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Lactitol, an emerging prebiotic: functional properties with a focus on digestive health

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Abstract

Lactitol is a sweet-tasting sugar alcohol and may be used as a functional ingredient in a variety of food products to replace sucrose. Having similar technical and physico-chemical properties as sucrose, lactitol is included in foods for the reduction of caloric value and glycaemic response. Lactitol is also used in oral health products where it can help to reduce the risk of dental caries, and it has been suggested as an alternative in the treatment of hepatic encephalopathy. With regard to digestive health, the shortening of intestinal transit time following lactitol consumption has been reported consistently. In addition, lactitol may fulfil the scientific criteria required for prebiotic classification and can hence be described as an emerging prebiotic. The scientific evidence for the selective increase in lactobacilli and bifidobacteria following lactitol consumption looks promising. However, additional research using molecular techniques is needed to confirm lactitol's status as a prebiotic.

Keywords: lactitol, polyol, prebiotics, gut microbiota, digestive health, colon, food ingredients

1. General characteristics of lactitol

Lactitol monohydrate is a disaccharide alcohol that is commonly used as a bulk sweetener in calorie-controlled products. It is formed by the catalytic hydrogenation of lactose. The glucose moiety of the disaccharide lactose is reduced, resulting in the formation of lactitol (4-O-β-D-galactopyranosyl-D-glucitol). After sedimentation (to settle the catalyst) the solution is filtered, purified, concentrated and crystallized. Lactitol was first used in foods in the 1980s (Ballongue *et al*. 1997). Its low hygroscopic activity ensures that products formulated using lactitol maintain their crispness. Thus, the shelf life of bakery, confectionery, and chewing gum products, for example, may be extended. Moreover, lactitol has a similar solubility to that of glucose, is stable under acid and alkaline conditions and remains stable under the high temperatures utilized during food processing. Due to lactitol's mild sweetness profile, it can be combined with other low-calorie sweeteners commonly used in today's low-calorie, sugar-free foods, such as acesulfame K, aspartame and saccharin (Livesey 2003).

Internationally, lactitol is approved for use in foods in many countries, including the European Union (European Communities 1994), USA, Canada, Japan, various countries in South East Asia, Brazil, Israel and Switzerland.

2. Effects of lactitol on digestive health

2.1 Gut microbiota

Currently, the manipulation of the human colonic microbiota in order to improve host health is of much medical and nutritional interest. The healthy human gastrointestinal tract contains a diverse population of microorganisms, which increases in quantity and metabolic activity along its length. Specific species of *Lactobacillus* and *Bifidobacterium* are members of the normal microbiota within the gastrointestinal tract. Few microbes are present in the stomach at pH 2–3; the resident microbial population of the stomach was found to be around 10^5/g of mucosa and was estimated at 10^3/ml contents (Kato *et al*. 2006). Microbial numbers increase in the small intestine, ranging from 10^4 to about 10^7 in the terminal ileum (Gibson and McCartney 1998). The microbiota of the upper small

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intestine is dominated by streptococci, staphylococci and lactobacilli microbiota (Gibson *et al*. 2001). The large intestine harbours an extremely complex microbial ecosystem, comprising over a thousand different microbial species (Vaughan *et al*. 2005). The colonic environment is more favourable for microbial colonization, with a longer transit time and a pH of 5.5–6.8. Microbial counts in the colonic contents and faeces usually exceed 10^{11}–10^{12}/g of dry content (Harmsen *et al*. 2002). Most of the microorganisms found in the colon are anaerobes, including members of the genera *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Ruminococcus, Atopobium* and *Clostridium*. Lactobacilli and enterobacteria (including coliforms), tend to be relatively minor components of the gastrointestinal microbiota (Harmsen *et al*. 2002).

Because exact numbers and proportions of the gut microbiota have yet to be identified, a healthy or balanced colonic microbiota can at present best be described as one that is predominantly saccharolytic and comprises significant numbers of bifidobacteria and lactobacilli (Cummings *et al*. 2004).

2.2 Definition of prebiotics and scientific criteria for prebiotic classification

Much attention is being directed towards dietary components that may beneficially influence the gut microbiota and thereby contribute to digestive health. In 1995, Gibson and Roberfroid coined the term prebiotic and defined a prebiotic as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health" (Gibson and Roberfroid 1995). Since then this concept has been further developed, and in order to qualify for prebiotic classification an ingredient is required to:

- Resist digestion (gastric acidity, hydrolysis by mammalian enzymes and gastrointestinal absorption)
- Be fermented by the gastrointestinal microbiota
- Selectively stimulate the growth and/or activity of intestinal bacteria associated with health and well-being (Gibson *et al*. 2004).

Prebiotics are generally accepted to alter the colonic microbiota towards a healthier composition and/or activity, by increasing the prevalence of saccharolytic microorganisms whilst reducing putrefactive microorganisms. Fructooligosaccharides, inulin and galactooligosaccharides are examples of non-digestible carbohydrates for which fulfilment of the prebiotic criteria has been demonstrated in human studies (Gibson *et al*. 2004; Tuohy *et al*. 2005), and their inclusion in certain functional foods has recently increased significantly. Other non-digestible carbohydrates, including polyols, have also been suggested to act as prebiotics (Crittenden 2006). The documentation on the potential prebiotic nature of lactitol will be discussed in the following sections.

2.3 Scientific evidence for lactitol as an emerging prebiotic

2.3.1 Resistance to digestion

Unlike the metabolism of lactose, lactitol is hydrolysed only minimally by human small intestinal tissue (Nilsson and Jägerstad 1987). Less than 2% of ingested lactitol is hydrolysed or absorbed. Absorbed lactitol is further metabolized by the liver, either for hepatic glycogen storage or for glucose production (Grimble *et al*. 1988). Hence, lactitol fulfils the first criterion required for prebiotic classification.

2.3.2 Fermentation by the gastrointestinal microbiota

A number of *in vitro* and *in vivo* studies have examined the possible effects of lactitol on and fermentation by the gut microbiota.

Its fermentation properties have been investigated *in vitro* by Kontula *et al*. (1999) who tested 9 strains of lactic acid bacteria as well as human faecal and biopsy isolates. Among those tested, *Lactobacillus acidophilus* strains and *L. rhamnosus*, enterococci, and streptococci were able to grow on lactitol and lactulose (4-O-β-D-galactopyranosyl-D-fructose). However, lactulose was better utilized, giving a shorter lag phase or higher cell yields by some of the tested *Lactobacillus* strains than lactitol (Saarela *et al*. 2003). A slow fermentation has been reported previously by Minekus *et al*. (1999), using a model simulating the human colon.

Klewicki and Klewicka (2004) assessed the *in vitro* potential of different polyols, including lactitol, to support the growth of strains of *L. acidophilus*, *L. casei* and *L. paracasei*. Lactitol supported the growth of the tested strains, as judged by a reduction in pH. In the presence of lactitol, the strains were also able to inhibit the growth of members of the Enterobacteriaceae family. Lactitol in particular improved the antagonistic activity of *L. acidophilus* strains compared to sorbitol. This effect may be related to the lower pH reached by growth on lactitol.

Probert and co-workers (2004) used a colon simulator to mimic the complex ecosystem of the human colon *in vitro* and showed that lactitol significantly decreased the number of *Bacteroides* and *Bifidobacterium*. *Lactobacillus* was below the level of detection and remained so following the addition of lactitol. Significantly, however, the level of total short chain fatty acids (SCFA) and butyrate

production almost doubled. A similar dramatic increase in butyrate production was observed by Minekus *et al*. (1999) when lactitol was administered to the TNO intestinal model. These findings are in line with results from an *in vitro* swine caecal fermentation (Piva *et al*. 1996), which also showed an increase in the concentration of butyrate when lactitol was added to low and high fibre diets (142 and 230%, respectively).

These findings suggest that lactitol is fermented by the gut microbiota and stimulates microbial metabolism towards the production of butyrate, an important fatty acid for intestinal health (Scheppach and Weiler 2004). Furthermore, evidence from studies in animals confirms the findings obtained *in vitro*. A recent study in rats (Peuranen *et al*. 2004) indicated beneficial effects of lactitol on gut microbiota-associated metabolism, whereby lactitol had a faecal pH-lowering effect and significantly increased the proportion of butyric and lactic acids without changing total caecal SCFA concentrations. Another study in rats investigated the effects of lactitol (7% of the diet) on SCFA formation versus a control for 16 days (Islam *et al*. 2004). Here too, total SCFA concentration in the caecal content did not differ between groups. However, concentrations of acetic acid were significantly lower, while concentrations of butyric and succinic acids were significantly higher with lactitol compared to the control group. Concentrations of propionic acid did not differ between groups. The origin of the butyric acid is likely to be as a result of cross-feeding, where organisms such as certain members of, for example, the genus *Eubacterium* consume lactic acid and produce butyric acid (Duncan *et al*. 2004).

Nilsson and Nyman (2005) compared the effects of lactitol, lactulose, and 4 fructans of different degrees of polymerization, in rats (8% of the diet) versus a control for 12 days. The caecal pool of SCFA was 2–4 times higher in the rats fed the test diets than in those fed the control diet. Lactitol resulted in a 2.3-fold increase, although this was not statistically significant and was lower than the increase observed with oligofructose, particularly butyrate. These findings are in contrast with the results of the *in vitro* study mentioned above (Probert *et al*. 2004), in which lactitol was more effective in producing butyrate than oligofructose.

The effects of lactitol (0.3% of the diet), tributyrin (a dietary source of butyric acid; 1% of the diet) or a mixture of both were also tested in piglets and compared to a control (Piva *et al*. 2002). Caecal concentrations of total SCFA were not significantly different between groups, but lactic acid concentrations in the caecum were 3-fold higher in animals fed lactitol compared to the other groups. Surprisingly, neither lactitol nor tributyrin increased butyric acid in the jejunum or caecum. This may be explained, at least in part, by the fact that the butyric acid originating from fermented lactitol or tributyrin could not be detected after slaughter due to the rapid absorption rate of butyrate by the intestinal mucosa.

Additional evidence reported in studies in humans confirms that lactitol is indeed fermented by gut microbiota. These studies mainly investigated the generation of SCFA or formation of gaseous products of colonic fermentation such as hydrogen, which passes into the circulation by diffusion and is then exhaled. Hydrogen breath tests were performed after the ingestion of lactitol (30 g) in 43 female adults (Oku *et al*. 2005). A substantial amount of hydrogen was excreted in the breath following the ingestion of lactitol. A similar observation was made by Griessen *et al*. (1986) and Livesey *et al*. (1993) indicating fermentation of lactulose by the intestinal microbiota. Thus, the metabolic fate of lactitol was determined by measuring hydrogen excretion in the breath and $^{14}CO_2$ excretion from labelled lactitol. The 3 routes for disposal of universally ^{14}C-labelled lactitol were evaluated in humans (Grimble *et al*. 1988). Lactitol was given as a 20 g daily dose to 6 healthy volunteers for 14 days, and on day seven, 10 μCi of L-[U-^{14}C]-lactitol was administered with the unlabelled carbohydrate; excretion of ^{14}C in breath, urine and faeces was recorded. The peak of $^{14}CO_2$ excretion occurred at 6 hours and total $^{14}CO_2$ accounted for approximately 63% of the isotope given, whilst 6.5 and 2.0% of the label were recovered from faeces and urine, respectively. These data suggests that lactitol is extensively metabolized in the human colon and that a significant proportion of the bacterial metabolites are available for colonic absorption. Of lactitol's theoretical energy content, 54.5% was utilized by the subjects in this study.

Measuring the production of individual SCFA following consumption of lactitol and lactulose (both 2×10 g/day) for 4 weeks in 36 healthy volunteers demonstrated that concentrations of acetic and lactic acid were significantly increased by both lactitol and lactulose compared to placebo, with lactulose exerting a greater effect (Ballongue *et al*. 1997). The concentration of propionic acid was significantly decreased by both compounds, with lactulose again exerting a greater effect. However, lactitol consumption was able to support a higher level of faecal butyrate than lactulose.

Lactitol (3×20 g/day) also produced a significant increase in the faecal concentration of acetic and lactic acid when studied in patients with liver cirrhosis (Hotten *et al*. 2003). However, no change in butyric acid levels was observed.

In summary, several studies *in vitro* and *in vivo*, in animals and humans, have demonstrated that lactitol is fermented by the gut microbiota and therefore fulfils the second criterion required for prebiotic classification. In animals, increases in butyrate were more pronounced compared to changes in acetic or lactic acid following lactitol consumption, whereas in humans increases in acetic and lactic acid were more evident.

2.3.3 Selective stimulation of growth and/or activity of intestinal bacteria associated with health and well-being

Four human studies have assessed the selective effects of lactitol on the growth of gut microbial populations.

The effect on the colonic microbiota of the consumption of 10 g lactitol daily for 4 weeks was studied in 36 healthy individuals in a double-blind, randomized, placebo-controlled clinical trial, and compared to the effects of an equivalent dose of lactulose (Ballongue *et al*. 1997). There was a slight but significant increase in the quantity of *Bifidobacterium* (from 8.5 to 8.9 $\log_{10}$) and *Lactobacillus* (from 6.3 to 7.0 $\log_{10}$) species following lactitol consumption, and a decrease in potential pathogens such as *Clostridium* (from 5.9 to 4.7 $\log_{10}$), *Bacteroides* (from 10.3 to 8.8 $\log_{10}$) and coliforms (from 6.6 to 5.6 $\log_{10}$). All changes were more pronounced and rapid following lactulose consumption.

Increased counts of lactobacilli were also found when the effects of lactitol and lactulose on the faecal microbiota were investigated in 21 cirrhotic patients without hepatic encephalopathy (HE; Riggio *et al*. 1990). The increase was more pronounced for lactulose; lactitol was found to result in decreased levels of enterococci and enterobacteria. All subjects were treated with an individualized disaccharide dose to achieve and maintain 2 semi-liquid stools per day (mean dose: 32.8 g/day of lactitol, 33.1 g/day of lactulose). Faecal flora was determined before and 10 days after stabilizing the laxative effect.

Lactitol (20 g/day) was also found to significantly increase populations of *Bacteroides* and bifidobacteria, while it had no significant effect on enterococci, enterobacteria or lactobacilli when tested for 4 weeks in 11 women suffering from constipation and compared to a placebo (Ravelli *et al*. 1995).

In patients with liver cirrhosis, high doses of lactitol (3 × 20 g/day) significantly increased the total anaerobic bacterial counts. This change was mainly accounted for by an increase in bifidobacteria (from 9.34 to 10.10 $\log_{10}$) and lactobacilli populations (from 8.15 to 8.63 $\log_{10}$). Contrary to a probiotic mixture, which was also tested in the study, lactitol did not produce any significant effect on *Bacteroides* and *Clostridium* (Hotten *et al*. 2003).

Table 1 summarizes the studies investigating whether lactitol can selectively stimulate the growth of intestinal bacteria associated with health and well-being. There are data indicating that lactitol beneficially stimulates the activity of intestinal bacteria; the majority of studies assessing the effects of lactitol on faecal pH compared to baseline or control demonstrated a decrease in faecal pH in the range of 0.5–0.6 units. This decrease has been observed in patients with cirrhosis and/or HE (Uribe *et al*. 1987; Riggio *et al*. 1990; Hotten *et al*. 2003) and in healthy subjects (Ballongue *et al*. 1997). However, one study failed to show any effect on faecal pH in constipated subjects (Ravelli *et al*. 1995). An acidic pH is believed to inhibit conversion of primary to secondary bile acids and may hence reduce the risk for colorectal cancer.

Lactitol also significantly decreased the activities of faecal enzymes that may play a role in carcinogenesis, such as azoreductase, 7α-dehydroxylase, β-glucuronidase and nitroreductase, when compared to a placebo. Similar effects were observed with lactulose (Ballongue *et al*. 1997). The same study also demonstrated that both lactitol and lactulose significantly decreased the faecal concentrations of aromatic compounds such as phenol, cresol, indole and skatol, as well as valeric acid, when compared to placebo or baseline.

Table 1. Summary of studies investigating whether lactitol can selectively stimulate growth of intestinal bacteria associated with health and well-being. Lactulose is included for comparison

Studies	Study design	Subjects	Experimental/ control intervention (dose)	Lactitol effects on faecal lactobacilli and bifidobacteria
Riggio *et al*. 1990	Parallel	21 patients with liver cirrhosis	Lactitol (mean 32.8 g/day) Lactulose (mean 33.1 g/day)	Increase in lactobacilli
Ravelli *et al*. 1995	Crossover	13 healthy women suffering from constipation	Lactitol (20 g/day) Placebo (10 g dextrose/day)	Increase in bifidobacteria (from 9.56 to 10.06 $\log_{10}$)
Ballongue *et al*. 1997	Parallel	36 healthy volunteers	Lactitol (2 × 10 g/day) Lactulose (2 × 10 g/day) Placebo (2 × 10 g/day)	Increase in lactobacilli (from 6.3 to 7.0 $\log_{10}$) Increase in bifidobacteria (from 8.5 to 8.9 $\log_{10}$)
Hotten *et al*. 2003	Parallel	30 patients with liver cirrhosis	Lactitol (3 × 20 g/day) Probiotic SCM-III Rifaximin (3 × 400 mg/day)	Increase in lactobacilli (from 8.15 to 8.63 $\log_{10}$) Increase in bifidobacteria (from 9.34 to 10.10 $\log_{10}$)

In summary, consistent selective increases in faecal lactobacilli, bifidobacteria or both were observed in all 5 studies in humans (healthy volunteers and patients). Both lactobacilli and bifidobacteria have been associated with a healthy gut microbiota. Furthermore, lactitol beneficially stimulated the activity of intestinal bacteria resulting in lower faecal pH, reduced concentrations of aromatic compounds and reduced activity of certain enzymes that are possibly associated with carcinogenesis.

However, the number of subjects tested in these studies was relatively small and/or the studies involved consumption of high doses of lactitol. Furthermore, the analysis of the microbiota was performed by culture-based methods, which are known to be less selective then molecular-based methods. Nevertheless, the data warrant further studies in humans, applying molecular-based methods to further substantiate the selective growth stimulation by lactitol of intestinal bacteria associated with health and well-being. In addition, such studies will be necessary to determine the minimum effective dose.

2.4 Intestinal transit time

Lactitol has an effect on constipation, as shown in a number of *in vivo* studies carried out in the elderly (Sachetta *et al*. 2000), children (Pitzalis *et al*. 1996) and adults (Delas *et al*. 1991). In 114 chronically constipated patients of both sexes, aged 18–70, without any main alteration of the colonic microbiota, lactitol (20 g/day) consumption resulted in good clinical and biological tolerability. Moreover, 80% of the patients reported stool frequency or consistency and ease of defecation (Delas *et al*. 1991). During a controlled randomized trial, lactitol showed a reduced risk for prolonged transit time in 18 physically inactive hospitalized individuals with healthy gastrointestinal tracts (Pontes *et al*. 1995). As a so-called osmotic laxative, lactitol promotes the hydration of the gut contents resulting in shorter transit times and the establishment of laxation (Petticrew *et al*. 1997). This has been indicated in a number of studies (Lee and Storey 1999; Soontornchai *et al*. 1999). However, attention should be drawn to the laxative effects of lactitol, as it may be desired in constipated but not in healthy individuals. It appears that lactose maldigesting subjects are more sensitive to the side effects of lactitol then lactose digesters (Soontornchai *et al*. 1999). In healthy non-constipated Japanese adults, the maximum permissive dose of lactitol that did not cause transitory diarrhoea was determined to be 0.36 g/kg body weight (Oku *et al*. 2005). A single dose of 8 g appears to be tolerated well by most subjects (Morgan *et al*. 1989), and in Western adults doses up to 40 g/day can be tolerated without side effects (Blanc *et al*. 1992). The relatively good tolerance for lactitol compared to the chemically similar lactulose may be due to a slower fermentation rate (Minekus *et al*. 1999).

3. Additional beneficial effects of lactitol

3.1 Effect on diabetes

As a sweetening ingredient, lactitol has a sweet taste that closely resembles the taste profile of sucrose but has only 40% percent of sucrose's sweetening power. A low glycaemic index (GI) of 2 ± 3 has been reported for lactitol (compared to the glucose reference with a GI of 100 and sucrose with a GI of 68 ± 5; Foster-Powell *et al*. 2002). It contributes half the energy of most other carbohydrates—8 kJ (2 kcal) per gram (Livesey 2003). The control of blood glucose, lipids and weight are the 3 major goals in diabetes management today. As GI refers to available carbohydrates and lactitol is not absorbed in the small intestine, it is more appropriate to look at relative glucose response (RGR). The RGR and relative insulin response (RIR) of lactitol have been estimated by Natah *et al*. (1997) following consumption of 25 g of lactitol and were found to be very low (RGR = 3, RIR = 6) compared to the values for glucose (RGR = 100, RIR = 100). This means that foods containing lactitol as a replacement for sucrose can be used by people with diabetes, giving them a variety of low-calorie and sugar-free choices (Natah *et al*. 1997; Sirajedin *et al*. 1997).

3.2 Effects on dental health

There are many factors involved in dental decay, such as oral microflora and substrate availability. Microorganisms in the oral cavity may reside in dental plaque, and some such as *Streptococcus mutans* and *S. sobrinus* are involved in a continuous fermentation leading to a drop in the pH of the dental plaque (British Nutrition Foundation 2000). The acidogenesis in plaque after sugar consumption can put teeth under carious attack when the local pH falls below pH 5.7. This has been reduced or even avoided when lactitol and other polyols (such as xylitol) are ingested (Imfield 1993), as they resist fermentation by the microorganisms of dental plaque (Kandelman 1997). Moreover, polyols including lactitol reverse the initial stages of dental caries by inhibiting demineralization of tooth enamel and enhancing remineralization of demineralized lesions (Takatsuka 2000). The usefulness of polyols including lactitol as alternatives to sugars and as part of a comprehensive programme, including proper dental hygiene, has therefore been recognized by the American Dental Association (1999). The US Food and Drug Administration (FDA) has approved the use of a "does not promote tooth decay" health claim in labelling for sugar-free foods that contain polyols, including lactitol (US Food and Drug Administration (FDA) Code of Federal Regulations 2002).

3.3 Effects on hepatic encephalopathy (HE)

HE is a complex neuropsychiatric syndrome that may complicate acute or chronic liver failure (Gitlin 1996). It

is characterized by changes in mental state, including a wide range of symptoms ranging from minor signs of brain dysfunction to deep coma.

HE is caused by disorders affecting the liver. These include disorders that reduce liver function (such as cirrhosis or hepatitis) and conditions where blood circulation bypasses the liver. The exact cause of the disorder is unknown. When the liver cannot properly metabolize and detoxify substances in the body, toxic substances build up in the bloodstream. One substance believed to be particularly toxic to the central nervous system is ammonia, which is produced by the body when proteins are digested but is normally detoxified by the liver. Many other substances may also accumulate in the body and contribute to damage to the nervous system (Lockwood 2004).

Treatment of HE thus aims at reducing the production and absorption of ammonia (Weissenborn 1992). The colonic microbiota is the primary producer of ammonia and thus non-absorbed antibiotics are used in the treatment of HE. Neomycin was first used in studies concerning the treatment of acute and chronic HE (Conn 1977; Atterbury 1978). However, antibiotics, and especially neomycin, are associated with many adverse side effects such as nerve deafness, renal toxicity and serious disturbance of the colonic microbiota (Conn 1977). An alternative treatment using lactulose was introduced by Bircher *et al*. in 1966, which inhibited the production and absorption of ammonia. Although, lactulose had fewer adverse side effects than neomycin, it was not well tolerated by all patients at the recommended effective dose, due to the overtly sweet taste and unfavourable gastrointestinal reactions including flatulence, vomiting and diarrhoea.

Importantly, lactitol was equally effective when compared with lactulose, and was found to be better tolerated with significantly fewer side effects (Blanc *et al*. 1992). *In vivo* studies have been performed to investigate how lactitol affects ammonia levels and to determine its effectiveness as an alternative HE treatment. Watanabe *et al*. (1995) examined the effect of lactitol on blood ammonia concentrations in experimental hyperammonia models such as portacaval-shunted rats. It was observed that lactitol significantly lowered the blood ammonia levels by inhibiting both its production and absorption, through reducing intestinal pH and thereby creating a hostile environment for survival of urease-producing members of the intestinal microbiota and shortening the residence time of intestinal tract contents. Moreover, Masini *et al*. (1999) performed a study with 8 cirrhotic males, who were given glutamine to increase their ammonia levels and subsequently received 20 g of lactitol 3 times a day for a total of 5 days. Results showed that lactitol significantly reduced the elevation of blood ammonia. The small intestinal ammonia generation was affected, as glutamine is mainly absorbed in the jejunum. Another human intervention including 28 cirrhotic patients was performed by Salerno *et al*. (1994), where lactitol was introduced and compared with other therapies. It was shown that lactitol not only decreased ammonia levels but also had a significant effect on the encephalopathy index. Lactitol's efficacy in the treatment of HE in comparison with lactulose has also been tested in a variety of different studies. Camma *et al*. (1993) compared the effects of lactitol on chronic HE with lactulose, and it was observed that the effectiveness was similar to that of lactulose, albeit with fewer side effects. These findings are in line with what had been shown previously (Morgan *et al*. 1987; Morgan and Hawley 1987). Despite these encouraging results, there are still a number of studies and reviews (Riggio *et al*. 2005; Als-Nielsen *et al*. 2004; Mas *et al*. 2003; Loguercio *et al*. 2003) that suggest that antibiotic treatment is superior to lactulose or lactitol administration in improving HE. This contradiction may be explained by differences in methodologies employed in the human trials performed. Furthermore, it may depend on the degree of severity of HE as lactose derivatives will be preferred where fewer side effects are essential to the patient (Dhiman and Chawla 2004).

Table 2 summarizes randomized trials with lactitol in the treatment of HE compared to lactulose or antibiotics.

3.4 Effects on bone health

Prebiotics have been suggested to improve calcium absorption. The general mechanism is thought to be via colonic fermentation of the prebiotic, which results in a reduction of the luminal pH and an improved solubility and thereby passive absorption of calcium. Although lactitol has been observed, *ex vivo*, to improve calcium absorption in the small intestine of rats through a direct effect on the intestinal epithelium (Mineo *et al*. 2002), human studies were not able to show any effect of the consumption of 15 g/day lactitol on the absorption of calcium (Griessen *et al*. 1989).

4. New health targets for lactitol

4.1 Effects on postprandial triglycerides and satiety

Consumption of lactitol-containing chocolate was found to attenuate the rise in serum glucose, insulin and triglycerides in humans compared to consumption of regular, sugar-containing chocolate (Shimomura *et al*. 2005).

Animal studies suggest that lactitol increased the transit of fat through the intestine. Interestingly, the inclusion of lactitol in the diet of caecectomized rats led to a smaller deposition of body fat (Islam *et al*. 2004). In this study, no difference in feed intake was noted between animals fed lactitol and the control animals. However, in another rat study reduced feed intake was observed, which was accompanied by an increase in plasma peptide YY (PYY) (Gee and Johnson 2005). PYY is thought to play a

Table 2. Summary of randomized trials with lactitol in the treatment of hepatic encephalopathy (HE) compared to lactulose or antibiotics

Studies	Study design	Quality[1]	Subjects	Type of HE	Experimental/ control intervention	Outcome
Mas *et al*. 2003	Parallel	High	103	Acute	Lactitol + placebo/ rifaximin + placebo	Greater effect on PSE index[4] with rifaximin than with lactitol
Loguercio *et al*. 2003	Parallel	Low	27	Chronic	Lactitol + placebo/ rifaximin + placebo	Rifaximin in combination with lactitol represents an effective and faster treatment of chronic HE than lactitol
Trovato *et al*. 1995	Crossover	NC[2]	10	Chronic	Lactitol/no treatment	Improvement of HE status and decrease in blood ammonia with lactitol
Blanc *et al*. 1992 (4 studies)	Parallel	NC	48	Chronic	Lactitol/lactulose	All studies showed clinical effectiveness of lactitol was similar to lactulose but with lower flatulence
Riggio *et al*. 1990	Crossover	NC	14	Chronic	Lactitol/lactulose	Lactitol was as effective in treatment of HE as lactulose with fewer side effects
Riggio *et al*. 1989	Parallel	NC	31	PSE[3]	Lactitol/lactulose	Lactitol and lactulose had similar effects on prevention of HE episodes, lactitol better tolerated
Heredia *et al*. 1988	Crossover	NC	25	Chronic	Lactitol/lactulose	Lactitol and lactulose had similar positive clinical effects but lactitol was significantly better tolerated
Morgan *et al*. 1987	Parallel	NC	25	Acute	Lactitol/lactulose	Significant clinical improvement with both lactitol and lactulose, patients with lactitol responded quicker
Uribe *et al*. 1987	Parallel	Low	45	Acute	Lactitol + lactose/ water enemas	Significant improvement in PSE index after lactitol + lactose enemas
Heredia *et al*. 1987	Parallel	NC	40	Acute	Lactitol/lactulose	Lactitol and lactulose had similar positive clinical effects
Morgan *et al*. 1987	Crossover	NC	9	Chronic	Lactitol/lactulose	Lactitol and lactulose had similar positive clinical effects but lactitol had fewer side effects than lactulose

[1]Quality of a trial is classified by Als-Nielsen *et al*. (2004). High-quality trials are classified as those with adequate concealment and blinding.
[2]NC: non-classified trials by Als-Nielsen *et al*. (2004).
[3]PSE: postal-systemic encephalopathy.
[4]PSE index is determined by electroencephalogram, blood ammonia levels.

role in satiety signalling. In humans, the effects on satiety were not observed in the short-term, but the postprandial reduction in PYY was attenuated (Gee and Johnson 2005).

4.2 Effects on Trypanosoma cruzi *infection*

Many pathogenic microbes protect themselves from the host immune system and other adverse environmental conditions by forming a protective layer of exopolysaccharides. *Trypanosoma cruzi*, the causative agent of Chagas disease, transfers host sialic acid to β-linked galactose. Of the tested lactose derivatives, lactitol in particular was found to function as a competitor and to impair the exopolysaccharide formation of *T. cruzi*, thereby reducing the ability of the agent to further infect cultured cells (Agustí *et al*. 2004). To what extent these findings can be translated to the *in vivo* situation will be the subject of an exciting new area of research into the benefits of lactitol.

5. Conclusion

Lactitol is resistant to digestion and is fermented by gastrointestinal microbiota. The scientific evidence for the selective increase in lactobacilli and bifidobacteria following lactitol consumption looks promising, but is mainly derived from culture-based methods and requires further substantiation using molecular techniques. Additional research is needed to confirm lactitol's status as a prebiotic, particularly in relation to its efficacy at lower dosages.

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