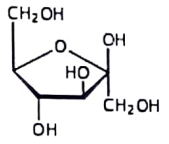
METABOLISM OF SUGARS OTHER THAN GLUCOSE

DEGRADATION OF FRUCTOSE

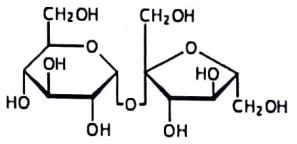
Notes: Starch is the most abundant carbohydrate in our diet, which makes glucose the most important dietary monosaccharide. However, our diet contains several other sugars in significant amounts. The guiding motif in the metabolism of these sugars is economy: instead of completely separate degradative pathways, there are short adapter pathways which merge into the main pathway of carbohydrate degradation, that is, glycolysis.

Lactose and sucrose are disaccharides. Degradation of both sugars begins with hydrolytic cleavage, which releases glucose and galactose or glucose and fructose, respectively. Fructose is also found in the diet as a monosaccharide. We already know how glucose is degraded, so we here only need to concern ourselves with the remaining monosaccharides. The degradation of sorbitol will be discussed as well, whereas ribose and deoxyribose will be covered in later chapters.

DEGRADATION OF FRUCTOSE AND SUCROSE



fructose

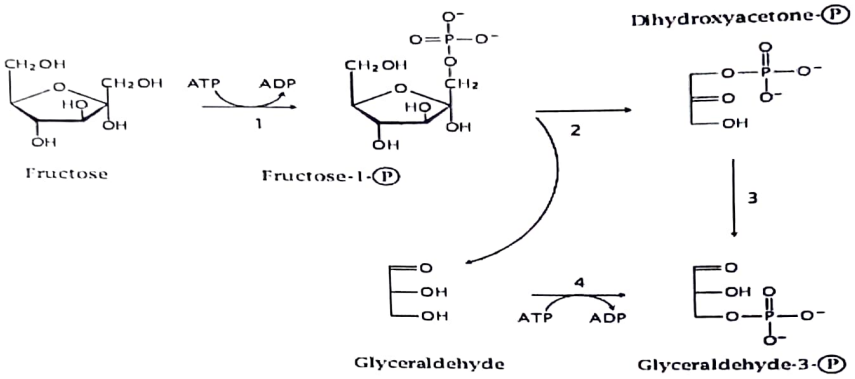


α-D-glucosyl-(1,2)-β-D-fructoside (sucrose)

Notes: Sucrose is produced from sugar cane and sugar beet, which contain it in high concentrations (15–20%). In a typical Western diet, it may amount to as much as 20% of the total carbohydrate intake. Sucrose consists of glucose and fructose joined by a β-glycosidic bond between the carbon 1 of glucose and carbon 2 of fructose.

The hydrolytic cleavage of sucrose, like that of of maltose, occurs at the surface of the intestinal epithelial cells. The enzyme responsible is β-fructosidase, also named sucrase. Both sugars are then taken up by specific transport: Glucose by the SGLT1 transporter, and fructose by the GLUT5 transporter, which is named after glucose but actually transports fructose more effectively than glucose.

Notes: Fructose degradation, also called *fructolysis*, runs mostly in the liver. In the first step, fructose is phosphorylated by fructokinase (1), which uses ATP as a cosubstrate. This yields fructose-1-phosphate. The latter is then cleaved by aldolase B (2). The products of this reaction are dihydroxyacetone phosphate, which is already a metabolite in glycolysis, and glyceraldehyde, which can enter glycolysis after phosphorylation by glyceraldehyde kinase (4).



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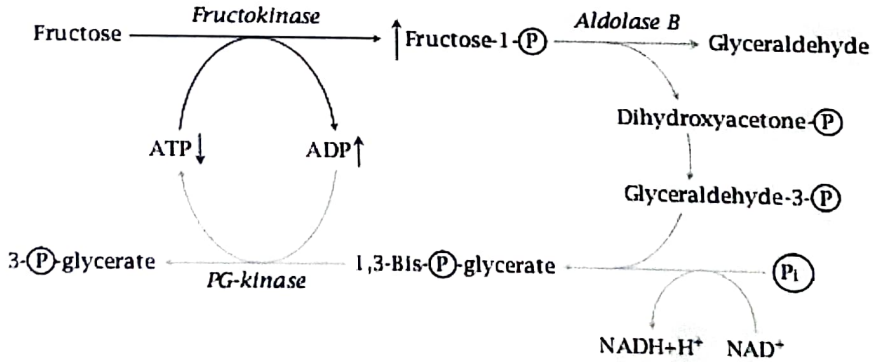
Glyceraldehyde can alternately be utilized by conversion to glycerol and then to glycerol-1-phosphate. The latter is a substrate in the synthesis of triacylglycerol, that is, fat. Fructose and sucrose appear to promote obesity more strongly than equivalent amounts of starch or glucose, and it has been suggested that its utilization via glycerol-1-phosphate, with subsequent triacylglycerol synthesis, may be among the reasons.

FRUCTOSE INTOLERANCE



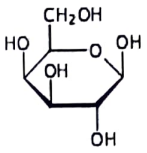
Notes: Fructose intolerance is a hereditary disease caused by a homozygous defect in the aldolase B gene. In this condition, fructose is still phosphorylated by fructokinase. The resulting fructose-1-phosphate, however, cannot be processed further, and therefore the phosphate tied up in it cannot be reclaimed. Since phosphate is required for the regeneration of ATP from ADP, this means that ATP will be lacking, too, which will sooner or later damage or even destroy the cell. Accordingly, the disease is characterized by potentially severe liver failure.

Fructose, alone or in combination with glucose, has been used in the past in the intravenous nutrition of intensive care patients; the perceived advantage of this treatment was the insulin-independent utilization of fructose. However, large intravenous dosages of fructose can significantly deplete liver ATP [7]; apparently, under heavy load, aldolase B may be unable to keep up with fructose kinase. Fructose is no longer a major component of intravenous nutrition schemes.

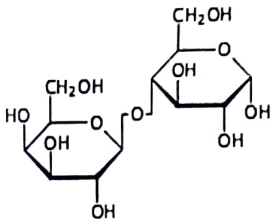
A defect in the gene encoding fructokinase leads to a condition named fructosemia or fructosuria. As these names suggest, fructose levels are increased both in the blood[1] and the urine. Since fructose is not phosphorylated, no phosphate depletion occurs, and the liver cells do not incur any damage. The disease is therefore quite benign.

LACTOSE AND GALACTOSE

Notes: Lactose, a disaccharide of glucose and galactose, is the major carbohydrate contained in milk. Like maltose and sucrose, it is cleaved at the brush border of the small intestine, and the monosaccharide fragments are absorbed and passed along to the liver. The enzyme that accomplishes the cleavage is lactase or, more precisely, β-galactosidase.



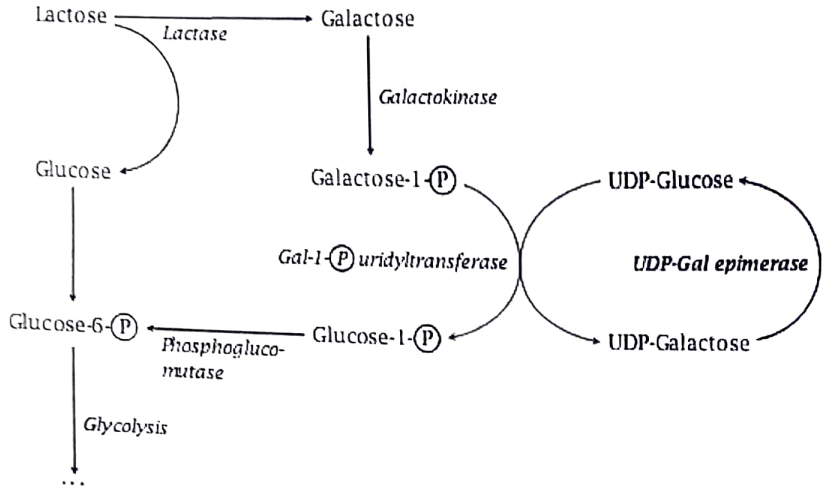
β-D-galactose



β-D-galactosyl-(1 → 4)-D-glucoside (lactose)

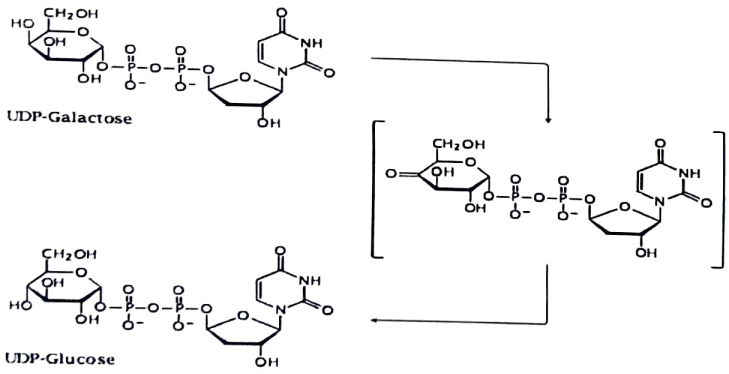
The Leloir pathway for galactose utilization

Notes: Galactose is utilized by conversion to glucose; this happens to a large extent in the liver, but the pathway is active in other tissues as well. The sugar is first phosphorylated by galactokinase. The resulting galactose-1-phosphate undergoes an exchange reaction with UDP-glucose, which is catalyzed by galactose-1-phosphate uridyltransferase and releases glucose-1-phosphate and UDP-galactose. Glucose-1-phosphate can be converted by phosphoglucomutase to glucose-6-phosphate, which is the first intermediate in glycolysis. UDP-galactose is converted to UDP-glucose by UDP-galactose epimerase.



In this pathway, UDP-glucose and UDP-galactose fulfill catalytic roles but are not subject to any net turnover, much like the intermediates in the citric acid cycle. It might therefore be said that they form a tiny metabolic cycle between the two of them. Also note that, save for the final epimerase reaction, the pathway is really just smoke and mirrors—performing the epimerization on galactose directly would accomplish the same net effect, without being chemically more difficult in any way.[2]

MECHANISM OG UDP-GALACTOSE EPIMERASE



Notes: One unusual feature of UDP-galactose epimerase is its use of NAD^+ as a coenzyme, rather than as a cosubstrate—that is, NAD^+ undergoes no net reduction or oxidation in this case. Nevertheless, it functions here much in the same way as it does in other enzyme reactions. The 4′-hydroxyl group of the sugar is transiently dehydrogenated to a keto group, and in this step NAD^+ accepts the abstracted hydrogen. The substrate is then rotated within the active site before the H_2 is transferred back to it, which causes the 4′-OH group to now point the other way.

Notes: Three different enzyme deficiencies in the pathway are subsumed under the name *galactosemia*, which means "galactose in the blood." All of these are rare; type I is the most common and most severe form. Here, the deficient enzyme is galactose-1-phosphate uridyltransferase. This leads to a buildup of galactose-phosphate, but also of several other metabolites. The disease becomes manifest in newborns with acute liver failure and is deadly if not promptly diagnosed and treated. In many countries, this enzyme defect is part of neonatal screening programs.

Therapy consists in the removal of galactose from the diet, but even so organ damage develops, most commonly affecting the CNS and, in girls, the ovaries. The residual pathology that develops in spite of the diet is ascribed to the endogenous synthesis of galactose, which proceeds via UDP-glucose and UDP-galactose; the UDP-galactose epimerase reaction is reversible.

For a long time, it was assumed that accumulation of galactose-1-phosphate and phosphate depletion are responsible for cell and organ damage, which is analogous to the pathogenic mechanism in fructose intolerance (see slide 4.2.2). However, this assumption has been thrown into question by the results of animal experiments. When galactose-1-uridyltransferase is genetically knocked out in mice, these develop a profile of metabolite accumulation that closely resembles human patients, but they do not display any of the pathology observed in humans [8]. What is more, some rare human cases have been reported that show the usual biochemical manifestations, but no clinical signs [9]. The quest for the true cause of the pathology affecting most human patients continues [10, 11].

In the order of the pathway, type II galactosemia comes first, as it involves a defect of galactokinase. In this case, galactose simply does not enter the Leloir pathway at all; it builds up in the blood and is mostly eliminated in the urine. The liver will not be adversely affected. However, there is a common complication elsewhere: the eyes will develop *cataract*, that is, obfuscation of the lenses. This is due to the reduction of galactose to galactitol in the cells of these organs by aldose reductase (see slide 4.4).

The rarest form of galactosemia is due to the defect of UDP-galactose epimerase. The biochemical pattern is similar to type I, except that UDP-galactose also accumulates, and as in type I, developmental delay seems to occur [12]. In this condition, both the utilization and the synthesis of galactose are inhibited, and it appears necessary to maintain a low level of dietary galactose to supply the synthesis of galactose-containing glycolipids and glycoproteins.