

Fructose - Transport, Degradation, and Biosynthesis

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Fructose is a carbohydrate that naturally occurs in fruits and is in the form of sucrose, included in many other foods. While congenital disorders of the fructose metabolism and fructose intolerance are relatively rare, numerous clinical trials have proven a correlation between increased fructose uptake and disorders such as metabolic syndrome and non-alcoholic fatty liver disease.



Chemical Properties of Fructose

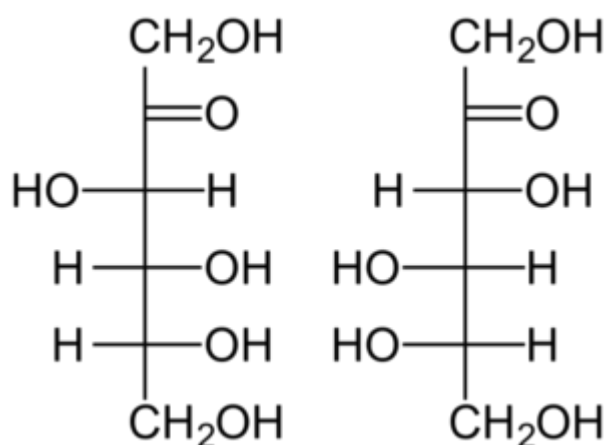


Image: "D-L-Fructose. D-Fructose left, L-Fructose right" by Poyraz 72, License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Fructose (formerly, levulose for 'counterclockwise') belongs with its molecular formula $C_6H_{12}O_6$ to the hexoses, sugars with 6 carbon atoms. Furthermore, it possesses a keto group, which is defined as a carbon atom with a double bond to an oxygen atom.

Therefore, fructose is also a ketose. As the molecule is optically active, it exists in 2 mirror-inverted isomers, called enantiomers. These are usually displayed in the **Fischer projection** which is an open-chain structure that illustrates the spatial structure of chiral compounds.

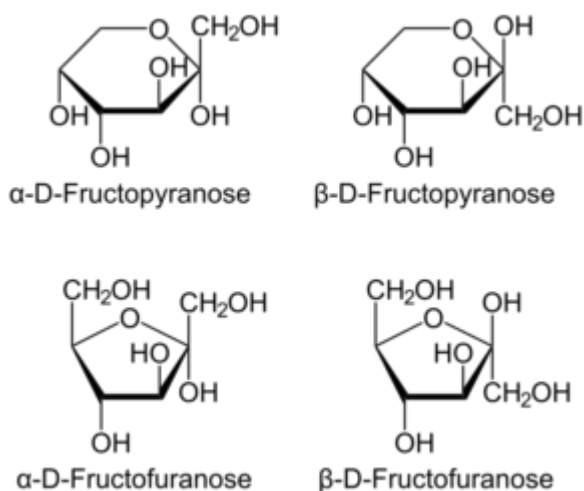


Image: "D-Fructose Haworth" by NEUROtiker, License: [Public Domain](https://commons.wikimedia.org/wiki/File:Public_Domain)

The stereo descriptor D stands for dexter (Latin for 'right') because of the horizontal high priority rest, i.e. the OH standing lowest in the Fischer projection faces to the right. Conversely, there is the L for *laevus* (Latin for left). The enantiomer L-fructose, however, is physiologically not significant.

Also, there exists the **Haworth notation** where the molecule is drawn as a plain ring. In the case of the fructose, this is a special character as it occurs in crystalline form as a 6-membered ring (called fructopyranose) and in bound form as a 5-membered ring (called fructofuranose). The α - and β -anomers of each ring shape can be converted into each other in an aqueous solution and are in equilibrium with each other.

Fructose Deposits in Foods

Fructose (from Latin, *fructis* = fruit) naturally occurs as a monosaccharide, i.e. as a simple sugar, especially in some fruit (e.g., 6 g fructose per 100 g apples) and honey (40 g per 100 g). The main part of fructose, however, that we absorb as disaccharide **sucrose** (Latin *saccharum* = sugar), is our usual industrial sugar. Sucrose consists of α -D-glucose and β -fructose that are linked via an α,β -1,2-glycosidic bond.

Industrially produced foods increasingly contain maize-derived fructose in the form of **high-fructose corn syrups**. Because of its very sweet flavor and good solubility in water, the syrup is mainly used for sweetening soft drinks.

Fructose Transport inside Cells

In the **upper small intestine**, sucrose is firstly split into glucose and fructose by the enzyme saccharase. The resorption of fructose from the small intestinal lumen into the enterocytes (Latin for intestinal cells) takes place **passively**, i.e. energy-independent in contrast to glucose. The **fructose transporter GLUT5** (to a lesser degree, also other class 2 sugar transporters such as GLUT7, 9, and 11) transports fructose along its concentration gradient into the cell interior.

When there is an intracellular/extracellular equilibrium reached, fructose uptake stops and is thus never completely absorbed. This means that in cases of very high dietary intake, fructose becomes osmotically active in the intestine and can cause diarrhea, especially in young children.

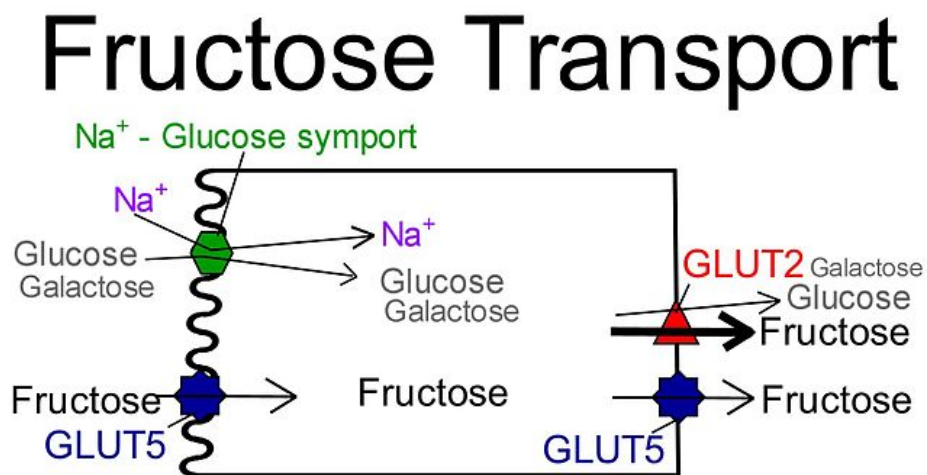


Image: "Intestinal monosaccharide transporters" by NuFS, San Jose State University, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

It is mainly utilizing the **GLUT2 transporter** that fructose passes through the basolateral membrane of the intestinal cells, i.e. the membrane facing the bloodstream. Through this transport protein, glucose and galactose are channeled into the blood. Next, the blood flow from the small intestine to the liver occurs via the portal vein.

Fructose Degradation in Liver Cells

Since the fructose uptake by cells is **insulin-independent**, fructose was used as a sweetener for so-called diet products for diabetics for a long time. Since 2010, however, those products are no longer available.

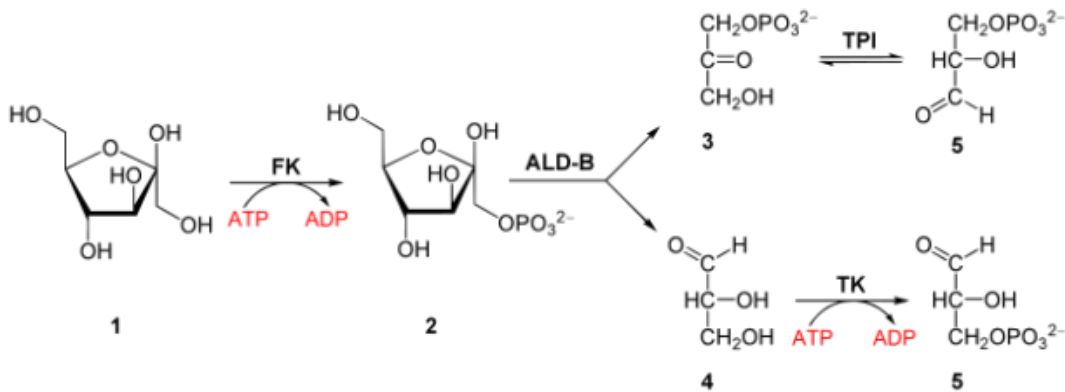


Image: "Fructose in glycolysis" by Yikrazuul, License: [Public Domain](#)

In the cells of the liver, the hepatocytes, **D-fructose** is converted into D-fructose-1-phosphate by the enzyme **fructokinase** (also called keto-hexokinase) and is thus no longer able to leave the cell. This reaction is adenosine triphosphate (ATP)-dependent.

Fructose-1-phosphate is split by aldolase B into dihydroxyacetone phosphate and glyceraldehyde. Dihydroxyacetone phosphate is a byproduct of glycolysis and is further metabolized by triose phosphate isomerase to produce energy.

In an ATP-dependent reaction, glyceraldehyde is phosphorylated into **glyceraldehyde 3-phosphate** by the triose kinase and, thus, may enter the glycolysis or the triglyceride synthesis and is deposited as depot fat.

Disorders of Fructose Metabolism

Following are some pathological conditions associated with fructose:

Essential Fructosemia and Fructosuria

The essential fructosemia and fructosuria are caused by a defect in the **fructokinase** of the hepatocytes. This enzyme failure leads to the accumulation of fructose in the blood (fructosemia) and urine (fructosuria). It is a benign and asymptomatic condition (other than fructosuria). This rare disease has **no pathological value** and is therefore in no need of treatment.

Hereditary Fructose Intolerance

The incidence of this rare, **autosomal recessive** inherited disease is between 1:20,000–1:130,000 depending on the source. The reason is a hereditary deficiency of **aldolase B**, which in hepatocytes normally splits fructose-1-phosphate into dihydroxyacetone phosphate and glyceraldehyde. Aldolase A, an enzyme of glycolysis, is not affected by this defect. The aldolase A, however, metabolizes fructose-1-phosphate 50 times slower than its actual substrate, fructose 1,6-bisphosphate.

This results in an **accumulation of fructose-1-phosphate in the hepatocytes**. This results in a decreased availability of phosphates which inhibits the enzymes of glycolysis and gluconeogenesis, e.g., fructose 1,6-bisphosphatase and glycogen phosphorylase. In periods of hunger, **life-threatening hypoglycemia** occurs because glucose cannot be synthesized from glycogen. Additionally, **hepatomegaly** with progressive liver destruction pending liver cirrhosis may develop.

Usually, the first symptoms appear at the start of feeding baby food containing fruits to the child, since breast milk is fructose-free. In mild forms, the child often has an aversion to fruit juices and other fructose-containing foods and cries a lot. In severe cases, the infants are hypoglycemic with symptoms of the adrenergic counter-reaction such as sweating, trembling, vomiting, seizures, and even coma.

Since the aldolase B is also present in the kidney, the hereditary fructose intolerance also results in **kidney damage** with proteinuria (the increased excretion of proteins along with the urine).

Diagnoses are made with molecular genetic tests that cover the 3 most common mutations (A149P, A174D, and N334K) of aldolase B. One of those 3 mutations can be detected in 90% of affected people. Newborn screenings do not detect the hereditary fructose intolerance.

As is the case with most congenital metabolic disorders, the only effective treatment is complete avoidance of fructose-containing food and sucrose (which is glucose + fructose). For small children, the vitamins contained in fruits and vegetables should be substituted with supplemental products. The **partial thromboplastin time (PTT)** and antithrombin III are **progression parameters** as these coagulation parameters respectively are factors that are already pathologically detectable in case of minor liver damage.

Particular caution should be exercised in case of **sorbitol infusions**. These are rarely used for the reduction of intracranial pressure, due to their osmotic activity. In case of fructose intolerance, sorbitol can also not be degraded and results in the same symptoms including death.

Intestinal Fructose Intolerance

The intestinal fructose intolerance is much more common than the hereditary fructose intolerance. About **1/3rd of the people** suffer from **fructose malabsorption**, which means that only a small amount of fructose is absorbed in the small intestine, so a significant portion passes into the large intestine. Fructose increases the osmotic pressure in the large intestine and, thus, deprives the intestine of liquid.

Furthermore, the bacterial flora of the colon ferments the fructose into carbon dioxide, short-chained fatty acids, and methane. This can lead to **diarrhea and meteorism** which is why we now speak of intestinal fructose intolerance. One-third of the people with fructose malabsorption suffer from intestinal fructose intolerance.

The causes of fructose malabsorption are diverse: for example, a **below-average number** or performance of **GLUT5** can be the reason but also a rapid intestinal passage of chyme. Fructose intolerance may be a **normal variation** than a disease, as is the case with lactose intolerance.

The intestinal fructose intolerance may also develop secondarily based on an

inflammatory bowel disease that affects the small intestine. In the case of Crohn's disease, e.g., the small intestine's mucous membrane is damaged so badly that fructose cannot be absorbed anymore. As in the case of hereditary fructose intolerance, the only effective therapy is the **avoidance of fructose**, sorbitol, and other oligo- (mannitol, xylitol) or disaccharides since those often trigger the same symptoms.

Nevertheless, most people affected by fructose intolerance tolerate sucrose because of the GLUT2 transport protein. GLUT2 is also localized in the apical membrane of small intestine cells. It is quickly integrated into the cell membrane when the transport protein SGLT1, an adenosine triphosphate (ATP)-dependent sodium-glucose co-transporter, transports glucose. **GLUT2 then transports glucose as well as fructose into the enterocytes, independent from GLUT5.**

Therefore, it is advisable rather than adhering to a diet without any fruits and fructose-containing vegetables to eat fruits that contain approximately equal proportions of glucose and fructose.

	Fructosemia/-uria	Hereditary fructose intolerance	Intestinal fructose intolerance
Frequency	Unknown due to often random diagnoses	1:20,000-1:130,000	About 10% of the population
Failure	Fructokinase	Aldolase B	GLUT5
Symptoms	None	Hypoglycemia, liver fibrosis/cirrhosis, and kidney damage	Meteorism, flatulence, and diarrhea
Therapy	Unnecessary	Strict diet without fructose	Diet low in fructose

Fructose Biosynthesis from Glucose

A biosynthesis of fructose from glucose in **extrahepatic tissue** is possible via the so-called polyol pathway. This takes place, particularly in the glandulae vesiculosae, a man's **seminal vesicles**, in a testosterone-dependent process. The seminal fluid then has a high content in fructose that serves the sperms contained in the ejaculate as nutrients. The fructose content of fresh ejaculate is determined via the fructose test. If the content is decreased, it indicates a hypofunction of testosterone-producing Leydig cells in the testes.

The **aldose reductase** initially reduces the aldehyde group at the glucose's C-atom 1 to a -CH₂OH group. The resulting compound is **sorbitol**.

Afterward, sorbitol is oxidized at C-atom 2 by the **sorbitol dehydrogenase**, and fructose is formed.

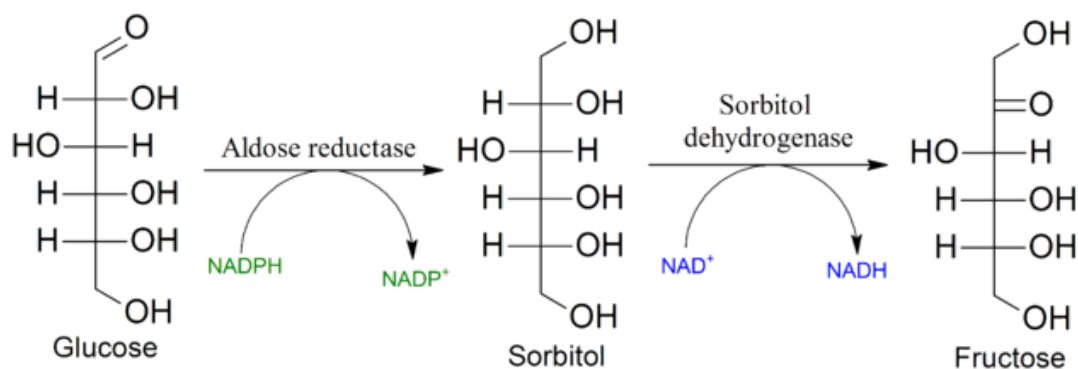


Image: "Polyol pathway" by LHcheM, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

NADPH serves as co-substrate for the aldolase reductase and is reduced (oxidized) to NADP. In a 2nd step, NAD⁺ is reduced to NADH by the sorbitol dehydrogenase. The overall result is the conversion of **NADPH** to NADH, which is suggested to be responsible for the long-term consequences of a permanently elevated blood sugar level. This is because NADPH has an antioxidant effect and is not present in the body as a substrate.

Furthermore, an increased fructose concentration in the eye lens, in case of diabetes mellitus, may lead to the development of **cataracts** via the polyol pathway. Sorbitol and glucose are highly osmotic and cause swelling of the eye lens.

Fructose as a Trigger for Diseases

Several studies prove a correlation between increased fructose uptake and **obesity**. Fructose does not only increase **lipogenesis** but also leads to an increased **feeling of hunger** since no insulin is released that also is a saturation hormone.

Also, a fructose-rich diet leads to an **increase in plasma lipids** and **insulin resistance**. Thus, fructose is permanently diabetogenic and to a higher degree than glucose. All in all, fructose increases the incidence of **metabolic syndrome**, which is defined as the joint appearance of obesity, dyslipidemia, impaired glucose tolerance, and hypertension.

Further studies show a correlation between fructose uptake and **non-alcoholic fatty liver** (steatosis hepatis) which is a preliminary stage of liver cirrhosis.

Also, the risk of developing gout is increased dramatically, particularly through fructose-sweetened soft drinks as evidenced by prospective studies including thousands of patients. The reason is the consumption of ATP during fructose degradation. Inosine 5'-monophosphate (IMP) accumulates and leads to an increase of uric acid concentration via purine metabolism.

According to recent studies, the risk of cancers such as **pancreatic carcinoma** increases through a fructose-rich diet. Fructose contributes to the synthesis of nucleic acids which encourages the proliferation of cancer cells.

For these reasons, the Food and agriculture organization of the United States recommends reducing the daily intake of free sugars such as fructose to less than 10% of the total amount of energy.

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