9.1: Monosaccharide metabolism

Fructose metabolism

Fructose is a dietary component of sucrose in fruit, as a free sugar in honey, and in high-fructose corn syrup. It is taken up by cells through facilitated diffusion through the GLUT5 transporter. Fructose is metabolized principally in the liver, and the initial step involves phosphorylation at the 1-position to form fructose 1-phosphate (figure 9.1). Fructokinase, the major kinase involved, phosphorylates fructose in the 1-position. Fructokinase has a high \(V_{\text{max}}\) and rapidly phosphorylates fructose as it enters the cell. Aldolase B cleaves fructose 1-phosphate into glyceraldehyde 3-phosphate and dihydroxyacetone-phosphate, which can enter directly into glycolysis.
Figure 9.1: Convergence of fructose and glucose metabolism.

Aldolase B is the rate-limiting enzyme of fructose metabolism, although it is not a rate-limiting enzyme of glycolysis. Aldolase B’s affinity for fructose 1-phosphate is lower than fructose 1,6-bisphosphate and is very slow at physiological levels of fructose 1-phosphate. Consequently, after high fructose consumption, fructose 1-phosphate will accumulate in the liver, and it is slowly converted to glycolytic intermediates over time (figures 9.1 and 9.2).

Deficiencies in fructose metabolism

Essential fructosuria (fructokinase deficiency) and hereditary fructose intolerance (HFI) (a deficiency of the fructose 1-phosphate cleavage by aldolase B) are inherited disorders of fructose metabolism. A deficiency in fructokinase is a benign genetic disorder. In this case, an individual will have fructosuria; fructose is not phosphorylated and trapped in the cell. Consequently, any ingested fructose is shed in the urine. Hereditary fructose intolerance is caused by a deficiency in aldolase B and results in an accumulation of fructose 1-phosphate in the hepatocytes. Inability to metabolize fructose 1-phosphate can cause significant clinical symptoms, most notably hepatomegaly and fasting hypoglycemia. The accumulation of fructose 1-phosphate eventually inhibits both glycogenolysis and gluconeogenesis (due to a lack of free phosphate), leading to bouts of fasting hypoglycemia.

Galactose metabolism

Galactose is consumed principally as lactose, which is cleaved to galactose and glucose in the intestine. Galactose is subsequently phosphorylated to galactose 1-phosphate by galactokinase (primarily in the liver). Following
phosphorylation, galactose 1-phosphate is activated to a uridine diphosphate (UDP)-sugar by galactosyl uridylyltransferase (GALT). The metabolic pathway subsequently generates glucose 1-phosphate, which enters into the glycolytic pathway (figure 9.2)

Figure 9.2: Fructose metabolism and reaction by aldolase B. Deficiencies in aldolase B can result in hereditary fructose intolerance, while deficiencies in fructokinase can result in essential fructosuria.

Deficiencies in galactose metabolism

Classical galactosemia, a deficiency of galactosyl uridylyltransferase (GALT), results in the accumulation of galactose 1-phosphate in the liver and the inhibition of hepatic glycogen metabolism and other pathways that require UDP-sugars. Cataracts can occur from the accumulation of galactose in the blood, which is converted to galactitol (the sugar alcohol of galactose) in the lens of the eye.

Figure 9.3: Galactose metabolism; glucose 6-phosphate is converted to glucose 1-phosphate, which enters the pathway.

The accumulating galactose 1-phosphate is especially toxic for the liver, kidneys, and central nervous system. If left untreated, the disease is fatal due to complications such as gram-negative sepsis or hepatic and renal failure. The absence of GALT activity can be detected any time after birth and screened for as part of newborn screening. It is essential to obtain results promptly, because children with classic galactosemia can have a life-threatening crisis within the first few days after birth. Infants with a positive result are placed on a lactose-free formula, and confirmatory testing is accomplished by measuring specific metabolite concentrations and enzyme activity in erythrocytes.

Nonclassical galactosemia causes fewer medical complications and presents with a different pattern of symptoms. Presentations can involve cataracts, delayed development, and kidney problems.
Figure 9.4: Comparison of classical and nonclassical galactosemia.

References and resources

Text


Figures


Grey, Kindred, Figure 9.2 Fructose metabolism and reaction by Aldolase B. Deficiencies in aldolase B can result in hereditary fructose intolerance while deficiencies in frutokinase can result in essential fructosuria. 2021. https://archive.org/details/9.2_20210926, CC BY 4.0.

Grey, Kindred, Figure 9.3 Galactose metabolism; glucose 6-phosphate is converted to glucose 1-phosphate which enters the pathway. 2021. https://archive.org/details/9.3_20210926, CC BY 4.0.