Fructose metabolism

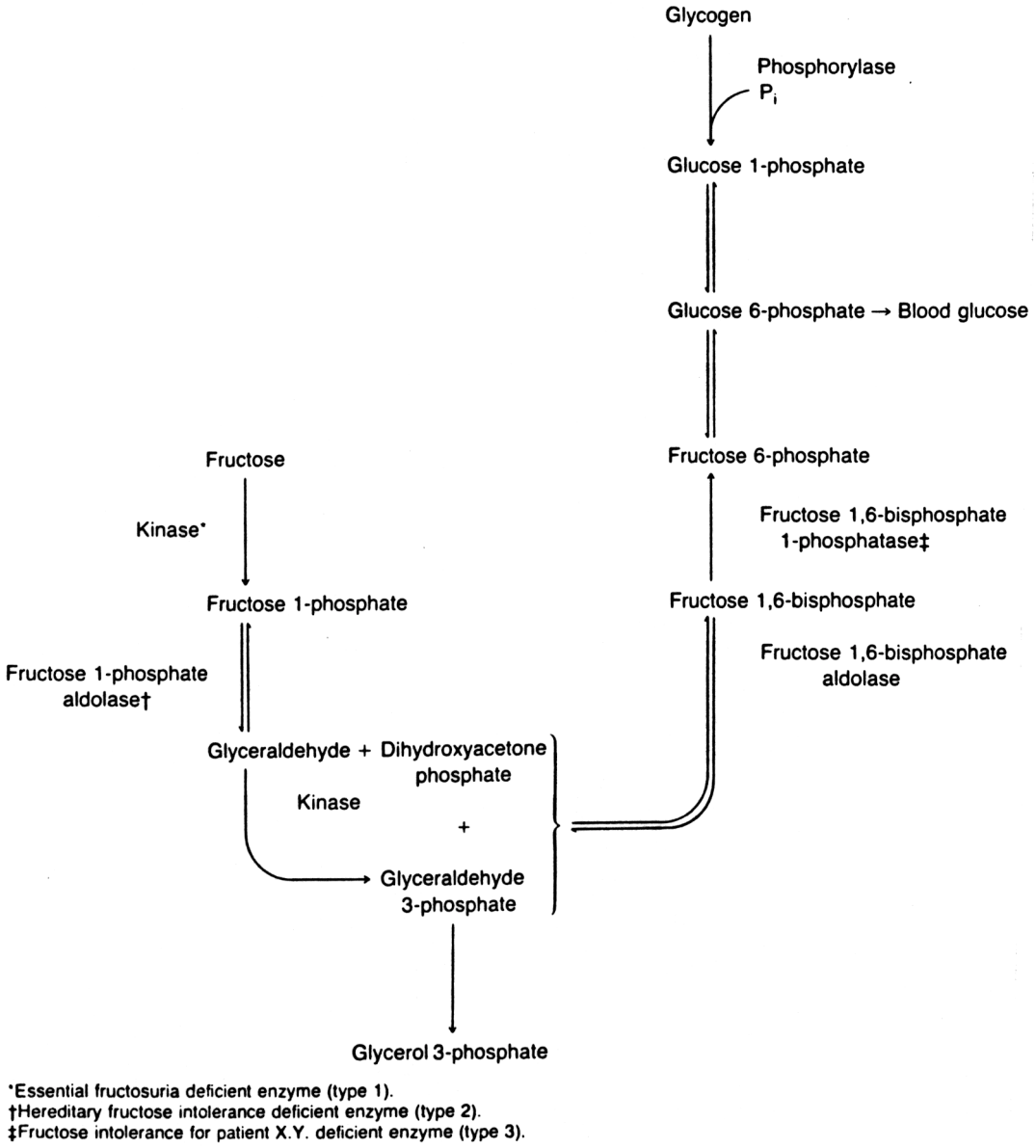
Clinical case: Hereditary fructose intolerance

A child had nausea, vomiting, and symptoms of hypoglycemia: sweating, dizziness, and trembling. It was reported that these attacks occurred shortly after eating fruit or cane sugar. This was resulting in a strong aversion to fruits, and the mother was therefore providing large supplementations of multivitamin preparations. The child was below normal weight and was an only child who had been breast fed, during which time none of these symptoms was evident. The clinical findings included some cirrhosis of the liver, a normal glucose tolerance test, and reducing substances in the urine that did not react positively with glucose test papers, in which glucose oxidase was used as the basis for test. A fructose tolerance test was ordered, using 3 g fructose/m^2 of surface, given intravenously in a single, rapid push. Within 30 min the child displayed the symptoms of hypoglycemia. Blood glucose analysis confirmed this and revealed that the hypoglycemia was maximal after 60 to 90 min. Fructose concentrations reached a maximum (3.3 mmol/L) after l5 min and gradually decreased to zero in 2.5 h. P_i concentrations fell by 50%, and AST and ALT elevations were noted after l.5 h. The urine was positive for fructose.

Biochemical questions

1. Explain why the fructose concentration in the blood remained elevated for an extended period.
2. What evidence exists to suggest that the aldolase for D-fructose 1-phosphate and D-fructose l,6-bisphosphate is the same protein?
3. Explain the elevations noted for AST and ALT in the fructose tolerance test.
4. Why are the symptoms of hypoglycemia not found in essential fructosuria (type 1)?
5. What would be the consequences of a deficiency of phosphofructokinase in the patient?

Case discussion
Hereditary fructose intolerance is caused by a deficiency of fructose 1-phosphate aldolase.
Fig 1. Fructose metabolism



l. Blood fructose The metabolism of fructose is initiated by its phosphorylation in liver to D-fructose 1-phosphate, as catalyzed by fructokinase. With a deficiency of aldolase, D-fructose l-phosphate accumulates and inhibits the kinase reaction, resulting in a slower removal of fructose from the blood. With high fructose concentration in the blood, some may be phosphorylated in

muscle and adipose tissue by hexokinase. The D-fructose 6-phosphate so produced is converted to D-glucose 6-phosphate, which may enter the catabolic pathways or be converted to glycogen. It cannot be released to the blood, however, to overcome the hypoglycemia that develops because muscle and adipocytes do not contain glucose 6-phosphatase.

2. Aldolase. Crystalline human liver aldolase functions with both D-fructose 1-phosphate and D-fructose 1,6-bisphosphate substrates. However, liver tissue from patients with hereditary fructose intolerance shows significant fructose 1,6-bisphosphate aldolase activity but reduced or no fructose 1-phosphate aldolase activity. Tissue from normal subjects shows approximately equal activities. The aldolase in this type of fructosuria may be a mutant of the normal enzyme in which fructose l,6-bisphosphate aldolase activity remains. It is known, for example, that antibodies against normal liver aldolase react to an extent of 30% with the liver enzyme of patients with hereditary fructose intolerance.

3. Enzyme elevations. Fibrosis or cirrhosis of the liver are some of the chronic results of the disease. After ingestion of D-fructose, the liver hepatocytes show histologic changes after 1 to 1.5 h and release increased amounts of AST(GOT) and ALT(GPT).

4. Essential fructosuria, type 1. Essential fructosuria is caused by the deficiency of fructokinase, without which there would be no accumulation of D-fructose 1-phosphate and no subsequent enzyme inhibition of the glycogen pathways or depletion of P_i or ATP. Without this enzyme deficiency, mechanisms to respond to hypoglycemia would be available, and this condition would not arise.

5. Phosphofructokinase deficiency. The glycolytic pathway is functioning normally in this patient. Therefore the fructose 1,6-bisphosphate aldolase can catalyze the breakdown of fructose 1,6-bisphosphate, which arises from the phosphorylation of D-fructose 6-phosphate. D-Fructose 6-phosphate is an intermediate in the catabolism of D-galactose, D-glucose, and other hexoses. If phosphofructokinase were also deficient in this case, the patient would be in a very difficult situation. The catabolism of all the hexoses in the diet could not proceed through glycolysis, so they would be converted to glucose and accumulate as glycogen. As more glycogen is built up, the liver would be damaged further. The absence of phosphofructokinase, which has not been reported clinically (not in the liver), is probably fatal to the fetus.

Further questions

1. Would you suggest fructose consumption for diabetic patients? What is the effect of fructose consumption on blood sugar level? Can sucrose provoke insulin release from pancreatic islets?
2. Parenteral administration of fructose to critically ill patients occasionally results in development of serious lactic acidosis. Similar phenomenon was not observed after intravenous glucose administration. Why?
3. Intravenous administration of fructose results in the decrease of [ATP] in liver cells. Explain the phenomenon.

References:

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