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Lactose digestion and the implications on the gut microbiota

Lactose digestion in humans depends upon the activity of the enzyme lactase. In adults, lactose maldigestion is often present due to a physiological decline in lactase expression in late childhood. Lactose maldigestion can lead to symptoms of lactose intolerance due to the presence of undigested lactose in the colon and the products of its fermentation by gut bacteria. Adaptive changes in the colonic microbiota are associated with decreased lactose intolerance.

The digestion of lactose, a disaccharide that is present in abundance in mammalian milk, takes place at the brush border of the small intestine where the sugar is hydrolysed into galactose and glucose by a β -D-galactosidase enzyme, lactase (or lactase-phlorizin hydrolase). While at birth, lactase is usually produced at high concentrations, the activity of intestinal lactase in late childhood declines and, despite continued dietary intake of lactose, lactose digestion may ensue (primary hypolactasia). However, several highly conserved single nucleotide mutations in the promoter region of the lactase gene (LCT) (for example DNA variant C/T-13901) are associated with a continued lactase activity in adults (lactase persistence) [1]. The global prevalence of lactose maldigestion is estimated at 67% although this is highly variable by region with estimates from 4 to 98% across northern and southern European countries [2]. Diagnosis of lactose maldigestion can be performed using various clinical tests including genetic assessment of lactase persistence, direct and indirect assessments of lactase activity [3, 4]. While individuals with lactose maldigestion may be asymptomatic, lactose intolerance is diagnosed in the presence of gastrointestinal symptoms (such as bloating and diarrhoea). These symptoms may be attributed to osmotically active undigested lactose or may be caused by certain gases (such as H₂, CO₂ or CH₄) that are produced during fermentation of lactose by colonic bacteria.

Interactions between colonic bacteria and lactose

Despite the association between lactose fermentation in the colon and symptoms of lactose intolerance, an adaptive functional role of colonic bacteria in the metabolism of lactose for individuals with lactose maldigestion has been described [5]. Indeed such adaptation underpins the dietary guidelines that permit a continued exposure to lactose at lower quantities (according to gastrointestinal tolerance) [6] and may explain in part why many individuals with lactose maldigestion do not experience gastrointestinal symptoms indicative of lactose intolerance after lactose intake. Colonic adaptation to lactose presence was characterised by Hertzler and Savaiano in 1996 as an increase in faecal content of β -galactosidase, lower systemic production of hydrogen, and improved gastrointestinal symptoms after lactose intake [5]. These effects were hypothesised by the authors to reflect a shift in the microbiota composition to favour bacteria able to express β -galactosidase. Various in vivo and in vitro studies have since confirmed that lactose administration to the colon does indeed lead to a shift in the microbial populations, in particular with increases in bifidobacteria [7–10] and lactobacilli populations [9, 10]. In a four-stage semi-continuous system that modelled regions of the colon, Makivuokko et al. observed that the microbial changes in response to lactose exposure were accompanied by an increase of short chain fatty acids and consequently a lowered pH, an environmental change that was proposed as one mechanism driving the transient change in bacterial populations. The specificity of these microbial changes to maldiges-

tion of lactose has been confirmed in two recent intervention studies that demonstrated that the microbiota composition was modulated differentially depending on whether subjects could digest lactose [7, 8]. Notably, milk supplementation was associated with significant increases in actinobacteria, *Bifidobacterium*, *Anaerostipes*, and *Blautia*, and a significant decrease in *Megamonas* but these associations were only observed in the lactose maldigesters group [8]. There are several lines of evidence including the bifidogenic effects described here that justify the suggestion that lactose, in populations with lactose maldigestion, could be considered a prebiotic (a substrate that is “selectively utilized by host microorganisms to confer a health benefit” [11]), but this claim is not yet substantiated. The potential for additional negative health consequences of continued exposure to lactose in those with lactose maldigestion was discussed in a controversial article on the systemic consequences of lactose intolerance [12]; however, the mechanistic evidence to associate such symptoms with lactose intake is currently lacking.

Dietary interventions in lactose intolerance and the gut microbiota

The total exclusion of lactose from the diet of individuals with lactose maldigestion is generally not advised [6], however, it may be considered as part of a wider dietary intervention that eliminates foods that are associated with intolerances. Interestingly, one such intervention led to significant changes in the gut microbiota, including decreases in bifidobacteria [13]. In line with dietary guidelines to reduce quantities of lactose ingested in the diet, the capacity of certain bacteria to

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metabolise lactose can be exploited *ex vivo* in dairy fermentation. In particular, yoghurt which is fermented by *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* has a lower lactose content and has been confirmed by EFSA as a product which can improve lactose digestion for individuals with lactose maldigestion [14]. This effect may be mediated in part by the activity of β -galactosidase produced by yoghurt cultures in the small intestine [15]. For these beneficial qualities, yoghurt cultures are recognised as probiotics, live microorganisms that promote the health of the host when administered in adequate quantities [16]. While other probiotic strains have shown some promise for improving lactose tolerance (particularly those strains with β -galactosidase activity) [17], no other health claims have been substantiated by EFSA to date.

The concept of manipulating the microbiota composition to improve lactose tolerance has also been explored with prebiotic supplementation. In particular, a recent study showed that a prebiotic formulation of short-chain galacto-oligosaccharides could induce

significant changes of the microbiota composition (with relative increases in *Bifidobacterium*, *Faecalibacterium* and *Lactobacillus*) that were accompanied by improved clinical tolerance of lactose [18]. The same prebiotic is currently being investigated by phase 3 clinical trials for its clinical use in lactose intolerance (ClinicalTrials.gov ID: NCT03597516).

Conclusions

The gut microbiota is increasingly recognised as playing a role in the modulation of various states of health and disease [19]. The aforementioned dietary strategies that may be used to manage lactose maldigestion (i.e. adaptation of lactose intake, and use of preprobiotics) may lead to a modulation of the microbiota; however, the impact of changing the microbiota of populations with lactose maldigestion on health outcomes is unclear. Further investigation in this field is warranted to help better elucidate associations between diet, disease and an intermediary role of the microbiota.

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Laktoseverdauung und die Auswirkungen auf die Darmflora

Die Laktoseverdauung beim Menschen ist von der Aktivität des Enzyms Laktase abhängig. Bei Erwachsenen liegt häufig eine Laktose-Maldigestion aufgrund einer physiologischen Abnahme der Laktase-Expression in der späten Kindheit vor. Eine derartige Störung der Laktoseverdauung kann aufgrund von im Darm vorhandener, unverdauter Laktose und den Produkten ihrer Fermentierung durch Darmbakterien Symptome einer Laktoseunverträglichkeit hervorrufen. Adaptive Veränderungen der Darmflora werden mit einer herabgesetzten Laktoseintoleranz assoziiert. Bakterien können über ihre Rolle bei der Laktoseverdauung im Darm hinaus auch in Milchprodukten zur «Vorverdauung» der Laktose eingesetzt werden und so die Unverträglichkeitssymptome verringern. Andere ernährungs-basierte Ansätze wie beispielsweise Präbiotika und Probiotika wurden auf ihre Fähigkeit zur Modulation der Darmflora und der damit verbundenen verbesserten Laktoseverdauung hin untersucht. Die Vorzüge einer solchen Modulation der Darmflora als Lösung für die Laktose-Maldigestion liegen zwar auf der Hand, allerdings müssen die Auswirkungen derartiger Strategien auf die Gesundheit noch untersucht werden.

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