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Physico-chemical properties of lactose, reasons for and effects of its intolerance in humans – a review

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Lactose is a unique disaccharide and mammalian milk is its sole natural source. The concentration of lactose in the milk of different mammal species varies considerably – the highest lactose content is found in the milk of equines (over 6%), while the lowest in the milk of marine mammals (about 1%). Lactose plays a significant role in the proper development of new-born mammals, being an important source of energy necessary for the activity of such organs as the heart, liver and kidneys. It is characterised by low sweetness, caloricity and glycaemic index. It has dietetic as well as probiotic properties and improves the absorption of calcium, phosphorus, magnesium and certain microelements. It leads to a better utilisation of vitamin D by the organism. Moreover, it stimulates the development of beneficial intestine microflora, increases the synthesis of short chain fatty acids and promotes regeneration processes in the intestine mucous membrane. Lactose is a source of galactose, which is indispensable for the correct functioning of the central nervous system. It is used not only as an ingredient of numerous foodstuffs, but also for the production of pharmaceutical preparations and feeds for animals.

KEY WORDS: glycosidases / intolerance / lactose / milk

Milk is an excellent source of readily absorbable lipids, proteins and carbohydrates, as well as minerals and vitamins [Strzałkowska *et al*. 2009ab, 2010, Claeys *et al*. 2014]. Lactose, also known as milk sugar, is the basic and most important carbohydrate in the composition of mammalian milk. In cow's milk it is, apart from fat and protein, the principal component of milk solids of this product [Strzałkowska *et al.* 2009c,

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Szwajkowska *et al*. 2011]. Lactose concentration in cow's milk is affected by various factors such as the stage of lactation, lactation number, health condition of the mammary gland and health condition of the animal in general [Jóźwik *et al*. 2012a, Jóźwik *et al*. 2012b, Strzałkowska *et al*. 2014].

It is responsible for about 30% of the caloric value of milk and gives milk its slightly sweet taste. This carbohydrate is characterised by a low glycaemic index, thanks to which it regulates the production of hormones responsible for hunger or satiety to a greater degree than sucrose or glucose do. The lactose glycaemic index is less than half that of glucose and maltose and almost 50% lower than that of sucrose [Foster-Powell *et al*. 2002]. Among sugars available in our daily diet only fructose is characterised by a slightly lower glycaemic index when compared with lactose (Tab. 1). Lactose is also characterised by a much lower sweetness when compared with sucrose [Schaafsma 2002]. In a 100-point scale (sucrose sweetness = 100) the sweetness of lactose in a water solution amounts to about 20 points and of ß-lactose – to about 50 points (Tab. 2). Also fructose, glucose, xylose and galactose are sweeter than lactose. The lower sweetness of lactose (as compared to sucrose) has a positive effect on the sense of taste, preventing overfeeding of babies and their obesity.

Table 1. The glycemic index of selected sugars and foods [Foster-Powell *et al*. 2002]

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

Table 2. Sweetness of selected sugars (relative to sucrose = 100) [Schaafsma 2002]

Sugar	Sweetness
Sucrose	100
Fructose	130
Glucose	60
Xylose	60
Galactose	70
Maltose	45
Sorbose	40
α-Lactose	**20**
β-Lactose	**50**

The content of lactose in milk obtained from mammals of different species varies considerably (Tab. 3). Lactose concentration in fresh cow's milk ranges between 4.5 and 5.2%, while in human milk it reaches about 7% [Schaafsma 2002]. The concentration of lactose similar to that observed for humans is also recorded in the milk of equines. In turn, the milk produced by marine mammals contains negligible amounts of lactose (dolphin – 1.1 %, seal – 0.1%). This is caused by the fact that milk originating from this group of mammals is characterised by a very high fat content, which is the principal and most important source of energy in the milk of those animals.

The synthesis of lactose from glucose supplied by blood takes place in the Golgi apparatus of the milk secreting cells. Lactose is composed of a glucose molecule and a galactose molecule, linked by a ß-glycosidic linkage between the first carbon atom in the galactose molecule and the fourth carbon atom in the glucose molecule. Galactose occurs in lactose always in the ß form, while glucose may appear both in the α and ß

Table 3. Lactose content (%) in milk of various mammals [Schaafsma 2002]

Type	Lactose in milk (%)
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

forms, for which reason lactose can appear in those two forms – α and ß. In a water solution both forms appear in equilibrium, but at room temperature the frequency of the beta form reaches about 63% [Lomer *et al*. 2008, Kuhn and White 2009]. Lactose is characterised by good water solubility, it exists in a hemiacetal ring form, with oxygen bonds between the first and fifth carbon atoms. In an alkaline environment lactose takes on an aldehyde form and is readily oxygenated to lactobionic acid which, due to its chemical form (a combination of gluconolactone with galactose), belongs to the group of polyhydroxyacids [Gambelli 2017]. Thus, for reasons presented above, lactose is classified to reducing disaccharides. Lactose is hydrolysed in solutions with a high acid concentration or when treated with the ß-galactosidase enzyme, occurring in the digestive tract of mammals, as well as in cells of plants, bacteria, moulds and fungi. In the hydrolysis process lactose is broken down to glucose and galactose molecules which, in the presence of oxygen, are oxidised to CO_2 and H_2O, while under anaerobic conditions are subject to lactic or alcohol fermentation [Gambelli 2017].

Lactose plays an important role in the correct development of new-born mammals as it is an important source of energy, indispensable for such organs as the heart, liver and kidneys [Fiocchi and Restani 2003]. During the first year of life lactose covers about 40-50% of the energy requirements of a child. The breakdown of lactose to lactic acid, taking place in the intestines, decreases the pH of the gastric contents and thus directly affects the microflora composition in the digestive tract by preventing fermentation processes [Socha *et al.* 1984, Szajewska *et al*. 2005]. Lactic acid, being the result of the breakdown of lactose by microflora, reduces the pH of the gastric content and thus leads to an increased solubility of calcium salts and an increase of absorbable calcium contents. Moreover, the effect of lactose on the intestine epithelial cells may also facilitate the passage of calcium to erythrocytes. It promotes the absorption of magnesium, phosphorus and certain microelements and leads to a better utilisation of vitamin D by the organism. This is of special importance for persons inhabiting regions with a low annual number of sunny days, and thus resulting in a lower production of vitamin D, which is responsible, among others, for calcium and phosphorus metabolism in the human organism. By stimulating the development of beneficial microflora and enhacing the synthesis of short-chain fatty acids lactose also assists in regeneration processes of intestine epithelial cells [Seiki and Saito 2012, Claeys *et al.* 2014]. Moreover, lactose is an important source of galactose, which is a necessary component for the development of the central nervous system. In new-borns and infants it is an important stimulant of the production of insulin and it intensifies the activity of glucose. After it is broken down to glucose in the metabolic cycle known as the Leloir pathway, it can also be used by the human organism as an energy substrate.

Lactose intolerance – reasons and symptoms

A favourable effect of lactose on the human organism takes place when this sugar is properly digested in the presence of an enzyme called the lactase-phlorizin hydrolase (LTC, lactase, β-D-galactosidase). Lactose intolerance is an inability to digest lactose, the principal milk disaccharide, which takes place when, due to various factors, the organism stops the production of the lactase-phlorizin hydrolase enzyme (or lowers its activity) [Fiocchi and Restani 2003, Heyman 2006, Brown-Esters 2012, Pal *et al*. 2015]. Lactase is produced in the human organism in the brush border of the small intestine and its activity has been confirmed on the surface of the epithelial cells of the embryo intestine since the 8th week of pregnancy. The activity of lactase increases until week 34 of pregnancy and reaches its maximum value in the infant after parturition. The ability to digest lactose is essential for the infant's health, as congenital lactose intolerance, not diagnosed at a very early stage, may be the cause of death. Lactase breaks down lactose into the constituent glucose and galactose monomers, which may easily move into the bloodstream. In the liver galactose is converted into glucose, which enters the bloodstream and increases the total blood sugar level. Three clinical forms of lactase deficiency are known: congenital, secondary and the most frequent primary LTC deficiency [Lomer *et al*. 2008, Marchiondo 2009]. Congenital lactase deficiency is extremely rare, it is determined genetically and characterised by a total inability to produce lactase [Rychlik and Marszałek 2013]. Secondary lactase deficiency is due to the injury of intestine villi caused by such diseases as rotavirus infections, enteropathy or helminthiasis. Moreover, temporary intolerance symptoms may appear in the Leśniweski-Crohn disease, ulcerative colitis, after chemotherapy and intestine surgery. Damage to intestine villi results in a limited lactase activity and intolerance symptoms. However, this type of intolerance is of a transient character and recedes with the regeneration of the intestine epithelium. Thus, in the case of this type of intolerance, after the underlying disorder has been cured, one can return to the consumption of milk sugar.

The primary lactase deficiency is the most frequent form of lactose intolerance and is related to hypolactasia in adults (ATH). This type of intolerance is characterised by a decreasing lactase activity as people age; persons showing ATH symptoms as adults have normal levels of lactase activity during childhood. In this type of intolerance a total lack of lactase secretion occurs rarely. The appearance of this intolerance is determined genetically and by the ethnic origin of the patient (Tab. 4). The genetic determination of ATH is related to the polymorphism of the lactase gene within the promoter region of this gene on chromosome 2q21. Genotypes 13910 C/T and 13910 T/T retain the activity of lactase, while genotype 13910 C/C is responsible for the decreased activity of this enzyme [Hollox 2005]. Ethnic origin has a considerable effect on the decrease of lactose activity with age. Caucasians demonstrate a primary lactose intolerance at the age of about 5 years, though inhabitants of Northern Europe rarely demonstrate such symptoms before ten years old. It is worth emphasising that in the Mongoloid and Negroid races lactase deficit may appear even before the third year of life [Newcomer *et al.* 1978]. Lactase deficiency may result in various symptoms, such as nausea, gas, diarrhoea and abdominal pain [Fiocchi and Restani 2003, Heyman 2006, Brown-Esters *et al.* 2012]. Additionally, some people show other symptoms, seemingly not connected with the digestive tract. Those may include skin changes (eczema), headaches, concentration disturbances, chronical rhinitis, sinusitis and even heart arrhythmia [Lomer *et al*. 2008, Rychlik and Marszałek 2013]. Such symptoms may appear about 30 minutes after milk consumption.

Table 4. Prevalence of adult primary lactase deficiency (percentage of adult population [Alm 2002]

Country	Prevalence of adult primary lactase deficiency (%)
France	30-40
Germany	15-20
Russia	20-30
Finland	15-20
Sweden	<5
Greece	70-80
Ethiopia	80-90
Nigeria	80-90
Sudan	60-65
China	90-100
Japan	95-100
India	60-65
Jordan	20-25
Israel	70-80
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

The measurement of lactose absorption in the human digestive tract and diagnosis of lactose intolerance is usually based on three indirect tests: changes in the blood level of glucose/galactose, hydrogen breath test and stool acidity test [Lomer *et al.* 2008]. The test for changes in the blood serum glucose level are performed on an empty stomach after administering a liquid with lactose (50 g) to the patient. Lactose concentration in the patient's blood serum is analysed two hours later and on this basis the digestion of lactose is determined. If the blood glucose level did not increase, lactose is not adequately digested and the test confirms the presence of intolerance.

The air exhaled by humans contains very small amounts of hydrogen. In a hydrogen breath test the patient receives every 30 minutes over a period of four hours (starting on an empty stomach) a liquid containing lactose (2 g per 1 kg of body weight but not more than 50 g). Next, at equal time intervals their breath is analysed. A deficient lactose digestion is confirmed when the level of hydrogen in the exhaled air exceeds 20 ppm [Ibba *et al.* 2014]. Persons with lactose intolerance do not fully digest lactose, which results in bacterial fermentation producing various gases, including hydrogens, which is transported by blood from the intestines to the lungs and next exhaled. An increased level of hydrogen in the exhaled breath indicates defective lactose absorption [Johnson *et al*. 1993, Heyman 2006, Lomer *et al*. 2008].

The third test consists in the determination of stool acidity and is performed in infants and small children. In stool samples the products of lactose fermentation are determined, including lactic acid. A low pH indicates intolerance as undigested lactose acidifies the stool [Fiocchi and Restani 2003, Heyman 2006].

Apart from the tests described above lactose intolerance may be diagnosed also by other methods, such as endoscopy, which is most effective, but also invasive. During this examination a small section of the small intestine is sampled and the lactose content determined. In recent years molecular tests of the lactase gene polymorphism (LCT) are becoming increasingly popular – this method confirms or excludes lactose intolerance in adults (ATH) [Zatwarnicki 2014].

A total resignation of milk consumption due to lactase deficiency in people from different world regions is not justified, as already in the 1970's Newcomer *et al.* [1978] reported on the basis of their investigations that even in the case of a total lack of this enzyme consumption of small amounts of milk during meals, i.e. about 250 ml containing about 11 g lactose, over a period of 24 hours, does not bring on symptoms of intolerance in consumers. The study by Johnson *et al.* [1993] showed that a high daily lactose consumption (20g-50g) by persons with lactase deficiency results in symptoms characteristic of lactose intolerance. It is worth emphasising that mammalian milk is the only natural source of lactose, similarly as dairy products, e.g. whey, buttermilk, cheese, cottage cheese, butter, puddings, ice cream and all dairy supplements [Alm 2002, Harju *et al.* 2016]. The content of lactose in such products usually varies, but the best tolerance is usually observed for those subjected to fermentation, such as yoghurts or certain types of cheeses. Yoghurts are produced as a result of lactic fermentation and thus are initially processed by bacteria, e.g. *Lactobacillus*. Such bacteria digest lactose during the process of yoghurt production and after consumption they are found in the intestines, where they continue to break down lactose, thus assisting the human digestive tract. It is important for yoghurt to contain live bacteria cultures [Zhong *et al*. 2006]. In the food industry lactose is used in the production of numerous foods, including sausages and other processed meats as well as seasoning [Alm 2002, Silanikove et al. 2015, Monti *et al*. 2017]. It is used also by the pharmaceutical industry – about 20% of medicines contain lactose. In pharmaceutical products it is used as an excipient, because it is cheap and gives the product its flavour. Moreover, lactose is used in the production of supplements, homeopathic preparations and oral contraceptives. It is also used in the production of animal feeds.

Despite the fact that lactose is used in the production of numerous foods and pharmaceuticals, most persons inhabiting Europe, especially Northern and Central Europe, do not show symptoms of lactose intolerance as in their organisms the enzyme breaking down lactose is produced throughout the whole life span. The presence of lactase is most important during the first stage of human life, when milk is the only food of the infant and its proper digestion and absorption determine the child's life. For this reason the production of lactase in a majority of people decreases gradually during childhood and milk becomes indigestible. In adults the activity of lactase is only about 10% of that observed in infants.

Investigations conducted by Burger [2007] demonstrated that the DNA of people inhabiting Northern and Central Europe about 7800-7200 years ago did not contain genes responsible for the production of the enzyme facilitating the breakdown of lactose in adults. According to Burger [2007], the mutation leading to the production of lactase in adults appeared about 20 thousand years ago, but remained rare until the development or agriculture and animal breeding, in particular breeding of milk producing animals. The beginnings of cattle breeding date back to about 10 thousand years ago, which means that this mutation developed and spread among Europeans over a period of 400 generations. This is a very short time span, which indicates that it was a favourable mutation and individuals with this mutation had a greater chance of passing on their genes to the following generations. Persons whose organisms produced an enzyme breaking down lactose were able to fully utilise all milk components and thus supplement their diet with this product throughout their whole life.

The ability to digest lactose is widely spread throughout Europe, in particular in the northern and central regions (Tab. 4). Also certain African tribes specialising in cattle breeding are well adapted to the digestion of lactose also in adult life. The deficiency of the lactase enzyme is frequent among the inhabitants of the south of Europe, the Middle East, India, parts of Africa and among their descendants living in various parts of the world [Hollox 2005, Vandenplas 2015].

Glycolytic enzymes and their importance

The principal property of enzymes is their catalytic activity and specificity. Reactions catalysed by enzymes take place rapidly under mild conditions and render it possible to obtain the required product with high efficiency.

Glycosidases are a group of enzymes of the hydrolyse type that assist in the hydrolysis of glycoside bonds in complex sugars, glycoproteins, glycolipids and other glycoside type compounds. β-D-galactosidase (EC 3.2.1.23) (lactase) is an enzyme synthetised by cells of most organisms, starting with bacteria and ending with mammals [Oriordan *et al.* 2015].

This enzyme is a catalyst of the hydrolysis reaction of O-glycosidase bonds in β-D-galactosidase. The best known galactosidase is the disaccharide found in milk, i.e. lactose. As a result of the enzymatically catalysed hydrolysis reaction of the β-1,4-glycosidic bond in lactose two monosaccharide molecules are created – D-glucose and D-galactose [Jóźwik *et al*. 2016].

The activity of β-D-galactosidase leads to the production of glucose-galactose oligosaccharides, which due to their valuable properties are classified as components of functional food, i.e. food which, apart from the typical nutritive value, has also a favourable effect on the health of humans [Ganzle 2012, Seki and Saito 2012, Idda 2016]. Galactoolygosaccharidases (GOS) are carbohydrates composed of D-glucose and D-galactose molecules linked by glycoside bonds and they are not liable to hydrolysis under the influence of human digestive enzymes. However, they are a substrate for the fermentation conducted by specific species of bacteria populating the large intestine. The principal quality of GOS is their ability to stimulate the development and activity of *Bifidobacterium and Lactobacillus* bacteria strains in the colon. This facilitates the maintenance of an equilibrium in the composition of intestinal microflora, inhibits the development of pathogens (*Escherichia coli, Salmonella tyhi, Staphylococcus aureus*) and prevents infections. Moreover, olygosaccharides assist in the restoration of beneficial intestinal microflora after an antibiotic treatment. A diet containing galactoolygosaccharides helps lower blood cholesterol level, decreases the risk of colon cancer and prevents hypertension [Ganzle 2012].

The author conducted investigations, in which the activity of glycolytic enzymes, including beta-D-galactosidase, was analysed in relation to selected genetic (breed) and environmental (nutrition system) factors. The activity of beta-D-galactosidase was determined in the milk of PHF and Montbeliarde breeds as well as PHF x Jersey crossbreeds during the autumn-winter and spring-summer seasons. The studies demonstrated that the glycosidase activity analysed in milk samples was determined by nutrition, i.e. an environmental factor. A lower activity of all the glycosidases examined was recorded in the milk of cows after the autumn-winter feeding season, when the cows received diets consisting of corn silage and haylages. After the end of the spring-summer feeding season, during which animals were fed green forage, a higher activity of beta-D-galactosidases was observed in the milk of PHF, PHF x Jersey and Montbeliarde cows. The results obtained indicate the presence of significant correlations between the activity of the glycosidases analysed and the percent content of lactose in the milk of cows during the spring-summer feeding season, The higher concentration of lactose was accompanied by a higher activity of the enzymes examined. During the autumn-winter feeding season no significant relations were observed between the activity of the glycosidases analysed and lactose concentration in the milk of cows [Jóźwik *et al*. 2016].

The results obtained in the farming practice in dairy herds confirm the effect of the nutrition system and animal breed on the glycolytic activity of milk. The use of green forages during the spring-summer feeding season results in an increased activity of beta-D-galactosidase, which determines the degree of lactose assimilability in consumers. The higher activity of beta-galactosidase in the milk of cows grazing during the vegetation season may lead to a better tolerance of milk by consumers [Jóźwik *et al.* 2016].

Recapitulating, it is worth emphasising that lactose is a unique disaccharide and milk is its only natural source. The milk sugar is characterised by low sweetness, caloricity and glycaemic index. It exhibits dietetic and probiotic properties, increases the absorption of calcium, phosphorus, magnesium and certain microelements. It leads to a better utilisation of vitamin D by the organism. Lactose is a component of foods, but is also used in the production of pharmaceuticals and animal feeds.

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