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Lactulose, Disaccharides and Colonic Flora

Clinical Consequences

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Summary

Lactulose is one of the most frequently utilised agents in the treatment of constipation and hepatic encephalopathy because of its efficacy and good safety profile. The key to understanding the possible modes of action by which lactulose achieves its therapeutic effects in these disorders lies in certain pharmacological phenomena: (a) lactulose is a synthetic disaccharide that does not occur naturally; (b) there is no disaccharidase on the microvillus membrane of enterocytes in the human small intestine that hydrolyses lactulose; and (c) lactulose is not absorbed from the small intestine. Thus, the primary site of action is the colon in which lactulose is readily fermented by the colonic bacterial flora with the production of short-chain fatty acids and various gases. The purpose of this review is to focus on some pertinent basic aspects of the clinical pharmacology of lactulose and to discuss the possible mechanisms by which lactulose benefits patients with constipation and hepatic encephalopathy.

1. Dietary Carbohydrate

Dietary carbohydrates may be divided into monosaccharides, disaccharides, oligosaccharides and polysaccharides. Their physiological properties and health benefits depend on the site, rate and extent of their digestion or fermentation in the human gastrointestinal tract. The polysaccharide fraction of plant cell walls (dietary fibre) and some forms of starch (resistant starch) are resistant to hydrolysis in the small intestine. These carbohydrate polymers as well as indigestible oligosaccharides, e.g. stacchyose and raffinose, enter the colon through the ileocaecal valve to be fermented by the colonic bacterial flora. Monosaccharide and disaccharide sugars are absorbed as they pass through the healthy small intestine and only become available to the colonic flora as a consequence of deficiencies in the transport system, or, more usually, specific disaccharidase deficiencies, e.g. lactase deficiency. Physiological carbohydrate malabsorption, that is, the fermentable carbohydrate entering the colon in healthy individuals, is in the range of 30-60 g/day in Western communities.[1] This load is normally fermented by the vast numbers of colonic bacteria.

1.1 Lactulose

Lactulose is a synthetic disaccharide composed of the monosaccharides galactose and fructose [β-(1-4)-galactosido-fructose]. The disaccharidases that split naturally occurring disaccharides into their hexose moieties do not include a lactulase, and lactulose is not metabolised or absorbed in the human small intestine.[2,3] Once in the caecum, lactulose is a fully fermentable carbohydrate. Lactulose is widely considered to be an effective agent in the management of constipation and hepatic encephalopathy. It is the purpose of this review to discuss the interaction of lactulose with the bacterial flora of the colon and the possible modes of action by which it achieves its therapeutic effects in patients with constipation and hepatic encephalopathy. The review deals almost exclusively with lactulose. The principles expressed, however, are applicable to any malabsorbed and fermentable disaccharide, e.g. lactitol, a disaccharide analogue of lactulose for which there is also no disaccharidase on the microvillus membrane of enterocytes, or lactose when it is administered to lactase-deficient individuals.

2. Colonic Fermentation and Production of Short-Chain Fatty Acids (SCFA)

Fermentation, the process whereby the microbial population that inhabits the human colon breaks down carbohydrates in order to obtain energy for maintenance of cellular function and growth, is an important component of normal colonic activity (fig. 1). Short-chain fatty acids (SCFA) and the gases H_2, CO_2 and, in some individuals, CH_4, are the principal end products of carbohydrate fermentation.[1] The major SCFA found in the human colon are the C2 (acetate), C3 (propionate) and C4 (butyrate) members of the aliphatic monocarboxylic acid series. Formate (C1), valerate (C5), hexanoate (C6), and the branched-

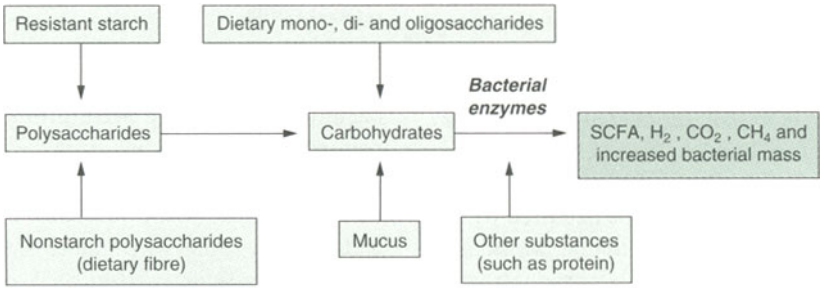

Fig. 1. Bacterial fermentation in the human colon. *Abbreviation:* SCFA = short-chain fatty acids.

chain fatty acids isobutyrate (iC4) and isovalerate (iC5), which are produced during amino acid fermentation,[4,5] are also present in the colon, though in smaller quantities. Other organic acids such as lactate and succinate are fermentation intermediates. They can be further metabolised to SCFA, and do not usually accumulate to any extent, except during rapid carbohydrate breakdown.[6-8]

The SCFA are weak acids and their pKa values are very similar, ranging from 4.76 to 4.87. Thus, more than 95% of the SCFA are present in their dissociated form at the physiological pH of the colon (pH 6-8). Total concentrations of SCFA are low in the small intestine, but in the colon and faeces SCFA constitute the predominant anions at concentrations ranging from about 80 to 130 mmol/L.[9,10] Concentrations are highest in the caecum, where substrate availability is greatest, and fall progressively towards the distal colon. By contrast, pH is lowest in the right colon and rises in the distal bowel.[9] SCFA are avidly absorbed by the colonic epithelium,[11,12] and used as a source of energy, either locally (colonic mucosa)[13-15] or systemically (liver, peripheral tissues).[16] In the colon, absorption of SCFA is accompanied by luminal bicarbonate accumulation and increased sodium and water absorption.[11,12] Thus, the microbial process converts unabsorbable material to rapidly absorbed SCFA, thereby reducing the effective osmotic pressure of the colonic contents, enhancing water and electrolyte absorption, and salvaging calories which would otherwise be lost in the faecal stream.

2.1 Fermentation of Lactulose

Lactulose, after arriving in the colon, is digested by bacterial disaccharidases and metabolised to organic acids, mainly acetate and lactate, H_2 and CO_2.[6] A variety of studies have shown that lactulose is usually vigorously fermented. In an *in vitro* experiment using human faecal homogenates, Vince et al.[17] showed that complete fermentation of 10 g/L (30 mmol/L) of lactulose occurred within 6 hours. By use of a similar technique, Mortensen et al.[18,19] showed that the total production of SCFA in faecal homogenates was increased 2- to 3-fold by the addition of 100 mmol/L lactulose or its monosaccharide constituents, galactose and fructose, during incubation for 6 hours, secondary to an isolated 4- to 6-fold increase in the synthesis of acetate. In patients undergoing elective cholecystectomy, caecal instillation of lactulose caused an immediate increase in portal plasma SCFA concentrations, principally acetate; peak concentrations were achieved in 15 to 45 minutes, confirming efficient fermentation of lactulose and absorption of the resultant SCFA.[20]

The various gases generated in the colon are either absorbed and expired in breath or expelled as flatus, and excess gas production may cause borborygmi and flatulence. Since H_2 produced in the human body derives entirely from bacterial fermentation of nonabsorbed carbohydrate, breath H_2 excretion in the absence of small intestinal bacterial overgrowth can be used as a marker of carbohydrate malabsorption.[21] The extent of malabsorption may be quantified by comparing breath H_2 excretion following a test dose of lactulose with that after ingestion of a different carbohydrate.[22]

Fermentation of a readily fermentable carbohydrate results in acidification of colonic contents. Using a pH-sensitive radiotelemetry device, Bown et al.[23] showed that lactulose 30 to 40g daily decreased the pH of the right colon from control levels of 6.0 to 4.85. As the intestinal content reached the left colon and rectum, the median pH rose, probably as a result of SCFA absorption and bicarbonate secretion. The effect of lactulose on faecal pH depends on the dose employed, and the drop in pH is usually maintained throughout the colon and the stool when larger doses of lactulose are administered.[24-26]

Although consistent changes in the relative proportions or in the absolute numbers of different bacterial species have been difficult to identify in patients treated with lactulose,[27-29] this compound does appear to have a significant effect on the metabolic activities of the microbes. In healthy volunteers, faecal levels of β-galactosidase activity increased significantly after an 8-day period of a nondiarrhoeogenic dose of lactulose (20g twice

daily).[6] Compared with day 1, caecal contents sampled on day 8 after lactulose administration exhibited a marked fall in pH, a faster disappearance of lactulose and its constitutive hexoses, and increased concentrations of SCFA and lactate.[6] The colonic microflora therefore are able to adapt to ferment lactulose, and the more efficient bacterial fermentation of lactulose modifies the diarrhoea induced by a larger load of this sugar.[30]

The colonic bacteria use fermentable carbohydrate, e.g. lactulose, as a source of energy, thus promoting their growth and multiplication.[31] It is believed that bacterial growth assimilates the ammonia produced by degradation and putrefaction of ingested proteins as a source of nitrogen, and faecal nitrogen excretion increases 2- to 4-fold after lactulose administration.[32,33]

3. Lactulose in the Management of Constipation

Lactulose is frequently used as an effective laxative in the management of constipation.[34] Based on the absence of its respective disaccharidase, the rationale for the use of lactulose as a laxative was to induce disaccharide malabsorption, a well known cause of diarrhoea. In spite of the frequency and importance of carbohydrate-induced diarrhoea, its pathophysiology is not fully understood. Until relatively recently, SCFA were thought to be poorly absorbed and to function as an irritating and osmotic force stimulating intestinal motility and impeding colonic water and electrolyte absorption.[35-38] Early work on carbohydrate malabsorption therefore implicated bacterial fermentation as the primary mechanism for diarrhoea in disaccharide malabsorption ('fermentative diarrhoea'). The strong correlation between faecal water output and output of SCFA[35,37] was thought to incriminate SCFA in the pathogenesis of diarrhoea. As colonic SCFA levels remain more or less constant despite dietary changes, any factor increasing stool weight will, however, increase their output. Later *in vivo* studies of intestinal SCFA absorption have consistently demonstrated efficient absorption of SCFA from the human colon.[11,12] This absorption markedly enhances net sodium and water absorption and bicarbonate secretion into the lumen. Thus, the intracolonic fermentation of nonabsorbed sugars into readily absorbable SCFA reduces the osmotic load, and suppresses or mitigates the diarrhoea which would have resulted from unmodified ileal output.

3.1 Colonic Compensation in Carbohydrate Malabsorption

The protective role of colonic fermentation in reducing the severity of carbohydrate-induced diarrhoea has been demonstrated in studies comparing the output of faecal water in response to a nonfermentable osmotic load with a load of fermentable carbohydrate. Hammer et al.[39] compared the diarrhoea resulting from increasing iso-osmolar loads of the nonabsorbable, nonfermentable and electrically neutral compound polyethylene glycol (PEG) and lactulose in healthy individuals. Increasing osmotic loads of PEG caused a near-linear increase in stool water output. At any load, lactulose induced less diarrhoea than did PEG. With low (45 g/day) or moderate (95 g/day) doses of lactulose, stool water losses were reduced by as much as 600 g/day (compared with equimolar osmotic loads of PEG). As lactulose doses of >45 g/day were ingested, faecal carbohydrate excretion rose progressively, thereby contributing more and more to the osmotic driving force for diarrhoea. With the largest dose of lactulose (125 g/day) the difference between lactulose- and PEG-induced diarrhoea markedly decreased. In lactulose-induced diarrhoea, daily stool collections contained an average of 1, 12 and 45g of carbohydrate when the participants were ingesting 45, 95 and 125g of lactulose/day, respectively, indicating a maximum capacity of the colonic bacteria to metabolise lactulose of approximately 80 g/day.[39]

Saunders and Wiggins[3] obtained dose-response curves for mannitol (a poorly absorbed sugar alcohol), raffinose, lactulose and magnesium sulfate in relation to faecal water output over 48 hours after the dose of test substance. With magnesium sulfate there was an immediate increase in faecal output,

whereas a lag period was observed for the non-absorbed sugars. When an increase in faecal water occurred after ingestion of mannitol, lactulose or raffinose, the sugar or its constitutive hexoses appeared in the stools. The dose-response experiments indicated that the colonic flora can normally convert 40 to 60g of single doses of carbohydrate to SCFA without the individual experiencing diarrhoea.[3]

3.2 Fermentation Capacity Threshold: Individual Variability

The human colon is obviously capable of removing appreciable amounts of fermentable carbohydrates from colonic contents, even in patients with malabsorbed carbohydrate.[3,39] If, however, the fermentative capacity of the colonic microflora is exceeded, unmodified and osmotically active sugars may produce an osmotic diarrhoea. The response threshold when a given amount of carbohydrate is malabsorbed differs among individuals. In the study by Saunders and Wiggins,[3] one participant tolerated a 73 mmol (25g) dose of lactulose whereas another tolerated 176 mmol (60g) before faecal water output rose above 400 ml/48 hours and test carbohydrate appeared in the stool. Similarly, doses of 120 mmol (22g) and 350 mmol (64g) of mannitol were tolerated by different participants.

The individual variability may, at least in part, be explained by differences in the fermentation capacity of the bacterial flora. Individuals with a limited fermentation capacity or a high dependence on the existing capacity for colonic carbohydrate degradation might be especially susceptible to an increased carbohydrate load. A similar situation may apply to the development of microbial fermentation in newborn animals. Argenzio et al.[40] produced carbohydrate malabsorption by administration of corona virus to newborn pigs. This resulted in diarrhoea in 3-day-old pigs, with high concentrations of carbohydrate and low concentrations of SCFA in colonic contents. Pigs 3 weeks of age showed no diarrhoea, with negligible amounts of carbohydrate and normal levels of SCFA in colonic contents, indicating that the more mature microflora in these older piglets were capable of fermenting the osmotic load to SCFA, which could then be rapidly absorbed from the colonic contents. Once the microbial process is well established, prolonged ingestion of carbohydrate results in an improved colonic fermentation capacity.[6,30]

The higher capacity to ferment carbohydrates may be a result of enzymatic induction in existing micro-organisms[6] and/or an alteration in microbial populations.[6,31] Flourié et al.[30] studied healthy volunteers for 2 test periods, at the beginning of which they ingested a diarrhoeogenic load (60g) of lactulose; the 2 periods were separated by a lactulose feeding period of 8 days, during which a nondiarrhoeogenic load (20g) of lactulose was taken twice daily. Stool weight and frequency, and faecal outputs of carbohydrates after the ingestion of lactulose 60g, dropped significantly after the lactulose maintenance period (20g twice daily for 8 days), indicating that the colonic flora can adapt to a nondiarrhoeogenic load of lactulose, and that this adaptation has a beneficial effect on the diarrhoea induced by a larger load of this sugar.

Similarly, Launiala[41] reported on a 3-week period during which an infant with congenital lactose malabsorption was maintained on a lactose-containing diet. In comparison with the first day of treatment, continued treatment resulted in a decreased stool volume and disaccharide output, and a sharp rise in faecal lactate concentration. No adaptation occurred in the small intestine.[41]

Hypothetically, regular consumption of carbohydrates malabsorbed in the small bowel may result in a more efficient colonic carbohydrate fermentation and an increased response threshold when a given amount of carbohydrate is malabsorbed. In addition to differences in colonic bacterial fermentation capacity, variations among individuals in the buffering capability of the colon may contribute to individual differences in the response to identical amounts of nonabsorbable carbohydrates. It is known that caecal pH decreases even with the amounts of unabsorbed carbohydrate normally entering the colon.[23] Furthermore, patients with severe carbohydrate malabsorption, ei-

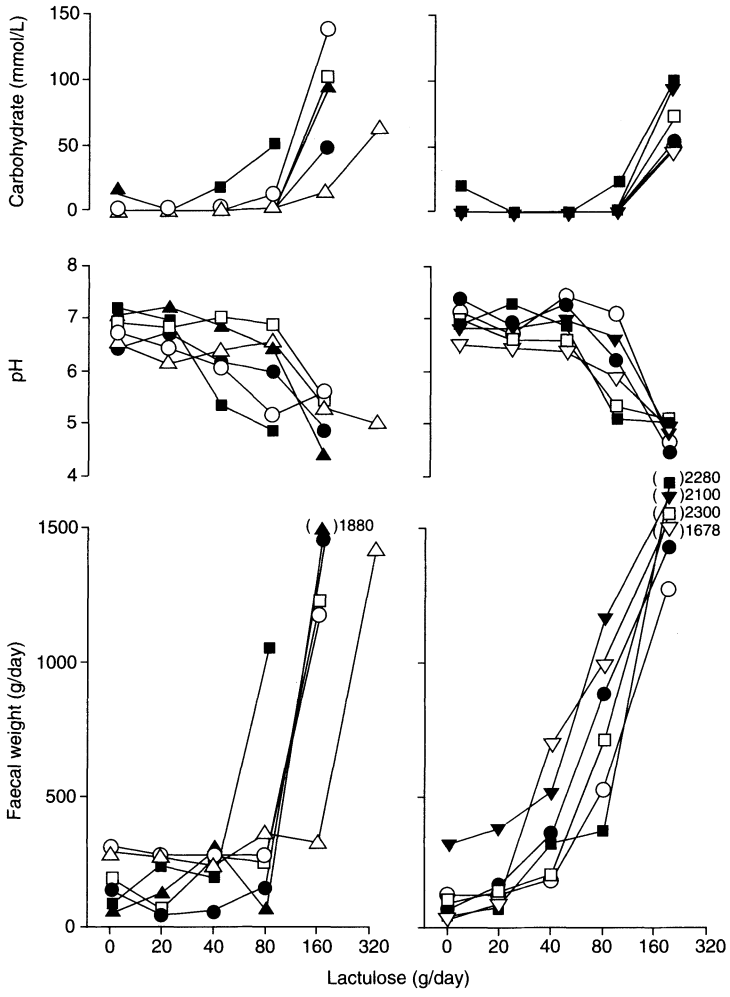

Fig. 2. Faecal weight, pH and carbohydrate concentration in faeces of 12 individuals taking increasing doses of lactulose. The results have been divided in accordance with the response in faecal output to low doses of lactulose (from Holtug et al.,[26] with permission).

ther due to disaccharidase deficiency or due to ingestion of excessive amounts of lactulose, have decreased faecal pH in the range of 4 to 5.[24,26,35]

This decrease in pH is sufficient to inhibit bacterial fermentation and SCFA production as shown *in vivo* and *in vitro*.[26,42,43] In subjects with a restricted colonic buffering system, the tolerance of carbohydrate malabsorption may be decreased as the low pH decreases fermentation leading to accumulation of undigested sugars and osmotic diarrhoea early on in the process.

3.3 Does Lactulose Exert Its Laxative Effect Through the Osmotic Activity of Unfermented Carbohydrate?

Many physicians believe that the change in stool output in the diarrhoea of carbohydrate malabsorption is due to the osmotic effect of malabsorbed and nonfermented sugars. This assumption seems to be supported by the studies mentioned above (sections 3.1 and 3.2) in which diarrhoea ensued when carbohydrate appeared in the stools. The study by Holtug et al.,[26] however, queries this

assumption. Healthy individuals were given lactulose twice daily for 3 consecutive days in each experimental period. Doses were doubled (20, 40, 80, 160 and 320 g/day) from each period to the next, with the end-point being diarrhoea in excess of 1000 g/day. Faecal output responded differently among individuals, and 2 types of behaviour were identified (fig. 2).

In accordance with the interpretation that carbohydrate-induced diarrhoea is due to the osmotic effect of nonfermented malabsorbed sugars, diarrhoea occurred suddenly in six of 12 individuals in association with the appearance of carbohydrate in faeces. In the 6 other subjects, however, faecal output gradually increased with increasing doses of lactulose and diarrhoea occurred before the appearance of faecal carbohydrates.[26] How does unabsorbed carbohydrate cause diarrhoea in those cases?

3.4 Capacity of the Colon to Absorb Fluid

The mechanism of action of lactulose as a laxative is probably multifactorial, involving effects on both the colon and the small bowel. Under normal circumstances, about 1500ml of fluid is estimated to enter the colon each day.[44] In disaccharide malabsorption an increased volume of fluid is retained in the lumen of the small intestine by the osmotic effect of disaccharide.[41,45] Analysis of distal ileal fluid collected during the passage of a lactose meal in lactase-deficient people and a lactulose load in healthy people indicates that about two-thirds of the osmotic load entering the colon consists of endogenous electrolytes.[30,41,45] Thus, the water load delivered to the colon is about 3 times that calculated to be osmotically held by the nonabsorbed sugar.

A logical extension of the above observations is to ask what the colon can accomplish under stress. In fact, the colon has a surprisingly large capacity to adapt to fluid overload. When the healthy human colon was subjected to a slow, continuous infusion of isotonic fluid (1.4 to 2.8 ml/min), net absorption of water increased markedly, up to 5 to 6 L/day.[46] The rate and pattern of fluid entry are, however, of major importance. Rapid infusion (8.3 ml/min) of a single bolus of 250ml of fluid did not influence faecal output whereas 500ml delivered at the same rate overwhelmed the absorptive capacity of the colon and produced liquid stools.[46] In healthy human volunteers, Chauve et al.[47] investigated pressure recordings in the right, transverse and left colon, while isotonic saline was continuously infused in the caecum. The data obtained indicated that once a certain volume of content is reached in the proximal part of the colon, it contracts and propels its content,[47] which may explain the different colonic responses comparing slow continuous and rapid bolus infusions of fluid into the caecum.[46]

The extra volume load to the colon due to lactulose can be estimated to be 1.65L at a lactulose intake of 60g,[30,41,45] and the sudden arrival in the caecum of this considerable amount of ileal discharge might lead to colonic 'decompensation' and prompt colonic evacuation.

3.5 Possible Mechanisms of Action of Lactulose in the Treatment of Constipation

A single primary mechanism for the laxative effect of lactulose cannot be determined because of multiple possible effects. Most likely, the laxative effect of lactulose results from the combination of:

- water retention in the small intestine through the osmotic activity of the unabsorbed disaccharide; and
- interference with net fluid absorption in the colon due to the osmotic effect of malabsorbed and intact sugars when the bacterial fermentation capacity is exceeded.

Whether or not the laxative effect of lactulose is accomplished is probably just a matter of dose. It is, however, important to realise that the response threshold when lactulose is prescribed differs among individuals (fig. 1). A gradual increase in faecal output with increasing amounts of lactulose occurs in some individuals, while others suddenly respond with severe diarrhoea.[26] Unfortunately, it is not possible to predict the response of a given individual, and firm guidelines for dosage recommendations are impossible.

4. Lactulose in the Management of Hepatic Encephalopathy

Lactulose has been successfully used in the treatment of hepatic encephalopathy ever since the pioneering experiments of Bircher et al. in 1966.[24] The exact mechanisms whereby lactulose exerts its beneficial effect on hepatic encephalopathy are not fully understood, but several hypotheses have been suggested.

Hepatic encephalopathy is a complex neuropsychiatric syndrome that appears to be characterised predominantly by augmented neuronal inhibition. The syndrome is associated with hepatocellular failure, increased portal-systemic shunting of blood and multiple metabolic changes, and is generally considered to be a potentially reversible metabolic encephalopathy. The precise pathogenetic mechanism responsible for the CNS dysfunction remains to be determined.

Products of bacterial metabolism in the colon, which are normally absorbed and extracted by the liver, tend to accumulate in the peripheral blood of patients with liver disease either because the diseased liver is unable to remove these compounds from the portal blood perfusing it, or because portal hypertension has led to the development of venous collaterals which transmit portal blood directly into the systemic circulation. If one or more of these metabolites can cross the blood-brain barrier and promote neural inhibition, they may contribute to hepatic encephalopathy. Despite decades of research endeavour, the nature of the toxic, gut-derived, substances defies identification. Three candidate toxins seem likely pathogenetic factors because they are present to excess in patients with liver failure and cause coma experimentally in animals. These are ammonia, SCFA and medium-chain fatty acids (MCFA), and mercaptans; of these, ammonia probably plays the most central role.[48]

4.1 Effects of Lactulose on Ammonia and Nitrogen Metabolism

Ammonia occupies a central position in nitrogen metabolism in the colon, both as an end-product of bacterial metabolism of amino acids, peptides and proteins,[49] and as the simplest nitrogenous compound which can be used by bacteria as a starting material in the synthesis of their own nitrogenous constituents. In the absence of active colonic fermentation most of the ammonia formed is absorbed to be converted to urea in the liver.

When lactulose was first used in the treatment of hepatic encephalopathy, it was presumed that the colonic acidification favoured the growth of acid-tolerant lactobacilli and other acidophilic, fermentative bacteria and reduced the growth of acidophobic, proteolytic bacteria responsible for ammonia formation.[24] However, quantitative studies failed to confirm this rearrangement of gut flora.[27,28] Alternatively, luminal acidification would reduce the proportion of ammonia available for reabsorption by passive nonionic diffusion by increasing the ratio of ionised to unionised ammonia, thereby enhancing the faecal excretion of ammonia.[50] Attempts to demonstrate increases in stool ammonia caused by lactulose administration have failed,[51,52] except when excessive amounts of lactulose (>80 g/day) have been given.[33] In that case, stool ammonia increases approximately 3-fold.[33] The main point is, however, that ammonia constitutes only a small percentage (3 to 5%) of total faecal nitrogen. The debate on whether or not lactulose increases faecal excretion of ammonia is therefore of minor importance in the context of total nitrogen excretion. Of more importance for faecal nitrogen clearance are other sources of nitrogen, constituting about 95% of total stool nitrogen.

By use of an anaerobic faecal incubation system, Vince et al.[17] demonstrated that net generation of ammonia by faecal bacteria can be converted to net utilisation of ammonia by the provision of a fermentable source of energy, e.g. lactulose, ammonia disappearing from the incubation system. The results may be explained by a combination of factors: (a) the availability of a readily fermentable substrate may encourage bacterial proliferation and assimilation of ammonia as a nitrogen source;[17,31] (b) preferential use of lactulose as a carbon and energy source may exert

a sparing effect on the metabolism of both exogenous and endogenous aminated compounds with a subsequent decrease in the generation of ammonia by colonic bacteria;[17,19] and, (c) low pH values such as are induced in the colon by lactulose may bring about a general reduction in bacterial metabolism, including that of ammonia-producing bacteria.[17,19,26,42] If, in the presence of lactulose, incorporation of ammonia into bacterial protein is stimulated, faecal nitrogen excretion should increase and hepatic urea production and total body urea pool should decrease during administration of lactulose.

This is exactly what Weber[32] and Mortensen[33] have shown. Administration of lactulose caused a 2- to 4-fold increase in faecal nitrogen content in patients with cirrhosis[32] and in healthy individuals,[33] and the increase in nitrogen excretion was accompanied by a significant reduction in the urea production rate leading to a reduction in the total body urea pool.[32] Using recently developed techniques that permit quantitative separation of faecal solids into bacterial, soluble and fibre fractions, Weber et al.[53] analysed the effects of lactulose on the compartmentalisation of faecal nitrogen. In patients with cirrhosis, administration of lactulose (56 ± 6 g/day) caused a marked increase in both the solid weight and nitrogen content of the bacterial and soluble fractions of stool; lactulose administration increased nitrogen excretion in the bacterial and soluble fractions by 165 and 135%, respectively. The major increment in nitrogen content of the bacterial fraction indicated that lactulose stimulated bacterial growth and multiplication significantly, and thereby increased the incorporation of nitrogenous compounds such as ammonia into bacterial protein.

The increase in faecal soluble nitrogen may be explained by reduced bacterial catabolism of nitrogenous compounds to absorbable metabolites, e.g. ammonia, due to: (a) the introduction of a carbohydrate which is preferentially used as a carbon and energy source;[17,19] (b) an increase in the hydrogen ion concentration which may bring about a general reduction in bacterial metabolism;[17,19,26,42] or (c) both. A direct effect of lactulose in reducing the colonic transit time may also be a factor contributing to an increase in faecal soluble nitrogen.

4.2 Role of Short- and Medium-Chain Fatty Acids in Hepatic Encephalopathy

The suggestion that SCFA and MCFA may play a role in the pathogenesis of hepatic encephalopathy is mainly based on animal experiments. Samson et al.[54] investigated the narcotic action of SCFA (acetate, propionate, butyrate, valerate and hexanoate) and MCFA (heptanoate and octanoate) in experimental animals. Intravenous or intraperitoneal injection of the sodium salts of these acids produced a reversible coma with a definite relationship between the amount of the fatty acid which would produce unconsciousness and the carbon length of the compound; i.e. the longer the carbon chain, the more potent the encephalopathic effect, acetate being almost nontoxic.[54]

In a subsequent experiment, White and Samson[55] demonstrated that intravenous injection of propionate, butyrate, valerate and hexanoate immediately induced electroencephalographic (EEG) changes from a resting type to one of sleep in unanaesthetised rabbits. During these EEG alterations, overt signs of drowsiness or sleep always occurred and the typical 'alert' EEG responses to nociceptive and auditory stimuli were diminished or absent. Again, the longer the carbon chain, the more potent the effect. In rats, the rate of blood-brain barrier penetration of straight-chain saturated monocarboxylic acids has also been shown to increase with chain length and is virtually complete at lengths greater than that of hexanoate (C6).[56] In humans, octanoate has been shown to cross the blood-brain barrier in both normal individuals and patients with cirrhosis.[57]

The mechanisms by which SCFA and MCFA interfere with CNS functions are not entirely clear. *In vitro* and *in vivo* studies have shown that SCFA and MCFA inhibit cerebral Na^+,K^+-ATPase activity,[58,59] and, as for the narcotic potency, the inhibitory capacity increases with increasing chain

length.[58] The consequences of inhibiting this enzyme would include an increase in intracellular sodium and possibly impaired neurotransmission.

Muto and Takahashi[60] were the first to suggest a role of SCFA in the pathogenesis of hepatic encephalopathy. In patients with hepatic coma, plasma levels of SCFA of 4- to 6-carbon length were increased 3- to 4-fold compared with controls and patients with other kinds of coma. Significantly elevated levels of SCFA in peripheral venous blood of patients with fulminant hepatic failure and portal systemic encephalopathy have been confirmed recently. Lai et al.[61] investigated 6 patients with fulminant hepatic failure due to paracetamol (acetaminophen) intoxication and hepatitis. All patients were in grade IV coma. Plasma levels of SCFA were significantly elevated in patients with encephalopathy (2034 ± 1134 μmol/L; mean ± 2 SD) compared with 10 healthy controls (1113 ± 662 μmol/L), but a correlation between SCFA concentrations and the clinical course could not be demonstrated.

Clausen et al.[62] investigated 32 patients with cirrhosis, 15 patients with and 17 patients without hepatic encephalopathy, and 11 healthy individuals. Plasma concentrations of SCFA were significantly elevated in patients with hepatic encephalopathy (362 ± 83 μmol/L; mean ± SEM) compared with patients without encephalopathy (178 ± 57 μmol/L) and healthy controls (60 ± 8 μmol/L). Repetitive sampling from the encephalopathic patients showed no relationship between SCFA concentrations and the grade of encephalopathy.[62]

In comparison with the encephalopathy associated with inborn errors of organic acid metabolism, elevated levels of SCFA in patients with hepatic encephalopathy are modest. Massive elevations of propionate are found in severe and fatal cases of propionic acidaemias (5400 to 38 000 μmol/L),[63-65] and levels of isovalerate in the range of 340 to 2990 μmol/L are associated with stupor and unconsciousness in children with isovaleric acidaemia.[66,67] Moreover, an 8- to 10-fold rise of venous propionate and octanoate (C8) is seen in patients with liver cirrhosis after duodenal or rectal instillation without any influence on the mental or neurological state.[68,69] It therefore seems unlikely that the elevated levels of SCFA in patients with hepatic encephalopathy are the primary cause of the neurological deterioration.

A secondary role for SCFA, however, cannot be excluded as the coma-producing potential of separate toxic substances may be multiplied several-fold when they are present together. In experimental animals the coma-producing effects of ammonia, fatty acids (octanoate) and mercaptans have been shown to be strikingly interdependent.[70,71] In healthy animals, the dose of ammonium salt required to produce coma is sharply reduced by the presence of a subcoma dose of either a fatty acid (octanoate) or mercaptan,[70,71] and the incidence of coma can be raised from zero to 100% by injection of subcoma doses of any of these substances simultaneously. In rats with acute experimental hepatic coma resulting from massive liver necrosis, the average blood levels of ammonia, free fatty acids (octanoate) and methanethiol are much lower than blood levels required to produce coma in healthy rats with each of these substances individually.[71] When, however, healthy rats are given a combination of doses of ammonia, octanoate and mercaptan which produce blood levels in the range of those observed in rats with experimental hepatic coma, they become comatose.[71]

4.3 Effect of Lactulose on Colonic SCFA Production in Hepatic Encephalopathy

Although SCFA may not be the major cause of encephalopathy in patients with cirrhosis, the evidence of synergism in animals[70,71] suggests that SCFA may play a role as an augmenter or intensifier of other putative neurotoxins, e.g. ammonia and mercaptans. In incubated stool samples, fermentation of lactulose results in the formation of acetate primarily, whereas bacterial degradation of blood, albumin and amino acids significantly increases the production of all C2-6-SCFA, especially the potentially toxic C4-6-fatty acids.[19,43] When lactulose is added to incubations of amino acids, protein and blood, the SCFA production is

shifted almost completely towards the nontoxic C2-fatty acid, acetate. At lactulose concentrations of 10 to 25 mmol/L, corresponding to a pH of approximately 5, this effect is largely mediated by the acidifying effect of lactulose.[43] pH-Independent inhibition of blood and amino acid degradation to SCFA requires concentrations of lactulose exceeding 50 to 100 mmol/L.[43] The concentration of lactulose after a single dose of 20g is 50 to 100 mmol/L in the caecum,[6] with a corresponding decrease in pH to values in the range of 3.5 to 6.1 in the proximal colon.[6,23]

In contrast, reduction of faecal pH by 20 to 40g of lactulose is small in magnitude[52] or even negligible[6] due to the rapid fermentation of lactulose and the neutralisation of luminal contents by bicarbonate secretion. The results obtained *in vitro*[43] indicate that lactulose should be given in doses that not only acidify the caecum but also exceed the buffering capacity in the left colon.

Enemas of lactulose or glucose may be beneficial supplements to aid in obtaining this effect.

4.4 Possible Mechanisms of Action of Lactulose in the Treatment of Hepatic Encephalopathy

Several mechanisms of action of lactulose in the treatment of hepatic encephalopathy apparently exist (table I). They include: (a) provision of a readily fermentable substrate, which encourages bacterial proliferation and converts the normal balance between ammonia generation and utilisation from a net increase to a net decrease (assimilation); (b) a preferential use of lactulose as a carbon and energy source, which exerts a sparing effect on the bacterial metabolism of both exogenous and endogenous aminated compounds with subsequent decrease in the generation of ammonia; (c) an acidifying effect, which brings about a general reduction in bacterial metabolism, including that of ammonia-producing bacteria; (d) a laxative action, which reduces the time for the production and absorption of ammonia and increases the soluble nitrogen content of faeces; and, (e) an ability to alter the production of SCFA towards the nontoxic acetate at the expense of the potentially toxic C4-6-SCFA.

5. Conclusions

A single primary mechanism of action of lactulose in the treatment of constipation and hepatic encephalopathy cannot be determined due to several possible effects the drug may have. In patients with constipation, the laxative effect of lactulose possibly results from the combination of: (a) fluid retention in the small intestine through the osmotic activity of the unabsorbed disaccharide; and (b) interference with net fluid absorption in the colon due to the osmotic effect of malabsorbed and intact sugars when the bacterial fermentation capacity is exceeded. However, individual sensitivities to the drug should be recognised, i.e. the therapeutic dose should start at a relatively low level with a gradual increase according to the frequency and consistency of the stools.

The possible mechanisms by which lactulose benefits patients with hepatic encephalopathy include: (a) increased faecal nitrogen excretion; (b) colonic acidification; (c) decreased transit time; and (d) reduced production of potentially toxic SCFA. In order to obtain these effects it is recommended that the faecal pH be measured in patients with hepatic encephalopathy treated with lactu-

Table I. Possible mechanisms of action of lactulose in the treatment of hepatic encephalopathy

Effect	Result
Utilisation	Stimulates bacterial growth and increases incorporation of ammonia into bacterial protein (assimilation), and exerts a sparing effect on the metabolism of aminated compounds with subsequent decrease in ammonia generation by colonic bacteria
Acidifying	Brings about a general reduction in bacterial metabolism, including that of ammonia-producing bacteria
Laxative	Reduces the colonic transit time, thereby decreasing the time available both for production and absorption of ammonia and other potentially toxic substances
SCFA modification	Enhances the production of the nontoxic acetate at the expense of the potentially toxic C4-6-SCFA

Abbreviation: SCFA = short-chain fatty acids.

lose, and that the lactulose dose should be titrated to pH levels <6.0. Acidifying enemas, e.g. of lactulose, lactitol or glucose, may be a beneficial supplement in obtaining this effect.

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