Metabolism of Monosaccharides and disaccharides

Glucose is the most common monosaccharide consumed by humans. Two other monosaccharides that occur in significant amounts in the diet are fructose and galactose. Galactose is an important component of cell structural carbohydrates. Catabolism of fructose and galactose are essential pathways of energy metabolism in the body (both illustrated with blue in the adjacent diagram). About 15-20% of calories in the diet are supplied by fructose (55 g/day). The major source of fructose is the disaccharide sucrose. Entry of fructose is not dependent on insulin. Galactose is an important component of cell structural carbohydrates.
Fructose needs to be phosphorylated to enter the pathway either by hexokinase or fructokinase. Hexokinase has low affinity towards fructose (high Km) therefore unless high concentrations of fructose exist very little fructose will be converted to Fructose 6-P. Fructokinase provides the main mechanism of phosphorylation to fructose 1-P. Fructose 1-P does not convert to Fructose 1,6 bisphosphate but is metabolized to Glyceraldehyde and DHAP by aldolase B. DHAP can enter glycolysis or gluconeogenesis while Glyceraldehyde can be metabolized by a number of pathways. The rate of fructose metabolism is more rapid than that of glucose because trioses formed from fructose 1-phosphate bypass PFK1, the rate limiting step in glycolysis. What disorders are associated with fructose metabolism? Where?
First lets summarize the various routes of Fructose metabolism in the diagram. Disorders of fructose metabolism can result from excessive fructose consumption. An increase in fructose 1-P due to rapid phosphorylation. This accumulation leads to sequestering of phosphate (A & B). The ADP & AMP are catabolized leading to hyperuricemia and gout. A genetic condition due to Fructokinase Deficiency (benign condition) Why? Or to adolase B deficiency severe disturbance of the liver. Why?
ESSENTIAL FRUCTOSURIA
- Lack of fructokinase.
- Autosomal recessive (1:130,000 births)
- Benign condition.
- Fructose accumulates in the urine.

HEREDITARY FRUCTOSE INTOLERANCE ("FRUCTOSE POISONING")
- Autosomal recessive (1:20,000 births)
- Absence of aldolase B leads to intracellular trapping of fructose 1-P.
- Causes severe hypoglycemia, vomiting, jaundice, hemorrhage, hepatomegaly, renal dysfunction, hyperuricemia, and lacticacidemia.
- Fructose, sucrose, and sorbitol can cause hepatic failure and death.
- Therapy: Rapid detection and removal of fructose and sucrose from the diet.

PHOSPHOGLYCERIDES

GLYCOGENESIS
Mannose (C-2 epimer of Glucose) is converted to mannose 6-P by hexokinase using ATP. Mannose 6-P is then converted to fructose 6-P which can enter glycolysis or gluconeogenesis. There is little mannose in dietary carbohydrates in fact most of the intracellular mannose is synthesized from fructose. Most sugars are rapidly phosphorylated following their entry into the cells. They are trapped because organic phosphates cannot freely cross membranes. Glucose can also be converted to fructose by the way of sorbitol. Glucose is reduced to sorbitol by the way of aldose reductase. It is found in many tissues such as lens, retina, schwann cells, kidney, placenta, RBC, cells of the ovaries and seminal vesicles. In the liver, ovaries, sperm and seminal vesicles a second enzyme (sorbitol dehydrogenase) oxidizes the sorbitol to fructose.
In some tissues such as sperms these two reaction pathways from glucose to fructose are the preferred energy source. In the liver these reactions provide a way to metabolize dietary sorbitol so that it could enter glycolysis or gluconeogenesis. Since insulin is not required for the entrance of glucose to certain tissues, elevated blood glucose such as in diabetes can enter and metabolized to sorbitol. When sorbitol dehydrogenase is absent, like in the lens then sorbitol accumulates creating osmotic problems and cell swelling. Cataracts, periferal neuropathy and vascular problems leading to neuropathy and retinopathy.
Galactose Metabolism. The major dietary source of galactose is lactose, obtained from milk and milk products. Lactose is digested by lactase in the intestinal mucosal membrane. Galactose can also be obtained from complex carbohydrates such as glycoproteins and glycolipids (membrane components). Like fructose entry of galactose to cells is not insulin dependent. It needs to be phosphorylated by galactokinase to galactose 1-P. Galactose 1-P cannot enter the glycolitic pathway unless it is converted to UDP-galactose.

UDP-galactose forms from UDP-glucose. UMP + galactose 1-P by glucose 1 phosphategalactose 1phosphate uridyltransferase. When enzyme is missing galactosemia devel.
Summary of Galactose metabolism and major diseases (galactosemia)

**CLASSIC GALACTOSEMIA**
- *Uridyltransferase* deficiency.
- Autosomal recessive disorder (1 in 23,000 births).
- It causes galactosemia and galactosuria, vomiting, diarrhea, and jaundice.
- Accumulation of galactose 1-phosphate and galactitol in nerve, lens, liver, and kidney tissue causes liver damage, severe mental retardation, and cataracts.
- Antenatal diagnosis is possible by chorionic villus sampling.
- Therapy: Rapid diagnosis and removal of galactose (therefore, lactose) from the diet.

**GALACTOKINASE DEFICIENCY**
- This causes galactosemia and galactosuria.
- It causes galactitol accumulation if galactose is present in the diet.

**ALDOSE REDUCTASE**
- The enzyme is present in liver, kidney, retina, lens, nerve tissue, seminal vesicles, and ovaries.
- It is physiologically unimportant in galactose metabolism unless galactose levels are high (as in galactosemia).
- Elevated galactitol can cause cataracts.
In order for UDP-galactose to enter the mainstream of glucose metabolism it must be converted to its C-4 epimer, UDP-glucose by UDP-hexose 4-epimerase. UDP-glucose donates UDP to 1-P galactose converted to UDP-galactose + G1-P which can then be converted to G6P which is converted to glucose or enters glycolysis by via fructase 6-P. Therefore the carbons of galactose are being converted to glucose.

UDP-galactose also serves as donor of galactose units in a number of synthetic pathways including lactose, glycoprotein, glycolipids and glycosaminoglycans
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**LACTOSE INTOLERANCE**
- Three types:
  1. Premature infants (transient or congenital deficiency).
  2. Deficiency secondary to surgery where part of the small intestine is removed.
  3. Deficiency due to mucosal cell damage.
- Deficiency of this intestinal cell enzyme eliminates the major source of dietary galactose.
- The body can produce sufficient quantities of UDP-galactose by the epimerase reaction.
Lactose metabolism

It is synthesized by lactose synthase (UDP-galactose:glucose galactosyltransferase at the golgi complex). This enzyme has two proteins (A&B). B is found in large quantities in milk and only in lactating mammary glands. This enzyme synthesis is inhibited by progesterone and after birth the synthesis of prolactin increases inducing the synthesis of B. So that lactose can be produced. A is found in a number of body tissues and produces N-acetyllactosamine important for N-linked glycoproteins. Protein A (transferase) changes its specificity by binding to B and produce lactose instead of N-Acetyllactosamine.
Figure 12.8
Key concept map for metabolism of fructose and galactose.

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