Dispelling myths in the treatment of hepatic encephalopathy

Debbie Shawcross, Rajiv Jalan

Lancet 2005; 365: 431–33

Institute of Hepatology, University College London, London WC1E 6HX, UK
(D Shawcross MRCP, R Jalan, FRCP)

Correspondence to:
Dr Rajiv Jalan
r.jalan@ucl.ac.uk

Context **Guidelines for the treatment of hepatic encephalopathy suggest ammonia reduction as the main focus, based on strategies to reduce ammonia's generation and absorption in the colon by using lactulose and a reduced protein diet.**

Starting point **Two studies provide compelling and provocative data questioning the relevance of these interventions. Bodils Als-Nielsen and colleagues, in a systematic review of randomised trials, found insufficient evidence about whether non-absorbable disaccharides are beneficial (*BMJ* 2004; 328: 1046–50). In a small randomised study, Juan Cordoba and colleagues showed that diets with normal protein content can be administered safely during episodic hepatic encephalopathy due to cirrhosis and that protein restriction does not have any beneficial effect during such episodes (*J Hepatol* 2004; 41: 38–43).**

Where next **Two approaches to new therapies for hepatic encephalopathy are needed. First, it is important to focus on the interorgan metabolism of ammonia. The small intestine and kidneys might be important producers of ammonia, and muscle is an important organ that can remove ammonia. Novel therapies targeting these organs reduce ammonia. Second, research is needed to explore factors other than ammonia that might be important in hepatic encephalopathy, including the synergistic role of inflammation. The lack of conclusive data about the efficacy of any treatment supports the view that placebo-controlled trials of newer agents are needed and ethical. The emphasis should shift to aggressive management of the precipitating event.**

Hepatic encephalopathy remains a major clinical problem in patients with cirrhosis and is the feature that defines prognosis in acute liver injury. Rapid deterioration in consciousness and increased intracranial pressure can result in brain herniation and death. The manifestations of hepatic encephalopathy in cirrhosis seriously affect quality of life. Severe hepatic encephalopathy in cirrhosis can lead to varying degrees of confusion and coma.[1] Since the description of ammonia in the pathogenesis of hepatic encephalopathy over 100 years ago, more than 1200 papers have explored its role and confirmed that ammonia is central. In patients with severe liver dysfunction and therefore impaired urea synthesis, glutamine is synthesised from ammonia and glutamate and acts as a major alternative ammonia-detoxification pathway. Glutamine is synthesised in astrocytes and causes brain swelling. The degree of brain swelling correlates with neuropsychological function and becomes normal after liver transplantation.[2] There is direct evidence for the ammonia-glutamine brain-swelling hypothesis.[3]

Current therapies for hepatic encephalopathy are based on ammonia lowering, with the hypothesis that the colon is the primary organ that generates ammonia. Therefore the mainstays of current therapy are non-absorbable antibiotics, lactulose, and protein-restricted diets. However, two recent studies[4,5] suggest that the colon is not the only focus for ammonia reduction.

Lactulose in hepatic encephalopathy

Traditionally, lactulose/lactitol has been the standard to which newer therapies have had to be compared. Its use was prompted by studies suggesting that colonic bacteria are the main ammonia producers in the body.[6] Colonic bacteria are thought to produce ammonia by splitting urea and possibly aminoacids.[7] Hence, poorly absorbed antibiotics, such as neomycin, were introduced and lactulose was introduced as a safer alternative.[8] After two small trials, lactulose was considered as effective as neomycin.[9,10]

For over 25 years, non-absorbable disaccharides have been the first-line drug treatment. In a systematic review of 22 randomised trials of lactulose/lactitol for hepatic encephalopathy, Bodils Als-Nielsen and colleagues[4] concluded that there is insufficient evidence to recommend or refute their use. Compared with placebo or no intervention, lactulose/lactitol had no significant effect on mortality, and the effect of encephalopathy severity was not conclusive. Only four placebo-controlled trials (a total of 57 patients) were of high enough quality to include (table).[11–14] Only low-quality trials in patients with minimal hepatic encephalopathy found that lactulose had a beneficial effect, as assessed by various non-validated psychometric tests. Furthermore, although lactulose/lactitol was inferior to antibiotics such as neomycin and rifamixin in reducing the risk of no improvement and of lowering blood concentrations of ammonia, there was no significant difference in mortality.

This review has important implications: non-absorbable disaccharides have been introduced into practice without the appropriate evidence base. Moreover, most randomised trials of new treatments for hepatic encephalopathy use lactulose as a comparator and doing large placebo-controlled trials has been viewed as unethical.

Protein restriction in hepatic encephalopathy

Historically, protein restriction has been advocated on the basis of anecdote,[15] despite the fact that, in cirrhosis, higher protein intakes are required to maintain a positive nitrogen balance. Jaun Cordoba and colleagues[5] showed, in a randomised study in 20 cirrhotic patients with hepatic encephalopathy, that diets with a normal protein content

	Design	Number of patients randomised	Type of hepatic encephalopathy	Experimental/ control intervention	Number of patients without improvement/total		Number of dropouts/total	
					Experimental	Control	Experimental	Control
Elkington, 1969[11]	Crossover	7	Chronic	Lactulose/sorbitol	Lactulose and sorbitol reported equally effective, but numerical data not available		Not described	
Simmons, 1970[12]	Parallel	26	Acute and chronic	Lactulose/glucose	4/14	5/12	3/14	2/12
Rodgers, 1973[13]	Crossover	6	Chronic	Lactulose/sorbitol	Lactulose and sorbitol reported equally effective, but numerical data not available		3/6	
Germain, 1973[14]	Parallel	18	Chronic	Lactulose/saccharose	4/9	3/9	0/0	

Table: **Randomised trials of non-absorbable disaccharides versus placebo or no intervention in patients with hepatic encephalopathy**

can be administered safely. Ten patients had protein restriction followed by progressive increments, while ten followed a normal protein diet (1·2 g/kg daily). The low-protein group received no protein for the first 3 days, increasing every 3 days until 1·2 g/kg daily for the last 2 days. Both groups received the same calories. On days 2 and 14, protein synthesis was similar in the two groups but protein breakdown was higher in the low-protein group. The lack of any significant differences in the course of hepatic encephalopathy and the reduced protein breakdown in the normal-protein group argues against the restriction of protein in these patients.

Future directions

Because the capacity of the liver to remove ammonia is severely curtailed in liver disease, a reduction in ammonia concentration requires focus on the different organs involved in its metabolism (figure). It has become clear that the small intestine is an important generator of ammonia via glutamine uptake.[16] Hyperammonaemia and hepatic encephalopathy in germ-free dogs with a portacaval shunt suggests that colonic bacteria have a limited role in producing ammonia.[17] Enterocytes have high glutaminase activity, making them a major ammonia-producing site during breakdown of glutamine. Indeed, in patients with cirrhosis, glutamine uptake and ammonia production has been seen, and increased glutaminase activity correlates with the severity of minimal hepatic encephalopathy.[18]

The kidneys can both produce and excrete ammonia.[19] During hyperammonaemia, the kidneys switch from net production to net excretion.[20] Volume expansion in cirrhotic patients produces significant increases in renal ammonia excretion, reducing plasma ammonia concentration. This effect improves mental state.[21]

During hyperammonaemia, muscle detoxifies ammonia by conversion to glutamine.[16,20] L-ornithine L-aspartate (LOLA) provides intermediates that increase glutamate availability, and muscle can detoxify ammonia. In animals with acute liver failure, LOLA reduces brain water.[22] In patients, LOLA, compared with placebo, improved hepatic encephalopathy.[23] However, only three of the 11 trials of LOLA have been fully published.[24]

Although ammonia is critical in the pathogenesis of hepatic encephalopathy, clinical observations do not always show a consistent correlation between the blood concentration of ammonia and the symptoms of hepatic encephalopathy.[25] Therefore other factors are probably important in modulating the effects of hyperammonaemia. Inflammation has been studied in the development of hepatic encephalopathy. Sepsis is a frequent precipitant of hepatic encephalopathy and those patients with acute liver failure who have worse inflammation may rapidly progress in the severity of hepatic encephalopathy.[26] Nitric oxide, proinflammatory cytokines, and free radicals are all, therefore, possible targets. Measurement of circulating inflammatory mediators might prove useful in evaluating the systemic inflammatory response and assist in tailoring the administration of anti-inflammatory agents. Altering the gut flora and modulation of gut permeability might justify the use of probiotic therapy.[27]

The use of a detoxification device in liver failure might lead to a temporary improvement in the patient's condition, allowing the liver to recover spontaneously. Liver-support systems, such as the Molecular Adsorbents Recirculating System (MARS), might have a role. MARS

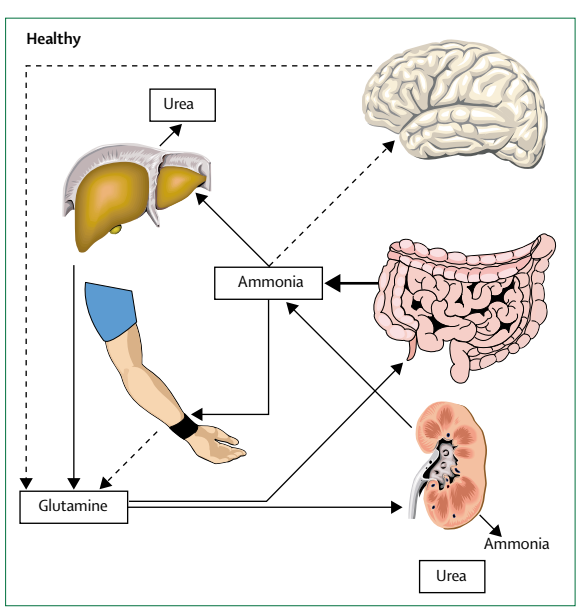

Figure: **Interorgan trafficking of ammonia in health and in cirrhosis**
In healthy individuals, liver removes ammonia by detoxification into urea. In patients with cirrhosis, metabolic capacity of liver is reduced, resulting in hyperammonaemia: muscle becomes important organ of ammonia detoxification into glutamine. Glutamine acts as temporary buffer that can both regenerate ammonia (enterocytes) and excrete ammonia (kidneys).

improved the grade of hepatic encephalopathy in patients with decompensated cirrhosis independently of changes in ammonia and cytokines.[28] Therefore other toxins, such as nitric oxide, oxygen-based free radicals, and endocannibinoids might be important.

Cerebral hyperaemia is critical in the development of intracranial hypertension in acute liver failure.[29] Moderate hypothermia was useful in the treatment of an uncontrolled increase in intracranial pressure in such patients by reducing cerebral blood flow.[30] In cirrhosis, changes in regional cerebral blood flow might account for the attention deficit that is a characteristic feature of minimal hepatic encephalopathy.[31] An acute increase in ammonia alters regional cerebral blood flow, which is associated with memory deficits.[32]

Conclusions

We have entered an exciting phase in research into hepatic encephalopathy, with novel therapies evolving from the discovery of new targets. Lactulose and low-protein diets should no longer be part of standard care, but this does not necessarily mean that these therapies do not work in selected patients. Further trials of lactulose, protein restriction, and newer agents should be placebo-controlled. Given that the variability in the improvement of hepatic encephalopathy with placebo is between 20% and 40%, power calculations will be difficult and a multicentre approach will be necessary to enrol adequate numbers. Current guidelines will need to be revised with strict attention being paid to treating the precipitating factors, with correction of dehydration, electrolyte and acid-base imbalance, constipation, and infection.

We thank all the members of the Liver Failure Group and our collaborators for their helpful advice and discussion. We declare that we have no conflict of interest.

References

1 Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, diagnosis and quantification. *Hepatology* 2002; **35:** 716–21.

2 Cordoba J, Alonso J, Rovira A, et al. The development of low-grade cerebral oedema in cirrhosis is supported by the evolution of 1H-magnetic resonance abnormalities after liver transplantation. *J Hepatol* 2001; **35:** 598–604.

3 Balata S, Olde Damink S, Ferguson K, et al. Changes in neuropsychology, magnetic resonance spectroscopy and magnetization transfer following induced hyperammonemia. *Hepatology* 2003; **37:** 931–39.

4 Als-Nielsen B, Gluud L, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ* 2004; **328:** 1046–50.

5 Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy. *J Hepatol* 2004; **41:** 38–43.

6 Wolpert E, Phillips S, Summerskill W. Ammonia production in the human colon. *N Engl J Med* 1970; **283:** 159–64.

7 Weber FJ, Veach G. The importance of the small intestine in gut ammonium production in the fasting dog. *Gastroenterology* 1979; **77:** 235–40.

8 Bircher J, Muller J, Guggenheim P, Hammerli U. Treatment of chronic portal-systemic encephalopathy with lactulose. *Lancet* 1966; **1:** 890–92.

9 Conn H, Leevy C, Vlacevic Z, Rodgers J, Maddrey W, Seef L. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. *Gastroenterology* 1977; **72:** 573–83.

10 Atterbury C, Maddrey W, Conn H. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. *Am J Dig Dis* 1978; **23:** 398–406.

11 Elkington SG, Floch MH, Conn HO. Lactulose in the treatment of chronic portal-systemic encephalopathy. *N Engl J Med* 1969; **281:** 408–12.

12 Simmons F, Goldstein H, Boyle JD. A controlled clinical trial of lactulose in hepatic encephalopathy. *Gastroenterology* 1970; **59:** 827–32.

13 Rodgers JB Jr, Kiley JE, Balint JA. Comparison of results of long-term treatment of chronic hepatic encephalopathy with lactulose and sorbitol. *Am J Gastroenterol* 1973; **60:** 459–65.

14 Germain L, Frexinos J, Louis A, Ribet A. Double blind study of lactulose in 18 patients with chronic hepatic encephalopathy after portocaval shunt. *Arch Fr Mal App Dig* 1973; **62:** 293–302.

15 Mullen K, Weber Jr F. Role of nutrition in hepatic encephalopathy. *Semin Liver Dis* 1991; **11:** 292–304.

16 Olde Damink S, Deutz N, Redhead D, Hayes P, Soeters P, Jalan R. Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. *Hepatology* 2002; **36:** 1163–71.

17 Nance F, Kayfman H, Kline D. Role of urea in the hyperammonemia of germ-free Eck fistula dogs. *Gastroenterology* 1974; **66:** 108–12.

18 Romero-Gomez M, Ramos-Guerrero R, Grande L, et al. Intestinal glutaminase activity is increased in liver cirrhosis and correlates with minimal hepatic encephalopathy. *J Hepatol* 2004; **41:** 49–54.

19 Dejong C, Deutz N, Soeters P. Renal ammonia and glutamine metabolism during liver insufficiency-induced hyperammonemia in the rat. *J Clin Invest* 1993; **92:** 2834–40.

20 Olde Damink S, Jalan R, Deutz N, et al. The kidney plays a major role in the hyperammonemia seen after a simulated or actual upper gastrointestinal bleeding in patients with cirrhosis. *Hepatology* 2003; **37:** 1277–85.

21 Jalan R, Kapoor D. Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid. *Clin Sci* 2004; **106:** 467–74.

22 Rose C, Michalak A, Rao K, Quack G, Kircheis G, Butterworth R. L-rnithine-L-aspartate lowers plasma and cerebrospinal fluid ammonia and prevents brain edema in rats with acute liver failure. *Hepatology* 1999; **30:** 636–40.

23 Kircheis G, Nilius R, Held C, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy. *Hepatology* 1997; **25:** 1351–60.

24 Delcker, AM, Jalan, R, Schumacher, M, Comes, G. Oral L-ornithine L-aspartate versus placebo in the treatment of hepatic encephalopathy: a meta-analysis. *Hepatology* 2000; **32:** 310A (abstr).

25 Olde Damink S, Deutz N, Dejong C, Soeters P, Jalan R. Interorgan ammonia metabolism in liver failure. *Neurochem Int* 2002; **41:** 177–88.

26 Shawcross D, Davies N, Williams R, Jalan R. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. *J Hepatol* 2004; **40:** 247–54.

27 Liu Q, Duan ZP, Ha dK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. *Hepatology* 2004; **39:** 1441–49.

28 Sen S, Davies NA, Mookerjee RP, et al. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. *Liver Transplant* 2004; **10:** 1109–19.

29 Master S, Gottstein J, Blei A. Cerebral blood flow and the development of ammonia-induced brain edema in rats after portacaval anastomosis. *Hepatology* 1999; **30:** 876–80.

30 Jalan R, Olde Damink S, Deutz N, Lee A, Hayes P. Treatment of uncontrolled intracranial hypertension in acute liver failure with moderate hypothermia. *Lancet* 1999; **354:** 1164–68.

31 Ahl B, Weissenborn K, van den HJ, et al. Regional differences in cerebral blood flow and cerebral ammonia metabolism in patients with cirrhosis. *Hepatology* 2004; **40:** 73–79.

32 Jalan R, Olde Damink S, Lui H, et al. Oral amino acid load mimicking haemoglobin results in reduced regional cerebral perfusion and deterioration in memory tests in patients with cirrhosis of the liver. *Metab Brain Dis* 2003; **18:** 37–49.