195-205.