Fructose And Galactose. Pentose Phosphate. Pathway

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FRUCTOSE METABOLISM

About 10% of the calories comprising the Western diet are supplied by fructose (approximately 55 g/day). The major source of fructose is the disaccharide sucrose, which, when cleaved in the intestine, releases equimolar amounts of fructose and glucose. Fructose is also found as a free monosaccharide in many fruits, in honey, and in high-fructose corn syrup (typically, 55% fructose/45% glucose), which is used to sweeten soft drinks and many foods. Fructose transport into cells is not insulin dependent (unlike that of glucose into certain tissues), and, in contrast to glucose, fructose does not promote the secretion of insulin.

A. Phosphorylation of fructose

For fructose to enter the pathways of intermediary metabolism, it must first be phosphorylated. This can be accomplished by either hexokinase or fructokinase. Hexokinase phosphorylates glucose in most cells of the body, and several additional hexoses can serve as substrates for this enzyme. However, it has a low affinity (that is, a high Michaelis constant [Km] for fructose. Therefore, unless the intracellular concentration of fructose becomes unusually high, the normal presence of saturating concentrations of glucose means that little fructose is phosphorylated by hexokinase. Fructokinase provides the primary mechanism for fructose phosphorylation. It is found in the liver (which processes most of the dietary fructose), kidney, and the small intestinal mucosa and converts fructose to fructose 1-phosphate, using adenosine triphosphate (ATP) as the phosphate donor. [Note: These three tissues also contain aldolase B, discussed in section B.].

B. Cleavage of fructose 1-phosphate

Fructose 1-phosphate is not phosphorylated to fructose 1,6-bisphos-phate as is fructose 6-phosphate, but is cleaved by aldolase B (also called fructose 1- phosphate

aldolase) to dihydroxyacetone phosphate (DHAP) and glyceraldehyde. [Note: Humans express three aldolases, A, B and C, the products of three different genes. Aldolase A (found in most tissues), aldolase B (in liver, kidney, and small intestine), and aldolase C (in brain) all cleave fructose 1,6-bisphosphate produced during glycolysis to DHAP and glyceraldehyde 3-phosphate, but only aldolase B cleaves fructose 1-phosphate.] DHAP and glyceraldehyde can directly enter glycolysis or gluconeogenesis.

Disorders of fructose metabolism

A deficiency of one of the key enzymes required for the entry of fructose into metabolic pathways can result in either a benign condition as a result of fructokinase deficiency (essential fructosuria) or a severe disturbance of liver and kidney metabolism as a result of aldolase B deficiency (hereditary fructose intolerance [HFI]), which is estimated to occur in 1:20,000 live births. The first symptoms of HFI appear when a baby is weaned from milk and begins to be fed food containing sucrose or fructose. Fructose 1-phosphate accumulates, resulting in a drop in the level of inorganic phosphate (Pi) and, therefore, of ATP production. As ATP falls, adenosine monophosphate (AMP) rises. The AMP is degraded, causing hyperuricemia (and lactic acidosis. The decreased availability of hepatic ATP affects gluconeogenesis (causing hypoglycemia with vomiting) and protein synthesis (causing a decrease in blood clotting factors and other essential proteins). Kidney function may also be affected. [Note: The drop in Pi also inhibits glycogenolysis] Diagnosis of HFI can be made on the basis of fructose in the urine, enzyme assay using liver cells, or by DNA-based testing. Aldolase B deficiency is part of the newborn screening panel. With HFI, sucrose, as well as fructose, must be removed from the diet to prevent liver failure and possible death. Individuals with HFI display an aversion to sweets and, consequently, have an absence of dental caries.

GALACTOSE METABOLISM

The major dietary source of galactose is lactose (galactosyl β-1,4-glucose) obtained from milk and milk products. Some galactose can also be obtained by lysosomal degradation of complex carbohydrates, such as glycoproteins and glycolipids, which are important membrane components. Like fructose, the transport of galactose into cells is not insulin dependent.

A. Phosphorylation of galactose

Like fructose, galactose must be phosphorylated before it can be further metabolized. Most tissues have a specific enzyme for this purpose, galactokinase, which produces galactose 1-phosphate. As with other kinases, ATP is the phosphate donor.

B. Formation of uridine diphosphate-galactose

Galactose 1-phosphate cannot enter the glycolytic pathway unless it is first converted to uridine diphosphate (UDP)-galactose . This occurs in an exchange reaction, in which UDP-glucose reacts with galactose 1-phosphate, producing UDPgalactose and glucose 1-phosphate. The enzyme that catalyzes this reaction is galactose 1-phosphate uridylyltransferase (GALT).

C. Use of uridine diphosphate-galactose as a carbon source for glycolysis or gluconeogenesis

For UDP-galactose to enter the mainstream of glucose metabolism, it must first be converted to its C-4 epimer, UDP-glucose, by UDP-hexose 4-epimerase. This “new” UDP-glucose (produced from the original UDP-galactose) can then participate in many biosynthetic reactions as well as being used in the GALT reaction described above.

Disorders of galactose metabolism

GALT is deficient in individuals with classic galactosemia. In this disorder, galactose 1-phosphate and, therefore, galactose accumulate. Physiologic consequences are similar to those found in hereditary

fructose intolerance (see p. 138), but a broader spectrum of tissues is affected. The accumulated galactose is shunted into side pathways such as that of galactitol production. This reaction is catalyzed by aldose reductase, the same enzyme that converts glucose to sorbitol. Treatment requires removal of galactose and lactose from the diet. GALT deficiency is part of the newborn screening panel. [Note: A deficiency in galactokinase results in a less severe disorder of galactosemia metabolism, although cataracts are common.

Study Questions

1. A 5-month-old boy is brought to his physician because of vomiting, night sweats, and tremors. History revealed that these symptoms began after fruit juices were introduced to his diet as he was being weaned off breast milk. The physical examination was remarkable for hepatomegaly. Tests on the baby's urine were positive for reducing sugar but negative for glucose. The infant most likely suffers from a deficiency of:

A. aldolase B.

B. fructokinase.

C. galactokinase.

D. β-galactosidase.

Correct answer = A. The symptoms suggest hereditary fructose intolerance, a deficiency in aldolase B. Deficiencies in fructokinase or galactokinase result in relatively benign conditions characterized by elevated levels of fructose or galactose in the blood and urine. Deficiency in β-galactosidase (lactase) results in a decreased ability to degrade lactose (milk sugar). Congenital lactase deficiency is quite rare and would have

presented much earlier in this baby (and with different symptoms). Typical lactase deficiency (adult hypolactasia) presents at a later age.

2. A 3-month-old girl is developing cataracts. Other than not having a social smile or being able to track objects visually, all other aspects of the girl's examination are normal. Tests on the baby's urine are positive for reducing sugar but negative for glucose. Which enzyme is most likely deficient in this girl?

A. Aldolase B

B. Fructokinase

C. Galactokinase

D. Galactose 1-phosphate uridylyltransferase

E. glucose-6-phosphatase

Correct answer = C. The girl is deficient in galactokinase and is unable to appropriately phosphorylate galactose. Galactose accumulates in the blood (and urine). In the lens of the eye, galactose is reduced by aldose reductase to galactitol, a sugar alcohol, which causes osmotic effects that result in cataract formation. Deficiency of galactose 1- phosphate uridylyltransferase also results in cataracts but is characterized by liver damage and neurologic effects. Fructokinase deficiency is a benign condition. Aldolase B deficiency is severe, with affects on several tissues, while cataracts are not typically seen.

Pentose Phosphate Pathway

OVERVIEW The pentose phosphate pathway (also called the hexose monophosphate shunt) occurs in the cytosol of the cell. It includes two irreversible oxidative reactions, followed by a series of reversible sugar–phosphate interconversions. No adenosine triphosphate (ATP) is directly consumed or produced in the cycle. Carbon 1 of glucose 6-phosphate is

released as CO2, and two reduced nicotinamide adenine dinucleotide phosphates (NADPHs) are produced for each glucose 6-phosphate molecule entering the oxidative part of the pathway. The rate and direction of the reversible reactions of the pentose phosphate pathway are determined by the supply of and demand for intermediates of the cycle. The pathway provides a major portion of the body's NADPH, which functions as a biochemical reductant. It also produces ribose 5-phosphate, required for the biosynthesis of nucleotides, and provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or the degradation of structural carbohydrates.

I. IRREVERSIBLE OXIDATIVE REACTIONS.

The oxidative portion of the pentose phosphate pathway consists of three reactions that lead to the formation of ribulose 5-phosphate, CO2, and two molecules of NADPH for each molecule of glucose 6-phosphate oxidized. This portion of the pathway is particularly important in the liver, lactating mammary glands, and adipose tissue, which are active in the NADPH-dependent biosynthesis of fatty acids (see p. 186); in the testes, ovaries, placenta, and adrenal cortex, which are active in the NADPH-dependent biosynthesis of steroid hormones; and in red blood cells (RBCs), which require NADPH to keep glutathione reduced.

Dehydrogenation of glucose 6-phosphate

A. Glucose 6-phosphate dehydrogenase (G6PD) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone in a reaction that is specific for oxidized NADP (NADP+) as the coenzyme. The pentose phosphate pathway is regulated primarily at the G6PD reaction. NADPH is a potent competitive inhibitor of the enzyme, and, under most metabolic conditions, the ratio of NADPH/NADP+ is sufficiently high to substantially inhibit enzyme activity. However, with

increased demand for NADPH, the ratio of NADPH/NADP+ decreases, and flux through the cycle increases in response to the enhanced activity of G6PD. Insulin upregulates expression of the gene for G6PD, and flux through the pathway increases in the absorptive state

B. 6-Phosphogluconolactone is further hydrolyzed by 6-phosphogluconolactone hydrolase. The oxidative decarboxylation of the product, 6-phosphogluconate, is catalyzed by 6-phosphogluconate dehydrogenase. This irreversible reaction produces a pentose sugar–phosphate (ribulose 5-phosphate), CO2 (from carbon 1 of glucose), and a second molecule of NADPH

II. REVERSIBLE NONOXIDATIVE REACTIONS

The nonoxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids. These reactions catalyze the interconversion of sugars containing three to seven carbons. These reversible reactions permit ribulose 5-phosphate (produced by the oxidative portion of the pathway) to be converted either to ribose 5-phosphate (needed for nucleotide synthesis) or to intermediates of glycolysis (that is, fructose 6-phosphate and glyceraldehyde 3- phosphate). For example, many cells that carry out reductive biosynthetic reactions have a greater need for NADPH than for ribose 5-phosphate. In this case, transketolase (which transfers two-carbon units in a thiamine pyrophosphate [TPP]-requiring reaction)and transaldolase (which transfers three-carbon units) convert the ribulose 5-phosphate produced as an end product of the oxidative reactions to glyceraldehyde 3-phosphate and fructose 6-phosphate, which are glycolytic intermediates. In contrast, when the demand for ribose for nucleotides and nucleic acids is greater than the need for NADPH, the nonoxidative reactions can provide the ribose 5-phosphate from

glyceraldehyde 3- phosphate and fructose 6-phosphate in the absence of the oxidative steps.

USES OF NADPH

The coenzyme NADPH differs from nicotinamide adenine dinucleotide (NADH) only by the presence of a phosphate group on one of the ribose units. This seemingly small change in structure allows NADPH to interact with NADPH-specific enzymes that have unique roles in the cell. For example, in the cytosol of hepatocytes the steady-state ratio of NADP+/NADPH is approximately 0.1, which favors the use of NADPH in reductive biosynthetic reactions. This contrasts with the high ratio of NAD+/NADH (approximately 1000), which favors an oxidative role for NAD+. NADPH can be thought of as a high-energy molecule, much in the same way as NADH. However, the electrons of NADPH are destined for use in reductive biosynthesis, rather than for transfer to oxygen as is the case with NADH. Thus, in the metabolic transformations of the pentose phosphate pathway, part of the energy of glucose 6-phosphate is conserved in NADPH, a molecule with a negative reduction potential, that, therefore, can be used in reactions requiring an electron donor, such as fatty acid and steroid synthesis

GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY

G6PD deficiency is a hereditary disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents. G6PD deficiency is the most common disease-producing enzyme abnormality in humans, affecting more than 400 million individuals worldwide. This deficiency has the highest prevalence in the Middle East, tropical Africa and Asia, and parts of the Mediterranean. G6PD deficiency is X linked and is, in fact, a family of deficiencies caused by a number of different mutations in the gene coding for G6PD. Only some of the resulting protein variants cause clinical

symptoms. [Note: In addition to hemolytic anemia, a clinical manifestation of G6PD deficiency is neonatal jaundice appearing 1–4 days after birth. The jaundice, which may be severe, typically results from increased production of unconjugated bilirubin] The life span of individuals with a severe form of G6PD deficiency may be somewhat shortened as a result of complications arising from chronic hemolysis. This negative effect of G6PD deficiency has been balanced in evolution by an advantage in survival—an increased resistance to Plasmodium falciparum malaria. [Note: Sickle cell trait and β-thalassemia minor also confer resistance to malaria.]

Study Questions

In male patients who are hemizygous for X-linked glucose 6-phosphate dehydrogenase deficiency, pathophysiologic consequences are more apparent in red blood cells (RBC) than in other cells such as in the liver. Which one of the following provides the most reasonable explanation for this different response?

A. Excess glucose 6-phosphate in the liver, but not in RBC, can be channeled to glycogen, thereby averting cellular damage.

B. Liver cells, in contrast to RBC, have alternative mechanisms for supplying the reduced nicotinamide adenine dinucleotide phosphate required for maintaining cell integrity.

C. Because RBC do not have mitochondria, production of ATP required to maintain cell integrity depends exclusively on the shunting of glucose 6-phosphate to the pentose phosphate pathway.

D. In RBC, in contrast to liver cells, glucose 6-phosphatase activity decreases the level of glucose 6-phosphate, resulting in cell damage.

Correct answer = B. Cellular damage is directly related to decreased ability of the cell to regenerate reduced glutathione, for which large amounts of

reduced nicotinamide adenine dinucleotide phosphate (NADPH) are needed, and red blood cells (RBCs) have no means other than the pentose phosphate pathway of generating NADPH. It is decreased product (NADPH), not increased substrate (glucose 6- phosphate), that is the problem. RBCs do not have glucose 6- phosphatase. The pentose phosphate pathway does not generate ATP.