

# Lactose digestion in humans: intestinal lactase appears to be constitutive whereas the colonic microbiome is adaptable

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## ABSTRACT

Globally, ~70% of adults are deficient in intestinal lactase, the enzyme required for the digestion of lactose. In these individuals, the consumption of lactose-containing milk and dairy products can lead to the development of various gastrointestinal (GI) symptoms. The primary solution to lactose intolerance is withdrawing lactose from the diet either by eliminating dairy products altogether or substituting lactose-free alternatives. However, studies have shown that certain individuals erroneously attribute their GI symptoms to lactose and thus prefer to consume lactose-free products. This has raised the question whether consuming lactose-free products reduces an individual's ability to absorb dietary lactose and if lactose-absorbers should thus avoid these products. This review summarizes the current knowledge regarding the acclimatization of lactose processing in humans. Human studies that have attempted to induce intestinal lactase expression with different lactose feeding protocols have consistently shown lack of enzyme induction. Similarly, withdrawing lactose from the diet does not reduce intestinal lactase expression. Evidence from cross-sectional studies shows that milk or dairy consumption is a poor indicator of lactase status, corroborating the results of intervention studies. However, in lactase-deficient individuals, lactose feeding supports the growth of lactose-digesting bacteria in the colon, which enhances colonic lactose processing and possibly results in the reduction of intolerance symptoms. This process is referred to as colonic adaptation. In conclusion, endogenous lactase expression does not depend on the presence of dietary lactose, but in susceptible individuals, dietary lactose might improve intolerance symptoms via colonic adaptation. For these individuals, lactose withdrawal results in the loss of colonic adaptation, which might lower the threshold for intolerance symptoms if lactose is reintroduced into the diet. *Am J Clin Nutr* 2019;110:273–279.

**Keywords:** lactose, lactase, lactase-phlorizin hydrolase, colonic adaptation, lactose intolerance, dietitians, nutritionists

## Introduction

In mammalian milk, the main carbohydrate and energy source is lactose. Lactose is a disaccharide consisting of 2

monosaccharides, glucose and galactose, linked together via a  $\beta$ -1 $\rightarrow$ 4 bond. Hydrolysis of this bond requires a specific enzyme called lactase which digests lactose to its components allowing the uptake of glucose and galactose from the intestine. In most mammals, intestinal lactase activity is high at birth but starts to progressively decline after weaning, eventually curtailing the ability to digest dietary lactose (1, 2). However, in some humans, a genetic trait enables intestinal lactase activity to persist into adulthood. Globally, ~30% of the world's population are lactase persistent as adults but the prevalence of lactase persistence varies between populations and ethnicities (3). Traditionally, cultures that have relied on pastoralism and dairy products in the past exhibit higher prevalence of lactase persistence than populations with little dairy consumption. For example, in Southeast Asia >90% are lactase deficient as adults, whereas in Scandinavia the prevalence of lactase deficiency is only ~10% (3). The now generally accepted culture-historical theory states that the lactase-persistent phenotype emerged as a result of positive selection due to a nutritional advantage conferred by the continued ability to consume milk and dairy products (2–5).

Today, over 6 billion people regularly consume milk and dairy products, and the per-capita consumption has nearly doubled in developing countries since the 1960s (6). Nutritionally, milk and dairy products are an important source of energy, proteins, fats, and nutrients such as calcium and vitamin D (2). However, upon consuming these products, some lactase-deficient individuals may experience various gastrointestinal (GI) symptoms, such as bloating, diarrhea, and abdominal pain, due to a condition called lactose intolerance. The primary solution to lactose intolerance

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Abbreviations used: GI, gastrointestinal; LPH, lactase-phlorizin hydrolase; *LCT*, lactase gene; LTT, lactose tolerance test.

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is to avoid lactose-containing dairy products altogether or to replace them with lactose-free alternatives (2). The dairy industry has responded to this need by developing several lactose-free products which are now readily available to consumers. In addition, cultural changes, such as the increased popularity of veganism and the globalization of the food industry, have also led to the introduction of novel lactose- and dairy-free products. Although an obvious need for these products exists, their increased availability has perhaps fueled some misconceptions about lactase deficiency and lactose intolerance. Firstly, lactase deficiency itself does not indicate lactose intolerance; many lactose-malabsorbers can tolerate certain amounts of dietary lactose without any symptoms (7). Secondly, some individuals who claim to be lactose intolerant fail to distinguish lactose from placebo in controlled settings (8). These findings suggest that certain people attribute their GI symptoms erroneously to lactose and thus opt to consume lactose-free products. This has subsequently raised the question whether consuming lactose-free products reduces an individual's ability to absorb dietary lactose and if lactose-absorbers should thus avoid these products.

The aim of this review was to evaluate the current evidence regarding the acclimatization of lactose processing in humans. An extensive literature search was undertaken of the PubMed and Scopus databases for the terms "lactase/lactose adaptation," and the reference lists of relevant review articles were also examined. This review included human studies measuring lactose absorption after periods of lactose or lactose-free diet consumption.

## Mechanisms of Lactose Absorption

Lactase-phlorizin hydrolase (LPH), or simply lactase, belongs to a group of intestinal disaccharidases located on the brush border of the small intestine. Spatially, the abundance of LPH is highest in the proximal part of the jejunum and progressively declines towards the ileum (1, 2). LPH contains 2 distinct enzymatically active sites: the  $\beta$ -galactosidase site (EC 3.2.1.23) and the glycosylceramidase site (EC 3.2.1.62). The  $\beta$ -galactosidase site forms the lactase domain which hydrolyzes lactose to glucose and galactose, whereas the phlorizin hydrolase activity located on the glycosylceramidase site cleaves phlorizin and several dietary glycolipids (2, 5). Despite the presence of this latter activity, lactose is the most significant nutritional substrate of LPH.

The expression of intestinal lactase is under developmental regulation. In humans, intestinal lactase activity starts to increase during the third trimester, eventually reaching its peak at birth (1). Healthy infants usually exhibit high lactase activity, but the post-weaning period sees the emergence of 2 phenotypes: lactase deficiency and lactase persistence. In lactase-deficient individuals, lactase expression begins to gradually decrease some time during childhood, eventually making them incapable of digesting dietary lactose. This condition is referred to as adult-type hypolactasia. The age of onset for hypolactasia varies considerably between individuals and populations with some children exhibiting low lactase concentrations at as young as 2 y of age (9). In contrast to lactase deficiency, lactase-persistent individuals continue to express high lactase activity after childhood (i.e., normolactasia)

and retain the ability to digest lactose. Generally, the cut-off value for hypolactasia is  $\sim 10$ – $15$  U/g of total protein whereas lactase-persistent individuals exhibit lactase activities  $> 50$  U/g of total protein.

The phenotypic differences between adult-type hypolactasia and normolactasia are explained by genetic polymorphism. In people with European ancestry, hypolactasia associates with 2 distinct allelic variants upstream of the lactase gene (*LCT*), C/T-13910 and G/A-22018 (10). Of these two variants, the C/T-13910 polymorphism residing on the enhancer region of *LCT* is the main regulator of lactase expression; the G/A-22018 polymorphism does not seem to affect lactase expression (11). The CC genotype implies reduced lactase activity, whereas the TT genotype is associated with normolactasia. Heterozygotes with the C/T genotype are usually lactase persistent but display lower lactase activities than TT homozygotes, although considerable overlap in lactase activities between these 2 genotypes exists (12, 13). Also, individuals with the CC genotype show varying lactase activities, suggesting that some lactase-deficient individuals might be better at digesting lactose than others (12). In addition to the C/T-13910 variant,  $\geq 4$  other allelic variants on the *LCT* enhancer region associate with lactase persistence in different ethnic populations: allelic variants C/G-13907, G/T-14009, and G/C-14010 are present at varying frequencies in East Africa, whereas the T/G-13915 variant is mainly found on the Arabian Peninsula (14). Despite the relatively well-characterized genetics of lactase deficiency, the exact molecular mechanisms behind the genetically programmed decline in lactase expression remain only partially understood. Recently, 2 independent research groups demonstrated C/T-13910 genotype-dependent differences in DNA methylation patterns that associate with *LCT* mRNA expression and lactase activity, indicating that intestinal lactase is mainly under transcriptional regulation (15, 16).

In addition to endogenous lactase activity, certain colonic microbes, such as the lactic acid bacteria *Lactobacillus* and *Bifidobacterium*, possess  $\beta$ -galactosidase activity (i.e., bacterial lactase) that allows them to digest and utilize lactose. These bacteria hydrolyze lactose to glucose and galactose and subsequently ferment them to lactate, SCFAs, and gases, such as  $H_2$ ,  $CO_2$ , and  $CH_4$  (17). In normolactasia, when intestinal lactase is high, only a small percentage of ingested lactose reaches the colon (18). However, when intestinal lactase activity is low, lactose escapes absorption in the small intestine, thus subjecting it to colonic fermentation. The colonic fermentation process might explain why certain lactase-deficient individuals experience intolerance symptoms to lactose whereas others do not (17). Although lactose-tolerant and lactose-intolerant lactose-malabsorbers exhibit similar fecal  $\beta$ -galactosidase activity (i.e., capacity to hydrolyze lactose) (19), the fecal bacteria of the intolerant subjects generate fermentation end products in response to lactose faster than those of the tolerant group (20). Together with undigested lactose, the rapid accumulation of fermentation products increases the osmotic load in the colonic lumen, leading to intolerance symptoms after lactose intake (17).

Researchers and clinicians have employed several methods to assess an individual's ability to absorb dietary lactose (21). Clinically, these methods are important because they can be used to exclude lactose intolerance when diagnosing functional GI

disorders. Intestinal lactase activity can be measured directly from intestinal biopsies or indirectly with a lactose challenge. Although direct measurement is the reference standard, obtaining biopsies is invasive and rarely available, making indirect measurements more practical for routine assessments. The 2 most frequently used indirect measurements of lactase status are the lactose tolerance test (LTT) and the H<sub>2</sub>-breath test (21). In both tests, a subject is challenged with an oral dose of 20–50 g lactose after which blood glucose concentrations (LTT) or H<sub>2</sub> concentrations in expiratory air are measured for every 30 min for 2–3 h. The LTT is based on intestinal lactase's ability to hydrolyze lactose to galactose and glucose: blood glucose concentrations failing to increase 20 mg/dL above pretest values are indicative of lactase deficiency. In contrast, the H<sub>2</sub>-breath test is based on the activity of colonic microbes: when lactase activity is low, unabsorbed lactose enters the colon where colonic microbes produce H<sub>2</sub> via a fermentation process. If breath H<sub>2</sub> concentration rises 20 ppm above pretest values, it is regarded as a sign of reduced lactase activity. Both the LTT and the H<sub>2</sub>-breath test are susceptible to confounding factors but the major advantage of these tests is that they allow symptom assessment during testing so they can also be used to diagnose lactose intolerance (21). In addition to these tests, a genetic test for the C/T-13910 polymorphism is available with the CC genotype interpreted as lactase deficiency. Although this polymorphism correlates well with lactase activity, it mainly reflects lactase status in European populations in which lactase persistence mostly depends only on the C/T-13910 variant (14). Because different allelic variants determine lactase persistence in other ethnicities, genetic testing for the C/T-13910 polymorphism is unsuitable for these populations (21).

### Does Lactose Absorption Acclimatize to Lactose Intake in Humans?

The first experiments on the induction of intestinal lactase in response to dietary lactose intake were conducted as long ago as the beginning of the 20th century when researchers fed different animal species milk or lactose and analyzed changes in their lactase activity. Although these experiments relied on cruder analytic methods than today, they showed that lactose feeding does not induce intestinal lactase activity in adult mammals (22). Subsequent animal studies with modern methods of analysis have produced conflicting findings, with some studies showing increased intestinal lactase activities following lactose feeding (23–28), whereas others have reported no such effect (29–33).

In humans, studies attempting to induce intestinal lactase with different lactose feeding protocols have consistently produced negative findings (Table 1). Cuatrecasas et al. (34) were the first to examine the induction of intestinal lactase in humans by feeding 150 g of lactose daily to 11 subjects (7 lactose-malabsorbers and 4 lactose-absorbers) for 45 d and reported no changes in intestinal lactase activity. Similarly, in by far the largest study in terms of subjects, Keusch et al. (35) reported no changes in intestinal lactase activity in 50 Thai marines following a lactose-feeding period of 22–38 d. Smaller studies and case reports with various lactose-feeding protocols have reported similar findings (36–42). In the only intervention study conducted

exclusively in children, feeding 25 g of lactose daily for 1 y did not improve lactose absorption in lactose-malabsorbing children (43). Additionally, lactose feeding did not seem to prevent the decline in lactose-absorbing capacity because 5 of 8 previously lactose-absorbing children became lactose-malabsorbers during the intervention. The 3 children who remained lactose-absorbers were all aged <5 y, suggesting that age, and not lactose intake, was the major factor affecting the status of lactose absorption in this population (43).

Intervention studies where lactose is eliminated from diet are scarce and have produced somewhat conflicting results (Table 1). Cuatrecasas et al. (34) put 2 lactose-absorbers on a lactose-free diet and observed a decline in their lactose absorption capacity. In 1 of the subjects, the lactose absorption capacity fell almost to half of the baseline value after only 2 mo but did not decline further. In this study lactose absorption capacity was measured as lactose absorption ratio, whereby the rise in blood glucose concentration after lactose intake is expressed as a percentage of the rise in blood glucose after ingesting a solution containing an equal amount of glucose and galactose (34). The authors established a cut-off value of 50% for lactose absorption. Notably, although both subjects exhibited decreased lactose absorption capacity after the intervention period, both would still be classified as lactose-absorbers according to the established cut-off value (34). In another study, removing lactose from the diet of 6 healthy lactose-absorbers for 42 d produced varying results: intestinal lactase activity increased in 2 subjects and decreased in 3 (44). However, these changes did not affect the results of the LTT, leading the authors to speculate that the observed fluctuations in lactase activity likely resulted from variations in the location of the biopsy specimen (44). This is a reasonable assumption considering the spatial differences in intestinal lactase expression and that other intestinal disaccharidases followed a similar pattern in their analyses. Furthermore, all subjects whose intestinal lactase activity decreased during the study still exhibited sufficient lactase activity and experienced no GI symptoms during the LTT, indicating that lactose withdrawal did not affect their ability to process dietary lactose (44). Taken together, the results from intervention studies show that intestinal lactase activity is not modified by the presence of lactose in the diet.

Cross-sectional studies offer another way to investigate the possible relation between lactose absorption and lactose intake. Obviously, this type of study cannot establish causality, i.e., whether lactose intake affects lactose absorption capacity or if poor lactose absorption causes avoidance of lactose-containing products. On a global level, populations with a high prevalence of lactase deficiency consume less lactose-containing dairy products than populations where lactase persistence dominates (3, 45). This most likely echoes the culture-historical theory of population-level adaptation, gradually leading to a high prevalence of lactase persistence in cultures where dairy products are commonly available for nutrition. However, on an individual level, milk or lactose consumption appears to be a poor indicator of a person's lactose absorption status. Lactose absorption capacity (enzyme activity or LTT) shows no correlation with daily milk intake in several populations (36, 46–50). Also, studies have identified multiple individuals incapable of absorbing lactose despite regular daily milk consumption (48, 51–54) or lactose-absorbing individuals who have consumed

**TABLE 1** Intervention studies investigating changes in intestinal lactase activity in humans after a lactose feeding period or a period of lactose withdrawal<sup>1</sup>

Study population	<i>n</i>	Age	Intervention	Result	Reference
Lactose-malabsorbers	7	Adults	150 g lactose/d for 45 d	No change in intestinal lactase activity	(34)
Lactose-absorbers	4	Adults	150 g lactose/d for 45 d	No change in intestinal lactase activity	(34)
Lactose-absorbers	2	Adults	Abstinence from milk and milk products for 5 mo	Lactose absorption ratio decreased in both subjects	(34)
Healthy Caucasian lactose-absorbers	2	Adults	50 g of lactose 3 times/d for 10 d	No change in intestinal lactase activity	(36)
Healthy Caucasian lactase-deficient subjects	1	Adult	Diet with 30% of calories from lactose for 14 d	No change in intestinal lactase activity	(37)
Healthy Caucasian lactose-absorbers	6	—	Lactose-free diet for 42 d	Varying results in intestinal lactase activity, no change in LTT	(44)
Healthy Thai marines	50	22–30 y	25 g of lactose 2 times/d for 22–38 d	No change in intestinal lactase activity	(35)
Lactose-intolerant Nigerian medical students	6	Adults	Gradual weekly increase of lactose intake from 5 to 100 g/d for 6 mo	No improvement in LTT	(42)
Japanese nursing students	14	18–20 y	360–540 mL milk/d for 52 d	No improvement in LTT	(38)
Healthy Indians	6	Adults	30 g of lactose for 4 wk	No change in intestinal lactase activity	(39)
Lactase-deficient subjects	10	21–65 y	0.7–1.4 L milk/d for 6–14 mo	No change in intestinal lactase activity	(40)
Lactose-malabsorbing children from a Singaporean girls' home	13	5–10 y	25 g lactose/d for 1 y	All but 1 child remained lactose-malabsorbers (per LTT)	(43)
Lactose-absorbing children from a Singaporean girls' home	8	3–7 y	25 g lactose/d for 1 y	Only 3 children (all aged <5 y) remained lactose-absorbers (per LTT)	(43)
Healthy lactose-malabsorbing Cameroonians	16	18–26 y	18 g lactose/d for 7 d	No change in intestinal lactase activity	(41)

<sup>1</sup>LTT, lactose tolerance test.

no or little milk products after weaning (46, 48, 55–57). For example, in a 10-y follow up study, Sahi et al. (52, 55) reported the development of hypolactasia in people who had regularly drunk milk for several years. In their study cohort, all previously identified lactose-malabsorbers also remained as such during the 10-y follow-up period even though some of them continued consuming milk regularly. One notable exception to the aforementioned studies is a report from Bolin and Davis (58) describing a lower incidence of lactose malabsorption in Australian-born Chinese than indigenous Chinese living in Singapore. In their study population, all lactose-absorbers also reported consuming >15 g lactose/d, whereas most lactose-malabsorbers reported lower lactose consumption (58). Nevertheless, the overall evidence from cross-sectional studies seems to support the findings of the intervention studies that lactose absorption capacity does not depend on the availability of dietary lactose.

Considering that the age of onset for lactase deficiency varies considerably between populations, studies examining the relation between milk consumption habits and intestinal lactase activity in young children are especially interesting. Cook (59) reported that Ugandan children exhibited a gradual fall in lactose absorption capacity from birth to childhood irrespective of their milk intake. Similarly, in a study conducted in Thailand, continuous milk intake since infancy did not prevent a decline in lactose-absorbing capacity (60). Furthermore, studies on Peruvian and Israeli children reported that the lactose-absorbing capacity in these populations was not related to milk consumption during childhood (61, 62). On the other hand, others have suggested that although lactase status is genetically determined, continued lactose intake after weaning could increase the age of onset for hypolactasia (51, 63). This is mostly supported by data showing that in populations where milk consumption is high,

hypolactasia appears at a later age than in populations with low milk consumption (39, 51, 54, 59, 60, 62–66). In a study cohort consisting of Mexican-American children and Anglo-American children, lactose malabsorption manifested earlier in the Mexican-American group who also consumed less milk than the Anglo-American children (64). Bolin et al. (65) also observed an increased prevalence of hypolactasia in non-milk-drinking children aged <5 y than in milk-drinking children of similar age. However, the causality of this relation is uncertain. In the only intervention study conducted in young children, milk supplementation for 1 y did not prevent or delay the development of hypolactasia (43). This study was conducted in a Singaporean population where the prevalence of hypolactasia is high. Possibly, the observed variations in the age of onset for hypolactasia in different populations are under generic or epigenetic regulation and lactose intake does not influence this process.

### Colonic Adaptation to Dietary Lactose

Although endogenous lactase activities remain unchanged during lactose feeding, lactose-malabsorbers frequently report experiencing fewer and less severe GI symptoms as feeding progresses. This would suggest that some adaptive mechanisms relating to lactose processing occur during prolonged intake of lactose. In one of the first studies to demonstrate adaptation to lactose feeding, Johnson et al. (67) fed gradually increasing amounts of lactose to 22 lactose-intolerant subjects and observed that 17 of them could tolerate >12 g of lactose daily without symptoms. In addition, when challenged with the maximum tolerated dose of lactose, 4 of these subjects exhibited no increase in breath H<sub>2</sub> concentration (67). Subsequent investigations

**TABLE 2** Intervention studies investigating colonic adaptation in humans after a lactose-feeding period

Study population	<i>n</i>	Age	Intervention	Result	Reference
Lactose-malabsorbing African Americans	22	13–39 y	Gradually increased daily lactose intake for 6–12 wk until tolerated dose was reached	Breath H <sub>2</sub> concentration <5 ppm in 4 of 22 subjects	(67)
Lactose-malabsorbing subjects	9	30 y (mean)	Gradually increased daily lactose intake for 16 d from 0.2 to 1.0 g lactose/kg body weight	Increase in fecal $\beta$ -galactosidase activity	(68)
Lactose-malabsorbing subjects	20	30 y (mean)	Gradually increased daily lactose intake for 10 d from 0.6 g to 1.0 g lactose/kg body weight	Decrease in breath H <sub>2</sub> concentrations	(68)
Lactose-malabsorbing subjects	24	20–47 y	17 g lactose 2 times/d for 14 d	Increased fecal $\beta$ -galactosidase activity and decreased breath H <sub>2</sub> concentrations	(69)
Lactose-malabsorbing African-Americans girls	14	11–15 y	33 g lactose/ d for 21 d	Decrease in breath H <sub>2</sub> concentrations	(70)
Healthy Sicilian man	1	32 y	Decreased daily lactose intake from 28.1 to 1.5 g for 2–3 wk and then increased daily lactose intake to 53 g	Increase in breath H <sub>2</sub> concentration followed by a decrease after reintroducing high daily lactose intake	(71)
Lactase-deficient subjects	23	32 $\pm$ 9 y	25 g lactose 2 times/d for 14 d	Increased fecal Bifidobacteria counts	(73)
Lactase-persistent subjects	18	26 $\pm$ 7 y	25 g lactose 2 times/d for 14 d	No changes in fecal bacterial counts	(73)

have produced similar findings: lactose-malabsorbing individuals show decreased breath H<sub>2</sub> concentrations after a lactose challenge following a lactose-feeding period (68–71) (Table 2). Although these reports have reported none or only minor improvements in GI symptoms, the findings imply that colonic microbes adapt to the presence of lactose in the colonic lumen. Indeed, fecal analyses have revealed that lactose feeding increases fecal  $\beta$ -galactosidase activity (68, 69) and the proportions of Lactobacilli and Bifidobacteria (72, 73). Interestingly, these bacterial taxa do not produce H<sub>2</sub> during carbohydrate fermentation, which likely explains the observed reduction in breath H<sub>2</sub> concentrations after lactose feeding (74). These results suggest that when dietary lactose reaches the colon, it stimulates the growth of lactose-fermenting bacteria, but whether this reduces intolerance symptoms to lactose is still a matter of debate. Studies have shown decreased flatulence during a lactose challenge following a lactose-feeding period, possibly because of microbial changes leading to reduced colonic gas production (68, 70). Colonic adaptation is also supported by a study showing that supplementing lactose-intolerant individuals with a prebiotic increases the proportion of lactose-fermenting bacteria, which leads to decreased abdominal pain when lactose is reintroduced in the diet (75, 76). Taken together, however, these studies mainly report only minor improvements in 1 intolerance symptom with no changes in other GI symptoms (68, 70, 75). Moreover, Briet et al. (69) did not observe any improvements in intolerance symptoms despite microbial adaptations to lactose intake, supporting the idea that at least part of the observed symptom improvements could be explained by the placebo effect. Another explanation could be individual differences in the composition of microbiota that contribute to GI symptom development after lactose intake. Although fecal  $\beta$ -galactosidase activity does not seem to differ between lactose-tolerant and lactose-intolerant lactose-malabsorbers (19), intolerant individuals produce lactose fermentation end products, such as lactate and SCFAs, faster than tolerant lactose-malabsorbers (20). These findings imply that colonic adaptation to lactose intake should probably extend beyond  $\beta$ -galactosidase-producing bacteria to achieve clear alleviation of intolerance symptoms. Nevertheless, these studies

show that lactose feeding increases the proportion of intestinal bacteria capable of hydrolyzing lactose and decreases colonic H<sub>2</sub> production, trends that might lead to some alleviation of intolerance symptoms in lactose-malabsorbers. This colonic adaptation to lactose feeding appears to be reversible, i.e., when lactose is excluded from diet, colonic adaptation also disappears, which in turn might lead to intolerance symptoms when lactose is reintroduced in the diet. However, despite colonic adaptation, the nutritional benefit of lactose for these individuals would still remain low compared with lactase-persistent individuals.

## Conclusions and Future Research Targets

Studies that have measured changes in endogenous lactase activity after an intervention period consistently show a lack of enzyme induction, suggesting that lactose intake does not affect an individual's lactase activity. Although these studies are scarce and have relatively few subjects, data from cross-sectional studies support the theory of purely genetic regulation. However, a few questions remain open. Firstly, the existing intervention studies have mainly been conducted on subjects from populations with a high prevalence of hypolactasia. This implies that most of the subjects in these studies are genetically homozygous for lactase deficiency, meaning that their ability to express lactase might have already been compromised permanently. Perhaps extending these analyses to include genetic polymorphisms with varying lactase activities would produce a wider range of outcomes. Secondly, considering that the age of onset for hypolactasia varies extensively between populations, it would certainly be of interest to investigate the genetic or epigenetic factors that trigger the downregulation of lactase expression at a certain age in different populations.

Contrary to endogenous lactase, the capacity of colonic microbes to process lactose can adapt to increased flux of lactose into the colonic lumen. Colonic adaptation occurs mainly in lactase-deficient individuals and is possibly responsible for the increased tolerance to lactose after a lactose-feeding period, but this matter is still being debated and requires more

detailed investigations. Nevertheless, in lactose-malabsorbing individuals, withdrawing lactose from the diet might lead to the loss of adaptation and subsequently lower the threshold for intolerance symptoms when lactose is reintroduced. Overall, however, it remains unclear if lactose intake leads to colonic adaptation in all lactose-malabsorbers and what are the possible differences between adapters and nonadapters. In addition, the microbial alterations contributing to colonic adaptation after lactose feeding should be investigated more thoroughly.

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