Fructose Metabolism

Fructose is one of the main sweetening agents in the human diet. It is found in its free form in honey, fruits and many vegetables, and is associated with glucose in the form of the disaccharide sucrose in numerous foods and beverages. Sorbitol, also widely distributed in fruit and vegetables, is converted into fructose in the liver by sorbitol dehydrogenase (Fig. 8.1).

Fig. 8.1. Fructose is mainly metabolized by a specialized pathway found in the liver, kidney cortex and small-intestinal mucosa and composed of fructokinase (1), aldolase B (2) and triokinase (3). Aldolase B also intervenes in the glycolytic-gluconeogenic pathway, which also includes the following enzymes: fructose-1,6-bisphosphatase (4), phosphofructokinase (5), glucose-6-phosphate isomerase (6), glucokinase and hexokinase (7), glucose-6-phosphatase (8) and glyceraldehyde-3-phosphate dehydrogenase (9). Also shown are glycogen phosphorylase (10) and sorbitol dehydrogenase (11). 1,3-P,GA, 1,3-bisphosphoglycerate; DHA-P, dihydroxyacetone phosphate; F, fructose; G, glucose; GAH, glyceraldehyde; P, phosphate; Pi, inorganic phosphate. The three enzyme defects in fructose metabolism are depicted by solid bars across the arrows; the diminished activity of aldolase B toward fructose-1,6-bisphosphate in hereditary fructose intolerance is depicted by a broken bar.
Two inborn errors are known in the specialized pathway of fructose metabolism depicted in Fig. 8.1. Essential fructosuria is a completely harmless anomaly characterized by the appearance of fructose in the urine after the intake of fructose-containing foods. In hereditary fructose intolerance (HFI), fructose provokes prompt gastrointestinal discomfort and hypoglycemia upon ingestion, although sensitivity varies from patient to patient; it may cause liver and kidney failure when taken persistently and becomes life threatening when given intravenously. Fructose-1,6-bisphosphatase (FBPase) deficiency is usually also considered an inborn error of fructose metabolism although, strictly speaking, it is not a defect of the specialized fructose pathway. It is manifested by the appearance of hypoglycemia and lactic acidosis (neonatally or during fasting) and may also be life-threatening.

Essential Fructosuria

Clinical Presentation

Essential fructosuria is a rare “non-disease”; it is detected by the routine screening of urine for reducing sugars [1]. It is caused by a deficiency of fructokinase [2], the first enzyme of the specialized fructose pathway (Fig. 8.1). Fructokinase is normally only found in the liver, kidney and small-intestinal mucosa.

Metabolic Derangement

In cases of deficiency, ingested fructose is partly excreted as such in the urine and is partly slowly metabolized by an alternate pathway, namely conversion into fructose-6-phosphate by hexokinase in adipose tissue and muscle.

Diagnostic Tests

Fructose gives a positive test for reducing sugars and a negative reaction with glucose oxidase. It can be identified by various techniques, such as thin-layer chromatography [3]. Fructose-tolerance tests (see “Hereditary Fructose Intolerance”) provoke neither an increase in blood glucose, as in normal subjects, nor hypoglycemia, as in HFI and FBPase deficiency.

Treatment and Prognosis

Dietary treatment is not indicated, and the prognosis is excellent.

Genetics

The mode of inheritance is autosomal recessive, and the frequency of the homozygotes has been estimated at 1:130,000 [4]. Two mutations, G40R and A43T, altering the same region of fructokinase, have been found in a family with three compound heterozygotes [5].