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Review

Lactose and lactose derivatives as bioactive ingredients in human nutrition

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Abstract

Lactose is a unique disaccharide, which occurs exclusively in the milk of mammals. It has wide applications as a food ingredient and in pharmaceutical preparations. Discouragement of milk consumption, because of the existence of lactase deficiency in the majority of the world population, is unjustified, because even in the complete absence of this enzyme, nutritionally significant volumes of milk, corresponding to about 11 g of lactose per day, are well tolerated, if the milk intake is distributed over the day and combined with meals. Lactose has interesting nutritional properties. These include a relatively low sweetening power, calorific value and glycemic index. It also has dietary fibre-like and prebiotic properties and enhances the absorption of calcium and magnesium. Its cariogenicity is low compared with that of other simple carbohydrates. The lactose derivatives lactulose, lactitol and galacto-oligosaccharides find applications in foods and pharmaceutical preparations as prebiotics to promote gut health. Similarly to non-digested lactose, these compounds enhance the intestinal absorption of calcium and magnesium. Other lactose-derived compounds (e.g., tagatose and lactobionic acid) have potential applications as bioactive ingredient in foods.

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1. Introduction

Lactose (β-D-galactosyl-D-glucose; Fig. 1) is a unique disaccharide, in the sense that it occurs exclusively in the milk of mammals. From a teleological point of view, one might speculate that lactose ingestion will result in specific benefits for the suckling animal, beyond just being a source of energy. Lactose can easily be separated from milk or whey in more or less pure form and used as an ingredient in feed, food and pharmaceutical preparations. Lactose can also serve as a precursor of lactose-derived bioactive substances, which, like lactose itself, have applications in food and pharma. It is the aim of this paper to review current knowledge about the nutritional significance of lactose and its derivatives.

2. Lactose in milk and whey

The lactose concentration of milk from various animals is given in Table 1. Human milk has the highest content (approximately 7 g per 100 mL) and in cows' milk the concentration is substantially lower (4.6 g per 100 mL). In fermented cows' milk, e.g., yoghurt or buttermilk, the lactose content is about one-third lower than that in milk, because of the conversion of lactose by lactic acid bacteria. During cheese production almost all the lactose in milk is transferred into whey and therefore hard cheeses contain virtually no lactose. Remaining lactose is fully converted into lactic acid by the starter bacteria. The lactose content of cheese whey is approximately 4.8 g per 100 mL. Lactose is an important product of the whey processing industry.

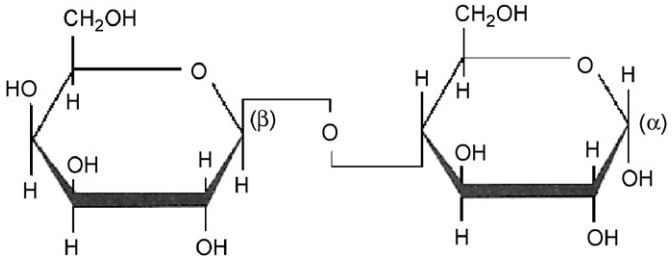

Fig. 1. Alpha lactose (4-*O*-β-D-galactosylpyranosyl-α-D-glucose).

Table 1
Lactose content (%) in the milk of various mammals[a]

Human	7.0
Horse	6.9
Donkey	6.1
Llama	5.6
Zebra	5.3
Pig	5.0
Goat	4.7
Cow	4.6
Dog	3.8
Mouse	3.0
Dolphin	1.1
Seal	0.1

[a]From Schaafsma (2002).

The global demand for lactose has grown appreciably over the last 10 years to amount to approximately 500,000 t per annum (Voorbergen & Zwanenberg, 2002). It is used in feed and food (baby food, cakes, biscuits, chocolate, sugar confectionary, soups and sauces) and has substantial applications in the pharmaceutical industry as an excipient of tablets and, in finely granulated form, as a carrier of medicines in dry powder inhalation preparations.

3. Digestion and metabolism of lactose

Lactose exists in two isomeric forms, alpha and beta, differing in configuration by the hydroxyl group in position 1 of the glucose moiety. In aqueous solution alpha and beta lactose exist in equilibrium with approximately 63% of the lactose in the beta form at room temperature. In suckling mammals, lactose from the milk is largely broken down into its monosaccharide components, galactose and glucose, mainly by a β-galactosidase (lactase), which is bound to the mucosal membrane of the small intestine and which prefers the beta form of lactose. After splitting, the monosaccharides are actively absorbed and transported to the liver via the portal vein. Both sugars share the same absorption pathway and they are the only sugars that are actively absorbed. The preference of the lactase for the beta isomeric form of lactose causes a shift in the equilibrium between alpha lactose and beta lactose in favour of the latter (mutarotation). After absorption, galactose is converted into glucose in the liver via the so-called Leloir pathway (Fig. 2). Deficiency in one or more of the enzymes involved in lactose digestion and galactose metabolism can lead to metabolic disturbances known as lactose intolerance and galactosemia. When the conversion of galactose into glucose in the liver is blocked by deficiency in one or more of the enzymes involved in the Leloir pathway (inborn errors of metabolism), galactosemia develops. Complete elimination of lactose from the diet is the only possible treatment. If untreated, fatal liver damage and blindness will follow. The blindness results from osmotic effects in the lens of the eye, caused by accumulation of galactitol. Galactitol is formed from high levels of circulating galactose by an NADPH-dependent reductase that is present in neural tissue and in the lens of the eye. Normal circulating levels of galactose do not cause pathological effects. Lactose intolerance may result from the incomplete intestinal digestion of lactose and bacterial

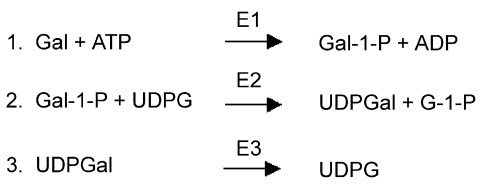

Fig. 2. Metabolic conversion of galactose into glucose in the liver according to the Leloir pathway. The conversion requires three enzymes: galactokinase (E1), galactose-1-phosphate uridyltransferase (E2) and uridine-diphospho-galactose-4-epimerase (E3).

fermentation of the sugar in the colon, causing bloating, cramps, gas formation (flatulence) and even diarrhoea. The main cause is the so-called primary adult lactase non-persistence.

4. Primary adult lactase non-persistence and lactose intolerance

Malabsorption of lactose, resulting from the combination of lactase deficiency and lactose intake levels of more than 10–15 g per day, and giving symptoms of lactose intolerance have often led to the rejection of milk as a food and to discouragement of milk in food aid programs for the third world. This was unjustified, because it is now well accepted that lactase deficient subjects can consume without side effects amounts of lactose up to 11 g per day (one to two portions of milk), when this amount is distributed over the day and ingested with meals (Heyman, 2006; McBean & Miller, 1998), as described in more detail below.

At birth mammals possess in their small intestine, particularly in the jejeunum, two β-galactosidases (lactases), one bound to the mucosal membrane and one intracellular in lysosomes and cytoplasm of epithelial cells. The latter enzyme does not play an important role in the breakdown of lactose. The brush border lactase is present in the foetus from the second half of pregnancy and reaches its maximum activity very shortly after birth. Normally in mammals, thus also in humans, the lactase activity decreases after the weaning period with varying rates at varying ages. Remarkably, humans belonging to the West European Caucasian race and to some isolated Indian and African tribes (in total approximately 20% of the world population) maintain throughout life a high lactase activity called lactase persistence. The normal decrease of the lactase activity is genetically programmed and is not caused by stopping lactose ingestion after the weaning period. According to Lewinsky et al. (2005), the persistence of the lactase activity at adult age is caused by a T/C polymorphism at position 13,910 upstream the lactase gene. Nuclear factors bind more strongly to the T-variant (resulting in lactase persistence) than to the C-variant (resulting in lactase non-persistence, also called adult primary lactase deficiency). Recently (Tishkoff et al., 2006), three other mutations in the gene encoding lactase, associated with lactase persistence, were detected in Eastern Africa: G/C 14,010, T/G 13,915 and C/G 13,907. The geographical distribution of lactase persistence (Table 2) parallels the parts of the world where milk was an essential supplement to the diet, providing a strong selective advantage (Simoons, 1981; Tishkoff et al., 2006).

The terminology used for lactase deficiency and lactose intolerance has changed over time. In fact the following terms have been described in the literature (Dahlqvist, 1984; Heyman, 2006):

- *Lactose intolerance*: gastrointestinal symptoms (cramps, bloating, flatulence, diarrhoea) upon the ingestion of lactose. The amount of lactose that will cause symptoms varies from individual to individual, depending on the amount of lactose consumed, the degree of lactase deficiency and the form of food substance in which lactose is ingested.
- *Lactose malabsorption*: exceeding of the capacity of the small intestine to digest ingested lactose.
- *Primary adult lactase non-persistence*, *hypolactasia or primary adult lactase deficiency*: genetically programmed reduction of lactase activity after the weaning period.
- *Secondary lactase deficiency*: lactase deficiency as a consequence of intestinal disease, like an infection, celiac disease or Crohn's disease. It is generally temporary.
- *Congenital lactose intolerance*: sporadic disease (inborn error of metabolism) with abnormal permeability of the gastric mucosa and with intact absorption of lactose, causing failure to thrive, lactosuria, dehydration and acidosis in early life, which is a fatal disease if untreated.
- *Congenital lactase deficiency*: rare disease (inborn error of metabolism) occurring in infants.
- *Milk intolerance*: clinical symptoms of lactose intolerance or of allergic reactions on milk protein upon the ingestion of milk.

Table 2
Prevalence of adult primary lactase deficiency (percentage of adult population)[a]

France	30–40
Germany	15–20
Russia	20–30
Finland	15–20
Sweden	<5
Greece	70–80
Ethiopia	80–90
Nigeria	80–90
Nomadic Fulani	<10
Sudan	60–65
China	90–100
Japan	95–100
India	60–65
Jordan	20–25
Israel	70–80
Israel, Jemenites	40–50
North America, Whites	10–15
North America, Blacks	65–70
North America, Indians	85–90
Mexico	50–60
Uruguay	60–65
South America, Indians	90–100
Greenland eskimos	85–90
Australia, Aborigines	80–85

[a]Data taken from Alm (2002).

Nowadays the preferred term for lactase deficiency is primary adult lactase non-persistence. This non-persistence is not the same as lactose intolerance, because lactose intolerance refers to the outcome of a test and does not implicate that lactose should be eliminated from the diet. Diagnosis of lactose intolerance was done in the past on the basis of a classical lactose intolerance test. Subjects

ingested on an empty stomach 2 g of lactose per kg of body weight (up to a maximum of 50 g) in a water solution. A maximum increase of the blood glucose level of less than 20 mg per 100 mL and/or appearance of clinical symptoms indicated lactose intolerance. Less invasive and more popular is the breath hydrogen test. Hydrogen expiration of more than 20 ppm, following the ingestion of lactose (2 g kg^{-1} body weight, maximum 25 g) after fasting overnight, is consistent with lactose malabsorption. The diagnosis of lactose intolerance has often resulted in the recommendation to avoid lactose in the diet. Nowadays this advice is no longer considered appropriate, since it is widely accepted that the lactose intolerance test is not representing real life situations (Scrimshaw & Murray, 1988) and that lactase non-persistent subjects can consume without adverse effects up to 11 g of lactose, if the amount is distributed over the day and combined with solid meals (Martini & Savaiano, 1988; Solomons, Guerrero, & Torun, 1985; Zaal, 1977). Such amounts of lactose in milk represent a milk intake of 200–250 mL per day, which is a nutritionally significant volume in the human diet. Combination with meals improves lactose digestion and reduces the rate of ileal delivery to the colon, so that lactose fermentation and gas formation by the intestinal microflora is relatively slow (Fig. 3). Intake of lactose with non-pasteurized yoghurt is tolerated well by lactase non-persistent subjects, because of the contribution of the microbial lactase from the yoghurt culture to lactose digestion in the small intestine (Kolars, Levitt, Aouji, & Savaiano, 1984; Schaafsma, 1993) and the slower release of lactose from the stomach after a yoghurt meal than after ingestion of milk (Labayen et al., 2001).

Adaptation of the metabolic activity of the intestinal microflora to lactose ingestion has also been reported to contribute to lactose tolerance in lactase non-persistent subjects (Dahlqvist, 1984). Recently, the American Academy of Pediatrics Committee on Nutrition (Heyman, 2006) concluded that treatment of lactose intolerance by elimination of milk and other dairy products is not usually necessary and the US National Medical Association (Wooten & Price, 2004) recommended that black people consume three to four servings per day of low-fat milk, cheese and/or yoghurt.

5. Nutritional benefits of lactose

5.1. Sweetness and cariogenicity

The sweetness of lactose, relative to that of other simple sugars, is illustrated in Table 3. It is only 20–30% of that of sucrose and this is one of the reasons that lactose is a suitable carbohydrate in infant formulas. It is thought that a high sweetness could encourage appetite and overeating and lead to the development of a taste preference for sweet foods in later life. Fermentation of sugars in the oral cavity leads to the formation of organic acids, which may erode the enamel of the teeth and cause caries. Of the different simple sugars, sucrose appeared to be the most cariogenic, not just because it is easily fermented, but also because *Streptococcus mutans*, a dominant species in the oral flora, forms sticky dextrans from sucrose that contribute to tooth plaque formation. Glucose and maltose may be marginally less cariogenic than sucrose. Lactose and galactose appeared to be less cariogenic than other simple sugars

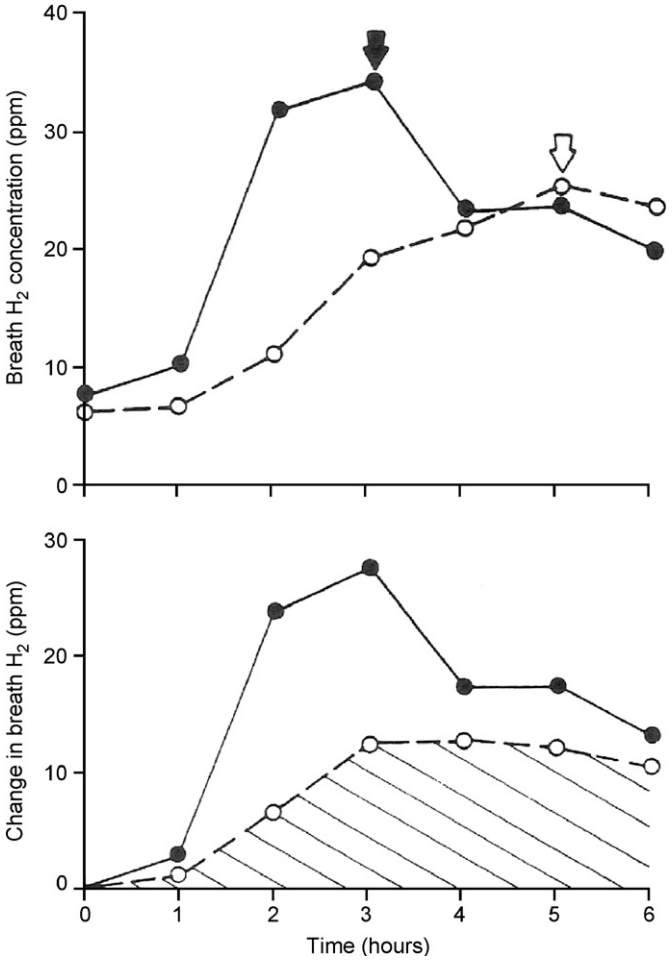

Fig. 3. Upper panel: postprandial breath hydrogen concentration in 13 lactose intolerant subjects after the ingestion of 360 mL milk, containing 18 g lactose (black dots) or this volume of milk with a meal (open dots); arrows indicate the shift in time of the peak value caused by the meal. Lower panel: changes of postprandial breath hydrogen concentrations of the same experiment, but values corrected for the effect of the meal as such. Taken from Solomons et al. (1985).

Table 3
Sweetness of some sugars (relative to sucrose = 1)[a]

Sucrose	1
Glucose	0.6–0.7
Maltose	0.4–0.5
Sorbose	0.4
Xylose	0.6–0.7
Lactose	0.2–0.4
Fructose	1.3
Galactose	0.5–0.7

[a]From Schaafsma (2002).

(Department of Health, 1989), probably because the acid formation from these sugars in the oral cavity is relatively slow; moreover, the buffering capacity of milk reduces the cariogenicity of lactose (British Nutrition Foundation, 1987).

5.2. Glycemic index

Long-standing elevated levels of blood glucose increase the risk of cardiovascular diseases. Dietary carbohydrates differ in their effect on the blood glucose concentration and in this regard the glycemic index (GI) is relevant. The GI was defined by Food and Agriculture Organization/World Health Organization (FAO/WHO) (FAO/WHO Expert Consultation, 1997) as the incremental area under the blood glucose response curve of a 50 g carbohydrate portion of a test food expressed as the response to the same amount of carbohydrate from a standard food taken by the same subject. The effect of dietary lactose, as compared with other carbohydrates, on the blood glucose level has been investigated in a variety of studies related to the measurement of the GI. From a simple comparison of the GIs of different sugars and carbohydrate-containing foods (Table 4), it can be concluded that the GI of lactose is relatively small. Therefore, lactose can have benefits for persons who are sensitive to get hyperglycemia, e.g., diabetic patients and subjects with a decreased sensitivity to insulin. The relatively low GI of lactose is attributable to several factors. Firstly, lactose is often incompletely digested in the small intestine. Secondly, the galactose monosaccharide component has to be converted into glucose in the liver before it can contribute to the blood glucose level.

5.3. Calorific value

When lactose is completely digested in the small intestine it will provide, like other digestible carbohydrates, 4 kcal g^{-1}. However, as described above, in many subjects lactose is not (or only partly) digested in the small intestine. Bacterial fermentation of lactose in the colon will yield approximately 2 kcal g^{-1}. This energy results from the colonic absorption of volatile fatty acids that are formed by fermentation (Van Dokkum & Schaafsma, 1998). Therefore, the calorific value of lactose varies between 2 and 4 kcal g^{-1}, depending on the ingested dose, the combination with meals (solid or liquid) and the intestinal lactase activity.

Table 4
The glycemic index of selected sugars and foods[a]

Glucose (reference)	100
Fructose	19
Lactose	46
Sucrose	68
Boiled white rice	83
Maltose	105
Baked potato	85
French fries	75
French baquette	95

[a]From Foster-Powell, Holt, and Brand Miller (2002), international table of glycemic index (GI) and glycemic load (GL) values.

5.4. Dietary fibre-like activities and prebiotic effects

According to the Health Council of The Netherlands (2006), dietary fibre is a collective name for food components that are not digested in the small intestine of humans and that, according to their chemical characteristics, can be described as carbohydrates, carbohydrate analogues, lignin and lignin-like compounds. Undigested lactose fits well into this definition. That lactose acts as a dietary fibre was recognized by Schulze and Zunft (1991a, 1991b) and Zunft and Schulze (1991). Non-digested lactose will increase the water content of stools and reduce transit time in constipated subjects. More recently prebiotic effects of lactose received attention (Schaafsma, 2002; Szilagyi, 2004). Lactose that escapes digestion will serve a substrate for the intestinal flora and enhance saccharolytic activities and favour the growth of bifidobacteria and lactobacilli. Saccharolytic activities are known to be associated with the formation of volatile fatty acids, lowering of the luminal pH and decreased formation of the toxic secondary bile acids. Stimulation of saccharolytic activities will depress microbial proteolytic activities, which are known to be associated with the formation of toxic bacterial metabolites, like ammonia, hydrogen disulphide, phenolic compounds and biogenic amines (Salminen et al., 1998). Non-digestible lactose derivatives, including lactulose, lactitol, lactobionic acid, galacto-oligosaccharides (GOS) and tagatose, are known to have similar effects as lactose that has escaped digestion.

5.5. Effects on mineral absorption

Carbohydrates that escape digestion in the ileum, and that are fermented in the colon, have been shown to enhance the colonic absorption of minerals, particularly calcium and magnesium (Abrams, Griffin, & Davila, 2002; Scholz-Ahrens, Schaafsma, van den Heuvel, & Schrezenmeir, 2001) Thus, paradoxically, malabsorption of lactose enhances mineral absorption. This explains why lactose did not increase calcium absorption in lactase persistent adults (Zittermann et al., 2000). The positive effect on mineral absorption is attributable to increased mineral solubility and/or enhanced osmotic pressure following fermentation. Both changes enhance the paracellular (passive) transport of minerals across the epithelial wall (Schaafsma, 1997). Using a stable isotope technique, Abrams et al. (2002) showed that a lactose-containing infant formula caused a 10.3% higher calcium absorption compared with a lactose-free formula. Part of the lactose must have escaped small intestinal absorption to have this positive effect.

6. Adverse effects of lactose

As described above, malabsorption of lactose can cause signs of lactose intolerance. De Groot and Engel (1957) described detrimental effects of lactose in growth experiments with rats fed with diets containing 10–25% of lactose. These effects included growth retardation, loss of hair, diarrhoea, distention of the abdomen, decreased appetite and increased water consumption. These effects are now known to be not specific for lactose, and attributable to carbohydrate malabsorption, in the case of lactose caused by lactase deficiency in the postweaning rats.

Lactose ingestion in lactase persistent subjects has been implicated as a factor associated with an increased risk of ovarian cancer (Larsson, Bergkvist, & Wolk, 2004). However, two recent studies could not confirm such an effect. In one of these studies, The Netherlands Cohort Study on Diet and Cancer, 11.3 years of follow-up yielded 252 incident cases of ovarian cancer in 2216 subcohort members. No association was seen between dairy products consumption and ovarian cancer risk (Mommers, Schouten, Goldbohm, & van den Brand, 2006). In the other study (Kuokkanen et al., 2005) of genotype investigations in 327 Finnish, 303 Polish, 152 Swedish patients and 938 Finnish, 296 Polish and 97 Swedish healthy individuals, no association was found between lactase persistence and ovarian carcinoma.

7. Nutritional benefits of lactose derivatives

7.1. Lactulose and lactitol

Lactulose (β-D-galactosyl-D-fructose) and lactitol (β-D-galactosyl-sorbitol) are synthetic derivatives of lactose. They are widely used in the treatment of patients with hepatic encephalopathy (intoxication of the brain caused by the failure of the liver to convert ammonia into urea) and in patients with chronic constipation (Blanc et al., 1992; Clausen & Mortensen, 1997; Kitler et al., 1992; Salminen & Salminen, 1997). Both lactulose and lactitol are not digested in the small intestine and are fermented by the colonic flora. Due to their prebiotic effects, they reduce the formation of ammonia by the intestinal flora. Like all non-digestible and fermentable carbohydrates, lactulose and lactitol will enhance the intestinal absorption of calcium and magnesium (Ammann, Rizzoli, & Fleisch, 1988; Scholz-Ahrens et al., 2001; Van den Heuvel, Muijs, van Dokkum, & Schaafsma, 1999). Using a stable isotope technique, Van den Heuvel et al. (1999) found a dose-dependent increase of calcium absorption in postmenopausal women, following the ingestion of 5 or 10 g lactulose (Fig. 4). Lactulose is formed in small amounts from lactose during sterilization of milk. Ingestion of lactulose and lactitol provides about 2 kcal g^{-1}. This energy results from the colonic absorption of volatile fatty acids (mainly acetate, propionate and butyrate). Lactulose and lactitol do not cause tooth decay and their sweetness makes them suitable for application in a large variety of products, including chewing gum, confectionary and ice cream. At higher dose levels they may cause gastrointestinal side effects, comparable to those of lactose intolerance.

7.2. Galacto-oligosaccharides (GOS)

Galacto-oligosaccharides (GOS; gal-$(gal)_n$-glu) are produced from lactose by application of a galactosyl transferase. These oligosaccharides are resistant to digestive enzymes and act as prebiotics (Bouhnik et al., 1997). They are used as bifidogenic ingredients in infant formulas (Boehm et al., 2002; Moro et al., 2002). Their application in a variety of foods (infant formulas, confectionary, chewing gum, yoghurt, ice cream and bakery) is increasing. GOS have a sweet taste and a low energy value (approximately 2 kcal g^{-1}). Tolerance to GOS was investigated (Van Dokkum, 1995) in male young adults. It was found that an intake by adults of 15 g of GOS per day, distributed over three meals, was well tolerated and did not cause serious side effects.

7.3. Lactobionic acid

Lactobionic acid (β-D-galactosyl-gluconic acid) is produced by oxidation of lactose. It is a relatively new compound that has not yet found application in the European food market. The acid combines a sweet taste with pH-reducing effects. It has strong mineral-complexing properties, making it suitable for applications as a food ingredient. The acid is resistant to digestive enzymes and will be fermented by the intestinal flora, probably exerting prebiotic effects. Lactobionic acid appeared to interfere with the digestion of lactose, by competing with lactose for binding to the intestinal beta galactosidase. The energy value is estimated at 2 kcal g^{-1}. Tolerance of lactobionic acid was investigated in healthy adult subjects by TNO (Van Dokkum, Wezendonk, van Aken-Schneider, & Kistemaker, 1994). It was found that consumption of lactobionic acid shows clear signs of colonic fermentation, that amounts up to 24 g are rather well tolerated and that

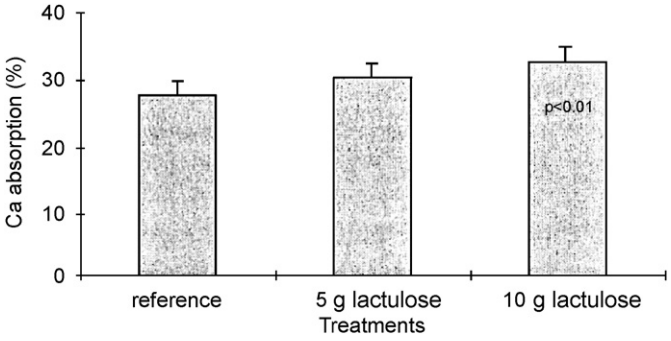

Fig. 4. Effect of lactulose (5 or 10 g per day) on true calcium absorption, as measured with stable calcium isotopes in postmenopausal women. Taken from Van den Heuvel et al. (1999).

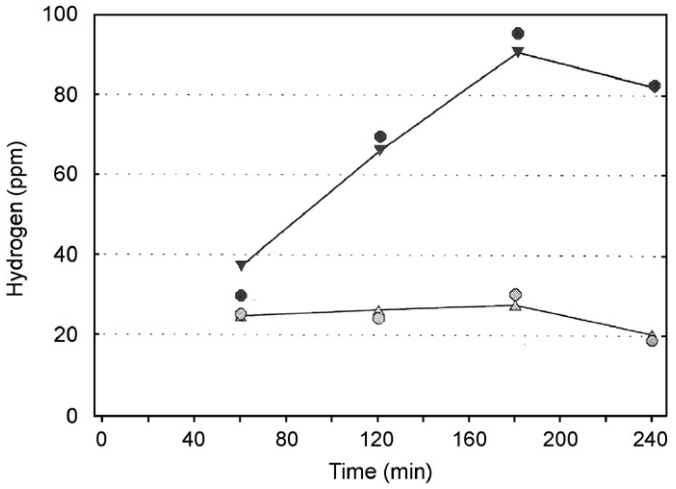

Fig. 5. Hydrogen concentration in expired air of eight lactose tolerant subjects after the intake of 40 g of lactose (lower line, grey symbols) and 40 g lactose plus 10 g lactobionic (upper line, black symbols). A cross-over design was used. Data taken from Van Dokkum et al. (1994).

the acid has a distinct negative influence on lactose digestion in lactase persistent subjects (Fig. 5). According to European food law, lactobionic acid will be viewed as a novel food. This requires assessment of safety before the compound can be marketed as a food ingredient.

7.4. Tagatose

Tagatose is also a relatively new compound. In 2005, it was approved as a food ingredient in the European Union, but its production was put on hold in April 2006, because of economy reasons (www.gaio-tagatose.com). Tagatose largely (80%) escapes digestion and is fermented in the colon where it exerts prebiotic effects, favouring the production of butyrate and the growth of lactic acid bacteria (Laerke, Jensen, & Hojsgaard, 2000; Levin, 2002; Venema, Vermunt, & Brink, 2005). As a low-calorie sweetener (approximately 2 kcal g^{-1}) and prebiotic, applications were foreseen in a large variety of products, including dairy, beverages, confectionary, bakery, health bars, chewing gum and dietary supplements.

8. Conclusion

Lactose and its derivatives appear to be valuable ingredients with a wide range of nutritional benefits, particularly in the field of gut health promotion. It is now widely accepted that lactose intolerance in lactase deficient populations should not be a reason to discourage milk consumption. In moderate doses, and distributed over meals, lactose may even act as a prebiotic in these populations.

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