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# Introductory Chapter: Lactose

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## 1. The biological role of lactose

Milk provides infants with essential nutrients to support the first months of life. Newborns and young animals obtain their energy mostly from milk lipids and lactose (~17 kJ per gram of lactose). Only lactose provides 40% of the energy needs of suckling mammals. This fact explains why almost all the mammalian milk contains 40–75 g of lactose per liter, and why the milk of mammals is the only source in nature with a significant content of lactose [1–3]. Congenital deficiency to digest lactose is rare in baby mammals since it can lead to growth delay, dehydration, and even the death [3].

Lactose is a disaccharide synthesized in the mammary gland of mammals, and only scarce plant species show this saccharide. The Golgi vesicles of mammary epithelial cells synthesize lactose from two molecules of glucose. One of this glucose is first epimerized to galactose (Leloir pathway) and phosphorylated. Then, condensation with the other glucose occurs through the lactose synthetase system. This system comprises the enzyme galactosyl transferase and the protein modifier  $\alpha$ -lactalbumin. When the protein modifier binds to the galactosyl transferase, it catalyzes the synthesis of lactose from uridine-diphosphate-galactose (UDP-gal) and glucose [1–3]. In the absence of the protein modifier, the galactosyl transferase does not synthesize lactose and instead catalyzes the synthesis of N-acetyl lactosamine on glycoproteins. This last reaction occurs in most tissues, but in the mammary gland of women after giving birth, the increase in prolactin and a decrease in progesterone hormones induce the formation of the protein modifier ( $\alpha$ -lactalbumin). Consequently, the breast can synthesize lactose in the milk for the nourishment of newborn mammals [2, 3].

Lactose digestion in humans involves the action of intestinal lactase. Lactose is a disaccharide containing galactose and glucose linked by a  $\beta$  1-4 glycosidic bond. This sugar cannot be transported across the epithelial cell membrane into the enterocytes and then into the bloodstream as a disaccharide. The release of galactose and glucose monomers by hydrolysis of the  $\beta$ -glycosidic bond allows their transport into the enterocytes through the  $\text{Na}^+$  dependent transporter SGLT1. Then, the GLUT2 transporter carries these monosaccharides into the blood [2, 3]. The  $\beta$ -glycosidic bond in lactose molecules is hydrolyzed in the small intestine by a  $\beta$ -galactosidase. There are three types of these enzymes in human tissue: (a) the  $\beta$ -galactosidase in the lysosomes, (b) the  $\beta$ -galactosidase in the cytosol of cells, and (c) the  $\beta$ -galactosidase in the small intestine. It is worth to mention that the human intestinal  $\beta$ -galactosidase has similarities to intestinal lactases reported in rabbit (83%) and rat (77%). However, this enzyme has no sequence homology with the other two types of  $\beta$ -galactosidases in human tissue, the  $\beta$ -galactosidase in bacteria, or different kinds of  $\beta$ -galactosidases found in eukaryotic cells [2, 4].

The intestinal  $\beta$ -galactosidase (like other carbohydrate-hydrolyzing enzymes) is situated close to the brush border on the upper surface of enterocytes on the microvilli. Hundreds of tiny finger-like structures (villi) protrude from the small

intestine wall. These villi have additional extensions (microvilli) that form the brush border of enterocytes. The small intestine has three segments, duodenum (5-6 cm long), jejunum (2.5 m long), and ileum (4-5 m long). The  $\beta$ -galactosidase is all over the small intestine, but primarily in the jejunum, where the pH is 7-8, and the bacterial concentration is low [2, 4]. The human intestinal  $\beta$ -galactosidase is unique because it has two different active sites within one polypeptide chain. Therefore, this enzyme can hydrolyze lactose, but also other types of substrates. One of the active sites hydrolyzes lactose into galactose and glucose and cleaves other substrates like cellobiose, cellotriose, cellotetrose, and cellulose (EC 3.2.1.108). The other active site hydrolyzes phlorizin, an aryl  $\alpha$ -glucoside linked to phloretin (EC 3.2.1.62). The active area for phlorizin also cleaves  $\beta$ -glycosides with a sizeable hydrophobic chain like cerebrosides, made up of ceramide (sphingosine with a fatty acid attached) bonded by a  $\beta$  link to galactose or another hexose. The hydrolysis of cerebrosides provides sphingosine, a key molecule maintaining the membranes of the brain. Consequently, the full name of the intestinal  $\beta$ -galactosidase is lactase-phlorizin hydrolase or LPH [2-4].

## 2. Lactose intolerance

The loss of intestinal  $\beta$ -galactosidase (LPH) reduces humans' capability to metabolize lactose. The synthesis of LPH starts in humans during the gestation (8-34 weeks) and reaches its peak at birth. After the first 6-12 months of life,  $\beta$ -galactosidase begins to decline. Over the four years, at least 60% of people reduce their levels of LPH to 5-10%. The decline in lactase after weaning occurs in all mammals. [1-4]. The levels of LPH during adulthood vary significantly between ethnic groups. For instance, more than 90% of Chinese and Japanese adults have low lactase levels and potential lactose intolerance, in contrast with the only 10% of white Northern Europeans. The domestication of cattle by European populations promoted for centuries milk as a food item for adults. Therefore, many people in this ethnic group developed a persistent lactase expression during adulthood (lactase persistent) [2, 3].

Most adult individuals have reduced activity of LPH in the small intestine (lactase non-persistent, or wild-type condition), and only a minority of humans have a high level of LPH activity (lactase persistent). Any deficiency of intestinal  $\beta$ -galactosidase is considered hypolactasia, and a total lack of LPH activity in the small intestine is referred to as alactasia. This last condition is infrequent, and before the twentieth century, infants with congenital alactasia had a little expectation of surviving. There are two conditions for hypolactasia: primary adult hypolactasia (lactase non-persistent) and secondary adult hypolactasia (acquired hypolactasia). The primary hypolactasia is due to the normal decrement with the age of lactase quantity in the small intestine. This decrement occurs because the human body reduces the transcription of the lactase gene (LCT; NCBI reference sequence XP\_016859577.1), or by a reduction in the translation of the mRNA. The reduction of lactase in adults does not mean automatically that these individuals will have problems digesting lactose. Some researchers estimate that 50% of the regular  $\beta$ -galactosidase activity is enough for adequate lactose assimilation. However, human adults with low quantities of LPH (<50%) in the small intestine cannot properly digest the lactose in 100 mL of milk (lactose maldigestion). The secondary hypolactasia is different; this derives from an intestinal infection (by bacteria, viruses, or protozoa), severe malnutrition, inflammatory bowel diseases, actinic enteritis, and extensive use of antibiotics (i.e., kanamycin, neomycin, polymycin, and tetracycline). Additionally, diverse substances in the gut lumen can induce inhibition of LPH activity. Nevertheless, secondary hypolactasia can be

treatable and potentially reversible [1–4]. On the other hand, lactose intolerance occurs when a lactose maldigester shows gastrointestinal problems. Bacteria in the large intestine convert lactose into gases and diverse metabolites if this sugar is not hydrolyzed in the jejunum by the LPH. The most common symptoms of lactose intolerance are the development of flatulence, abdominal distention, and diarrhea. There is no exact data, but about two-thirds of adult humans cannot digest lactose properly [2]. Therefore, nowadays, the dairy industry is looking to develop dairy products without lactose for consumers suffering from lactose intolerance.

### 3. Physicochemical properties of lactose

Lactose is a reducing disaccharide of galactose and glucose discovered in milk in the 17th century. Both the galactose and the glucose can form a hemiacetal link and create a ring structure. A  $\beta$ -glycosidic link connects the two pyranose structures deriving in a 4-O- $\beta$ -D-galactopyranosyl-D-glucopyranose molecule. This disaccharide has a chiral center that exists as two isomers:  $\alpha$ -lactose and  $\beta$ -lactose. The  $\alpha$ -isomer rotates the plane of polarized light  $+92.6^\circ$  and the  $\beta$ -isomer  $+34^\circ$  at  $20^\circ\text{C}$ . When lactose is in an aqueous milieu, its ring structure opens and closes interchanging between the  $\alpha$ - and  $\beta$ -isoforms (mutarotation). At some point, these isoforms acquire an equilibrium (mutarotation equilibrium). Lactose mutarotation is a slow process that is very temperature-dependent. For instance, at  $18.8^\circ\text{C}$  the mutarotation equilibrium is achieved in 6.5 hours with a proportion of 40% of  $\alpha$ -lactose and 60% of  $\beta$ -lactose; but at  $0^\circ\text{C}$ , the stability can take up to 72 hours. Overall, the proportion of  $\beta$ -lactose is always higher than the  $\alpha$ -lactose at mutarotation equilibrium, because the  $\beta$ -isoform is more soluble than the  $\alpha$ -isoform. For example, at  $35^\circ\text{C}$  the solubility of  $\alpha$ -lactose is 7 g per 100 g of water, in contrast, the solubility of  $\beta$ -lactose is 50 g per 100 g of water [2, 5–7]. Certainly, the solubility of both isoforms will decrease if the temperature drops. Like other sugars, lactose molecules nucleate and crystallize when the concentration of this sugar overcomes its maximum solubility at a specific temperature. The dairy industry applies this principle to crystallize lactose from whey, a by-product of cheesemaking [8].

This by-product of cheesemaking contains 0.8 – 1% protein, 0.06% fat, 4.5 – 6% lactose, and 90 – 92% of water. To crystallize lactose from the cheese whey, it needs to be first, defatted, deproteinated and evaporated to concentrate lactose between 39 and 56%. At this concentration, lactose will crystallize when the evaporated whey is cooled enough (i.e.,  $20\text{--}25^\circ\text{C}$ ). During the cooling step, lactose moves through and beyond the metastable zone (MZ), a region between the solubility and supersolubility of lactose. The spontaneous nucleation of lactose occurs when the supersolubility is exceeded, outside the MZ. Therefore, the width of the MZ determines the temperature drop necessary to induce lactose nucleation. After nucleation, crystals' growth depends on the degree of lactose saturation and the temperature, since the last one affects lactose solubility [7, 9–13]. The overall process of lactose crystallization is slow. In consequence, mutarotation can occur during the nucleation or the growth of crystals. However, if the mutarotation rate is lower than the crystallization rate, the kinetics of mutarotation will dominate over the nucleation and crystal growth. The industrial process of lactose crystallization from cheese whey is slow (up to 48 h) and requires an elevated lactose concentration to induce nucleation (high evaporation cost). Different approaches have been studied to overcome the drawbacks of lactose crystallization. Among these are the seeding of lactose nuclei, anti-solvents (i.e., ethanol and acetone), and the appliance of high-power ultrasound. Alternatively, methods other than crystallization have been investigated to recover lactose from the cheese whey, like the use of membranes [9, 11, 14–17].

#### 4. Final remarks

Despite the persistence of lactose intolerance in the population, the dairy industry produces 400,000 tons of crystalline lactose worldwide [6]. The food and pharmaceutical industries use large amounts of lactose. Foods like instant coffee, infant formula, baked foods, and many others utilize lactose as an ingredient. This saccharide has a lower caloric value and a lower glycemic index than other carbohydrates. Additionally, lactose is less sweet than sucrose, and it has good plasticity and compressibility. These properties of lactose explain why most pharmaceutical pills contain lactose as a filling material. Derivative lactose compounds like lactic acid, lactitol, lactulose, and oligosaccharides gain interest in the food industry [5, 6, 12].

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