



# Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy

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**Summary** In order to reduce ammonia production by urease-positive bacteria Solga recently hypothesised (S.F. Solga, Probiotics can treat hepatic encephalopathy, Medical Hypotheses 2003; 61: 307–13), that probiotics are new therapeutics for hepatic encephalopathy (HE), and that they may replace antibiotics and lactulose. This influenced our view of the effect of antibiotics, prebiotics, e.g., lactulose, and probiotics on intestinal bacteria in the treatment of HE.

Intestinal ammonia arises from aminoacids after bacterial de-amination and not from urea making urease-positive bacteria irrelevant.

Antibiotics are not preferred in the treatment of HE, since ammonia-producing antibiotic-resistant bacteria may survive and replace ammonia-producing antibiotic-susceptible bacteria. Intestinal prebiotics are carbohydrate-like compounds, such as lactulose and resistant starch, that beneficially affects host's health in a different manner than normal food. In the small bowel prebiotics are not absorbed and digested, but are fermented in the colon by colonic bacteria. Fermentation of prebiotics yields lactic, acetic and butyric acids, as well as gas especially hydrogen (H<sub>2</sub>). The massive H<sub>2</sub> volumes cause rapid intestinal hurry and thus massive amounts of colonic bacteria, not only urease-positive bacteria, but also deaminating bacteria, are removed and intestinal uptake of toxic bacterial metabolites, e.g., ammonia, reduced.

As living non-pathogenic micro-organisms, probiotics beneficially affect the host's health by fermenting non-absorbed sugars, especially in the small bowel. Thus, they reduce the substrate of the other bacteria, and simultaneously they create a surplus of fermentation products which may affect the non-probiotic flora. Regarding the fermentation products (lactic acid, ethanol, acetic acid and CO<sub>2</sub>) five groups of probiotic micro-organisms are known. It is argued that probiotic, CO<sub>2</sub>-producing (facultatively) heterolactic lactobacilli, i.e., lactobacilli, that produce both lactic acid and CO<sub>2</sub> from sugars, such as glucose, are preferred in the treatment of HE.

Our ideas concur with the practice guidelines regarding HE as formulated by Blei, Cordoba and the Practice Parameters Committee of the American College of Gastroenterology, and does not alter the final conclusion of Solga as regards the beneficial use in future treatment of HE.

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## Introduction

Hepatic encephalopathy (HE) is a common and dreaded complication of liver disease. It is defined as "a disturbance in central nervous system function because of hepatic insufficiency" [1]. Even minimal HE has a major impact on the life of patients who suffer from it [2,3]. It is almost certainly multi-factorial [1]. Gut-derived ammonia is thought to be an important critical factor in the unknown pathogenesis.

The present treatments for HE include the cathartic agent lactulose and poorly absorbable antibiotics. Previously, Solga [4] argued for the use of probiotics as a treatment for HE. There was however, little clear coherence in his arguments. Probiotics appeared to work by magic, whereas in fact they are quite normal bacteria with coherent biochemical pathways. With our microbiological and biochemical knowledge and experience in the field of intestinal microflora and probiotics, we can explain the several lactulose-mediated and probiotic effects [5,6]. Here, we argue our view on the role of antibiotics, prebiotics and probiotics in the treatment of HE. This view should be regarded as a supplement to Solga's hypothesis rather than as a critical comment although we do present a critical remark on urea as the source of ammonia.

## Origin of ammonia in the pathogenesis of HE

It is generally known that our intestinal flora may produce ammonia. This flora contains several urease-positive bacterial species [4]. The role of these bacteria is dubious. The basic question is: Where does the urea come from? Normally the concentration of urea in our food is minimal. In our body urea is mainly produced from ammonia and carbon dioxide by the (hepatic) urea-cycle, although minimal intestinal bacterial production from purines and pyrimidines also occurs [7,8]. Urea is removed from blood by renal filtration and excreted in the urine. This means that the intestinal urease-positive bacteria cannot hydrolyse the urea present in blood and urine. Therefore, the gut-derived ammonia is thought to be the product of another bacterial process: the enzymatic de-amination of amino-acids, which are massively present in most food, either free or incorporated in peptides and/or proteins.

Ammonia is not only produced from amino-acids in the intestinal lumen, but also in other organs. The amino groups of most amino-acids are transferred onto  $\alpha$ -ketoglutarate to produce glutamate. By the action of glutamate dehydrogenase, an enzyme occurring in the mitochondria of all tissues, glutamate is converted to ammonia and  $\alpha$ -ketoglutarate. If the amino-acid load is high due to a protein-rich diet, internal degradation of proteins may cause a marked increase of ammonia leading to toxic concentrations in the blood and tissues.

## Treatments for HE

Treatment for HE should be directed at lowering intestinal ammonia production. This means that treatment must aim at both intestinal ammonia sources and the causal intestinal microbial flora. Treatment of the microbial flora may involve antibiotic, prebiotic or even probiotic treatment. Oral antibiotic treatment is common and the antibiotic principles of this treatment are clear: the growth of ammonia-producers must be stopped, and these bacteria removed. Although treatment with the prebiotic lactulose has become an alternative to antibiotics, the use of prebiotics other than lactulose might be equivalent, if not better. At present interest in probiotic treatment is growing. Our ideas concerning treatment with prebiotics or probiotics is based on our experience with lactobacilli and probiotics in short small bowel patients. These ideas [5,6] elucidate the intestinal processes that occur during the treatment of HE.

Restriction of dietary protein and other possible ammonia sources may be important elements in the treatment of HE.

## Antibiotics in the treatment of HE

Antibiotics inhibit the growth of susceptible bacterial species and may even kill them. This means that resistant bacteria will survive. Due to a relative surplus of substrates they will flourish and the normal intestinal micro-flora will be disturbed. In the short term, when susceptible bacteria are inhibited and the resistant ones are increasing (possibly one day), the patient may feel better. The subsequent effect is unpredictable, since both antibiotic-mediated growth inhibition and antibiotic resistance are not linked to ammonia production. Therefore, treatments with better perspectives are preferred.

## Prebiotics in the treatment of HE

Lactulose, a non-absorbable, synthetic disaccharide with multiple effects on gut flora, is regarded as an intestinal prebiotic, i.e., a food ingredient (supplement) that is non-digestible in the small bowel, and that beneficially affects host health due to its fermentation by bacteria in the colon. Many if not all the multiple effects of lactulose may be explained as the result of bacterial fermentation in the colon, especially by the massively present anaerobic *Bacteroides* spp. (normally about  $10^{11}$ – $10^{12}$  cfu/g faeces). In the same way that glucose, sucrose and lactose are easily fermented in the small bowel, is lactulose fermented by anaerobic bacteria, especially *Bacteroides* spp. in the colon. Fermentation of lactulose by these bacteria yields lactic, acetic and butyric acid and gas, especially molecular hydrogen ( $H_2$ ). These weak acids are excellent substrates for the colonocytes. Since a total daily dose of 10–20 g is small compared to 500–1000 g faeces/day, the impact on the faecal flora is limited. The production of  $H_2$  in the colon is more important. Due to the molar gas volume (24 L), a gas volume of about 1 L in the colon is created by only 0.04 mole or 0.08 g of the gaseous fermentation product  $H_2$ . If one  $H_2$  molecule is produced from one monosaccharide moiety (i.e., two  $H_2$  molecules from one lactulose molecule), this means that 1 L  $H_2$  gas is produced from 7.0 g lactulose. Such massive volumes cause flatulence and intestinal hurry and this removes massive amounts of colonic bacteria [9]. In this way not only urease-positive bacteria are lost, but also ammonia-producing bacteria. During colonic stasis increased amounts of toxic bacterial metabolites, e.g., ammonia, are taken up from the intestine. As soon as the stasis ends, the uptake of toxic compounds immediately drops. Thus, the main effect of lactulose is a rapid stool transit due to the bacterial gas-mediated activation of intestinal peristalsis. The same applies to other low molecular sugar-like compounds like lactitol and even high molecular polymeric carbohydrates, e.g., various fibres, as resistant starch, that are indigestible in the small bowel, whereas they are excellent substrates for the large amounts of colonic bacteria.

## Probiotics

Probiotics are living non-pathogenic micro-organisms, which as food ingredients (supplements) also beneficially affect host's health. These non-pathogenic micro-organisms may be lactic acid

bacteria, such as lactobacilli, lactococci and bifidobacteria, or yeasts, such as *Saccharomyces cerevisiae* subspp. *boulardii*. The most important common effect of all probiotics seems to be the fermentation of non-absorbed sugars. With lactobacilli and lactococci or yeasts this occurs in the small bowel and with bifidobacteria in the colon.

All probiotics need sugar as a fermentative energy source. Fermentation depends on the amount of probiotic micro-organisms and fermentable substrates, that are available, and on a suitable environment. The acidotolerant lactobacilli [10] thrive in an acidic environment unlike other intestinal bacteria. This implies that the acidic barrier of the stomach should be intact (i.e., no inhibition of gastric acid production or neutralisation of gastric acid). The principles of probiotic action are simply based on fermentation of easily fermentable sugars, such as the monosaccharides, glucose and fructose, the disaccharides, sucrose and lactose, and the fructose-derived oligosaccharides, called FOS, and fructose polysaccharides, called inulin. The fermentation takes place mainly in the small bowel. In the past we have postulated two primary effects for each probiotic treatment [5]:

1. The first primary effect concerns the substrate: the probiotic creates a shortage of substrate for other bacteria.
2. The second primary effect concerns the end products: the probiotic creates a surplus of fermentation products, which may affect the non-probiotic flora.

Both these effects imply that highly concentrated probiotic formulas are likely to be the most effective.

## Functional differentiation between probiotics

With regard to the probiotic fermentation products, i.e., lactic acid, ethanol, and  $CO_2$ , theoretically five major groups of probiotics may be distinguished. An essential differentiation within each of the three groups of lactobacilli is based on the production of D- and/or L-lactic acid (indicated with [D], [D + L], or [L], respectively). These groups are:

- (a) Lactococci (*Lactococcus lactis* [L]) and the obligately homolactic lactobacilli (e.g., *Lactobacillus salivarius* [L] and *Lactobacillus*

- acidophilus* [D + L]) [10,11]: these bacteria produce only lactic acid (2 moles from 1 mole glucose) and no CO<sub>2</sub>.
- (b) The facultatively heterolactic lactobacilli (e.g. *Lactobacillus casei* [L], *Lactobacillus rhamnosus* [L] and *Lactobacillus plantarum* [D + L]) [10]: these bacteria produce mainly lactic acid (nearly 2 moles from 1 mole glucose) and only a small amount of CO<sub>2</sub>.
- (c) The obligately heterolactic lactobacilli (e.g., *Lactobacillus bif fermentans* [L] and *Lactobacillus fermentum* [D + L]) [10]: these bacteria produce 1 mole lactic acid, 1 mole ethanol and 1 mole CO<sub>2</sub> from 1 mole glucose.
- (d) Yeasts (e.g., *Saccharomyces cerevisiae* subsp. *bouardii*): these micro-organisms produce 2 moles ethanol and 2 moles CO<sub>2</sub> from 1 mole glucose;
- (e) The strictly anaerobic bifidobacteria, which are all obligately heterolactic (e.g., *Bifidobacterium bifidum*, *B. longum* and *B. infantis*) [12]: these bacteria produce 2 moles L-lactic acid, 3 moles acetic acid and no CO<sub>2</sub> from 2 moles glucose.

The preferred intestinal niche of (a)–(d) is the small bowel. In the order from (a) to (d) the amount of lactic acid produced from 1 mole glucose decreases from 2 moles via 1 to 0 mole per fermented glucose molecule and the amount of CO<sub>2</sub> produced from 1 glucose molecule increases from 0 via 1 to 2. This implies that with highly active probiotics the acidity in the small bowel lumen will be highest with (a) and the expulsive force (seen as diarrhoea) highest with (d). Patients with liver disease, e.g., liver cirrhosis, should especially take care with regard to the use of probiotic yeast, since these probiotics produce 2 moles ethanol (with an adverse effect on liver function) from each mole glucose. However, the use of the obligately heterolactic lactobacilli is not always safe, since these probiotics produce 1 mole ethanol from each glucose molecule. Additional secondary effects, which may contribute to the total probiotic effect, concern killing by several antimicrobial agents, e.g., nisine [5]. The last group, the bifidobacteria ((e)), is not mentioned in the comparison with (a)–(d), since these bacteria are known as colonic bacteria, but they still mostly resemble (a) as regards the absence of ethanol and CO<sub>2</sub> production.

A closer differentiation of the groups (a)–(c) with regard to the production of lactic acid (D- and/or L-lactic acid) is important with regard to neonates and young children because of the

toxic effects of D-lactic acid [13]. For these children the D-lactic acid-producing obligately homolactic lactobacilli, *Lactobacillus bulgaricus* [D] and *Lactobacillus lactis* [D] should not be used. In adults this toxic effect of D-lactic acid is not observed because of the presence of the enzyme D-2-hydroxy-acid dehydrogenase, that converts D-lactic acid to pyruvic acid.

## Probiotic activity in the treatment of HE

When used as treatment for HE, highly concentrated probiotics will prevent other bacteria from growing and multiplying by taking away substrates and by either lactic acid-mediated pH-related growth inhibition or (non-infectious) CO<sub>2</sub>-driven diarrhoea. Thus, at the intestinal sites with high probiotic concentrations the amounts of other bacteria will diminish. This also means a decrease of: (i) total ammonia in portal blood; (ii) inflammation and oxidative stress in the hepatocyte; (iii) uptake of both microbial toxins, such as LPS, and toxic metabolites, such as phenol. The use of obligately homolactic lactobacilli [10] as probiotics, that produce only 2 moles of lactic acid from 1 mole glucose and no CO<sub>2</sub>, is not recommended. They cannot create any gaseous pressure that contributes to expulsion of the flora, although they will inhibit bacterial growth. The use of probiotic bifidobacteria is also not specifically recommended, since they are strict anaerobes that live in the colon, and do not produce CO<sub>2</sub>. The colon is the place for storage of materials that are indigestible in the small bowel. Due to the combined action of a cocktail of bacterial enzymes with proteolytic and saccharolytic activity (cellulase activity included) the stored indigestible materials are still partly digested. However, the number of probiotic bifidobacteria that will arrive in the colon will be low compared to the resident flora and thus they are thought to be irrelevant. The use of a probiotic with an antibiotic is not recommended since the probiotic micro-organisms may be susceptible to the used antibiotic(s). Despite the theoretical arguments in certain patients the administered probiotic may not grow. To prevent this, one may choose a mixture of the most suitable probiotics. For HE we think that the best choices are probiotics from groups (b) and (c). In severely ill patients the obligately heterolactic ethanol-

producing lactobacilli are probably the most useful because of the enormous gas production.

## Discussion

For new ideas to be accepted, it is necessary that the ideas are well explained and understood. The aim of this article is to present the many effects summarised by Solga [4] regarding lactulose and probiotics, as logical consequences of a few basic bacterial processes. The essential aim of probiotic therapy in HE is to undo the ammonia-producing process in the small bowel by removing the causative bacteria. Since prebiotics mainly remove the content of the colon, but not necessarily of the small bowel, and probiotics remove the small bowel content and the colon content, it may be expected that probiotics are more effective than prebiotics. For a quick and optimal effect one might consider combining a probiotic with a prebiotic [14], especially if patient is worsening or is already comatose.

Emptying and cleansing the gut, especially the small bowel, is thought to be essential in order to stop the influx of toxic ammonia from the intestinal lumen into the tissues and organs. Several expedients may be useful, e.g., an enema or artificial intestinal gassing by means of harmless gas, that is intestinally produced from encapsulated chemicals.

Our ideas do not alter the final conclusion of Solga regarding the beneficial use in future treatment of HE [4]. Nevertheless, they may help to understand closer studies regarding the "gut-liver axis" [15]. In addition, they also fully fit to the practice guidelines [1] regarding the "treatment goals" and "treatment options", especially concerning "reduction in the nitrogenous load arising from the gut". They may broaden the possibilities concerning "bowel cleansing", "nonabsorbable disaccharides" and "other therapies". We expect that "probiotics" will become a recognised treatment among the therapies for reducing the nitrogenous load arising from the gut.

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