433e Glycogen Storage Diseases and Other Inherited Disorders of Carbohydrate Metabolism

Priya S. Kishnani, Yuan-Tsong Chen

Carbohydrate metabolism plays a vital role in cellular function by providing the energy required for most metabolic processes. The relevant biochemical pathways involved in the metabolism of these carbohydrates are shown in Fig. 433e-1. Glucose is the principal substrate of energy metabolism in humans. Metabolism of glucose generates ATP through glycolysis and mitochondrial oxidative phosphorylation. The body obtains glucose through the ingestion of polysaccharides (primarily starch) and disaccharides (e.g., lactose, maltose, and sucrose). Galactose and fructose are two other monosaccharides that serve as sources of fuel for cellular metabolism; however, their role as fuel sources is much less significant than that of glucose. Galactose is derived from lactose (galactose + glucose), which is found in milk products, and is an important component of certain glycolipids, glycoproteins, and glycosaminoglycans. Fructose is found in fruits, vegetables, and honey. Sucrose (fructose + glucose) is another dietary source of fructose and is a commonly used sweetener.

Glycogen, the storage form of glucose in animal cells, is composed of glucose residues joined in straight chains by α1-4 linkages and branched at intervals of 4–10 residues by α1-6 linkages. Glycogen forms a treelike molecule and can have a molecular weight of many millions. Glycogen may aggregate to form structures recognizable by electron microscopy. With the exception of type 0 disease, defects in glycogen metabolism typically cause an accumulation of glycogen in the tissues—hence the designation *glycogen storage diseases* (GSDs). The structure of stored glycogen can be normal or abnormal in the various disorders. Defects in gluconeogenesis or glycolytic pathways, including galactose and fructose metabolism, usually do not result in glycogen accumulation.

Clinical manifestations of the various disorders of carbohydrate metabolism differ markedly. The symptoms range from harmless to lethal. Unlike disorders of lipid metabolism, mucopolysaccharidoses, or other storage diseases, many carbohydrate disorders have been effectively managed with dietary therapy. All of the genes responsible for inherited defects of carbohydrate metabolism have been cloned, and mutations have been identified. Advances in our understanding of the molecular basis of these diseases are being used to improve diagnosis and management. Some of these disorders are candidates for enzyme replacement therapy, substrate reduction therapy, and early trials of gene therapy.

Historically, the GSDs were categorized numerically in the order in which the enzymatic defects were identified. They are also classified by the organs involved (liver, muscle, and/or heart) and clinical manifestations. The latter is the system followed in this chapter (Table 433e-1). The overall frequency of all forms of GSD is ~1 in 20,000 live births. Most are inherited as autosomal recessive traits; however, phosphoglycerate kinase deficiency—one form of liver phosphorylase kinase (PhK) deficiency—and lysosomal-associated membrane protein 2 (LAMP2) deficiency are X-linked disorders. The most common childhood disorders are glucose-6-phosphatase deficiency (type I), lysosomal acid α-glucosidase deficiency (type II), debrancher deficiency (type III), and liver PhK deficiency (type IX). The most common adult disorder is myophosphorylase deficiency (type V, or McArdle disease).

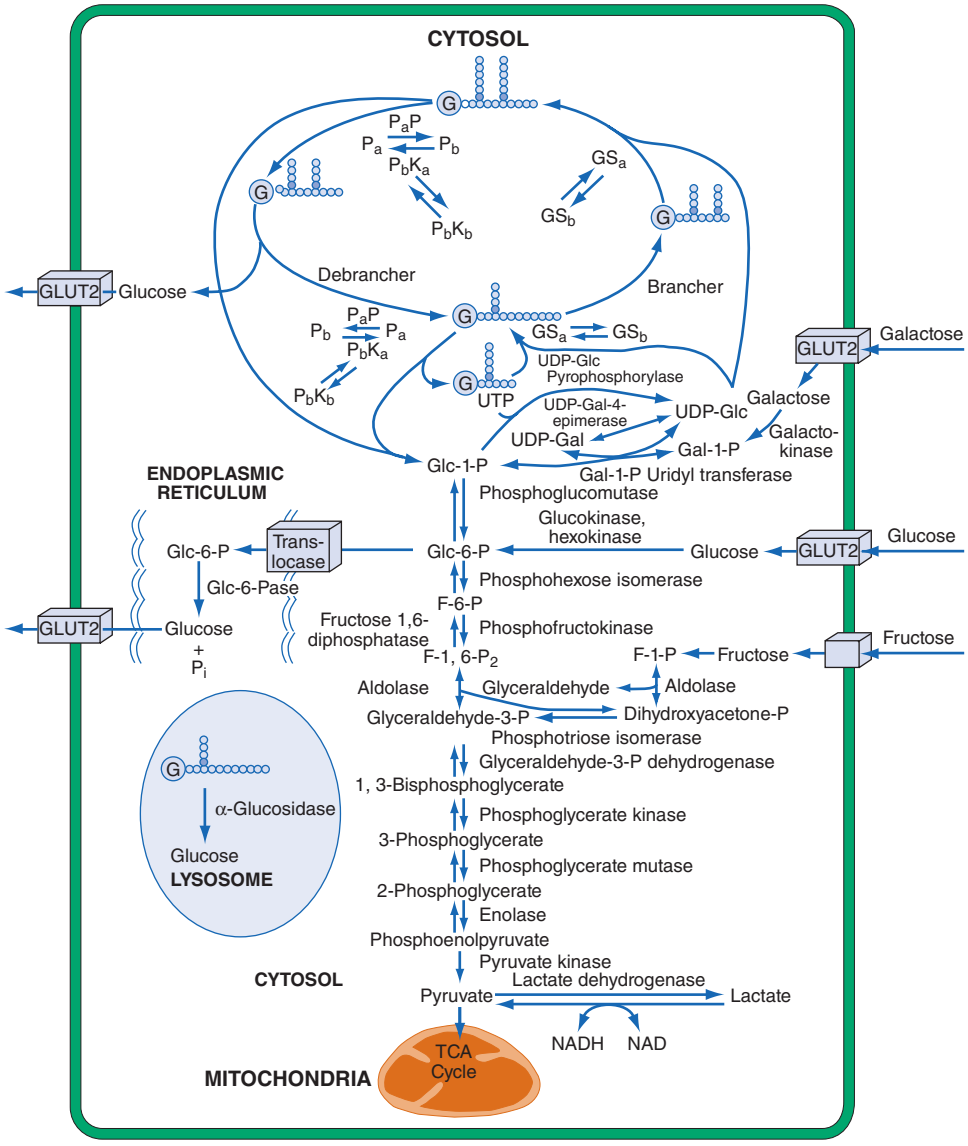

FIGURE 433e-1 Metabolic pathways related to glycogen storage diseases and galactose and fructose disorders. Nonstandard abbreviations are as follows: GS_a, active glycogen synthase; GS_b, inactive glycogen synthase; P_a, active phosphorylase; P_b, inactive phosphorylase; P_aP, phosphorylase *a* phosphatase; P_bK_a, active phosphorylase *β* kinase; P_bK_b, inactive phosphorylase *β* kinase; G, glycogenin, the primer protein for glycogen synthesis. *(Modified from AR Beaudet, in KJ Isselbacher et al [eds]: Harrison's Principles of Internal Medicine, 13th ed., New York, McGraw-Hill, 1994, p 1855.)*

SELECTED LIVER GLYCOGENOSES

DISORDERS WITH HEPATOMEGALY AND HYPOGLYCEMIA

Type I GSD (Glucose-6-Phosphatase or Translocase Deficiency, Von Gierke's Disease)

Type I GSD is an autosomal recessive disorder caused by glucose-6-phosphatase deficiency in liver, kidney, and intestinal mucosa. There are two subtypes of GSD I: type Ia, in which the glucose-6-phosphatase enzyme is defective, and