Metabolism of disaccharides: Fructose and Galactose

BCH 340 lecture 10
Fructose metabolism

• Diets containing large amounts of sucrose (a disaccharide of glucose and fructose) can utilize the fructose as a major source of energy.

• Fructose is found in foods containing sucrose (fruits), high-fructose corn syrups, and honey.

• The pathway to utilization of fructose differs in muscle and liver.
• **In liver**, dietary fructose is converted to Fructose-1-P by fructokinase (also in kidney and intestine).

• Then, by the action of Fructose-1-P adolase (aldolase B), Fructose-1-P is converted to DHAP and glyceraldehyde.
The utilization of fructose by fructokinase then aldolase bypass the steps of glucokinase and PFK-1 which are activated by insulin.

Glyceraldehyde is converted to glyceraldehyde-3-P by triose kinase which together with DHAP may undergo:
1. Combine together and converted into glucose (main pathway)
2. They may be oxidized in glycolysis

This explains why fructose disappears from blood more rapidly than glucose in diabetic subjects.
Fructose metabolism

• The aldolase B is the rate-limiting enzyme for fructose metabolism.

• Muscle which contains only hexokinase can phosphorylate fructose to F6P which is a direct glycolytic intermediate.

• However, hexokinase has a very low affinity to fructose compared to glucose, So it is not a significant pathway for fructose metabolism. Unless it is present in very high concentration in blood.
Fructose-6-P can be converted to **glucosamine-6-P** which is the precursor of all other amino sugars.
Galactose Metabolism

• The major source of galactose is lactose (a disaccharide of glucose and galactose) obtained from milk and milk products

• Galactose enters glycolysis by its conversion to glucose-1-phosphate (G1P). This occurs through a series of steps.

• **Site:** liver
• First the galactose is phosphorylated by galactokinase to yield galactose-1-p.

  ▶ Epimerization of galactose-1-phosphate to G1P requires the transfer of UDP from uridine diphosphoglucose (UDP-glucose) catalyzed by galactose-1-phosphate uridyl transferase.

  ▶ This generates UDP-galactose and G1P. The UDP-galactose is epimerized to UDP-glucose by UDP-galactose-4 epimerase.

  ▶ The UDP portion is exchanged for phosphate generating glucose-1-phosphate which then is converted to G6P by phosphoglucomutase.

▶ Glucose can be converted to galactose, thus galactose is not essential in the diet.
Hereditary defects of fructose metabolism

1. Essential fructosuria

- **Cause:** due to deficiency of fructokinase enzyme
- **Effect:** not serious condition. The excess accumulated fructose is lost in urine

2. Fructose 1,6 biphosphatase deficiency

It leads to accumulation of fructose 1,6 biphosphate which inhibits phosphorylase enzyme (glycogenolysis) and fasting hypoglycemia
Hereditary defects of fructose metabolism

3. Hereditary fructose intolerance

- **Cause:** due to deficiency of aldolase B. This leads to accumulation of fructose-1-P

- **Effect:** the accumulation of fructose-1-P leads to:
  - Damage of liver and kidney tissues
  - Inhibition of glycogen phosphorylase leading to inhibition of glycogenolysis and fasting hypoglycemia
Galactosemias

• **Definition:** it is increase blood galactose concentration due to inability of the body to metabolize galactose

• **Causes:** inherited defects in galactokinase, uridyltransferase (the most common) or 4-epimerase.

• **Effect:**
  1. **Cataract** (opacity of eye lens): Galactose is reduced in the eye by aldose reductase to form galactitol which accumulates causing cataract
  2. **Liver failure**
  3. **Mental retardation**
  4. **Galactosuria** (excretion of galactose in the urine)
Abnormalities and disorders in CHO metabolism
Digestion and absorption of CHO

Normal: monosaccharides are absorbed

Abnormal: passage of undigested CHO into the large intestine

Water is drawn from the mucosa into the large intestine, causing osmotic diarrhea.

Any defect in a specific disaccharidase activity of the intestinal mucosa

Caused by

Bacterial fermentation of the remaining carbohydrate to 2 and 3C compounds

Large volumes of CO$_2$ and H$_2$ gas

Abdominal cramps, diarrhea, and flatulence.
Digestive enzyme deficiencies

- **Genetic deficiencies** of the individual disaccharidases result in disaccharide intolerance.
- **Acquired deficiencies** can also be caused by a variety of intestinal diseases, malnutrition, or drugs that injure the mucosa of the small intestine.
Lactose intolerance

• Up to 90% of adults of African or Asian descent are lactase-deficient
• Less able to metabolize lactose
• Treatment:
  1. reduce consumption of milk. Eat yogurts and cheeses, and green vegetables (calcium)
  2. lactase-treated products
  3. lactase pill prior to eating

Figure 7.11
Abnormal lactose metabolism.
Sucrase-isomaltase complex deficiency

- Intolerance of ingested sucrose
- **Treatment:**
  1. restriction of sucrose
  2. enzyme replacement therapy
Glycolysis

- Pyruvate kinase deficiency:
- 95% of all inherited defects in glycolytic enzymes
- restricted to erythrocytes

Pyruvate Kinase Deficiency

Hemolytic anemia —
Red blood cells swell and lyse

- RBC's lack mitochondria; rely on glycolysis for ATP.
- PK deficiency
- No ATP for Na/K pumps to maintain cell shape

Na/K pump

PK

Spiculated

normal

Figure 8.20
Alterations observed with various mutant forms of pyruvate kinase.
TCA cycle

• Pyruvate dehydrogenase deficiency:
  • inability to convert pyruvate to acetyl CoA
  • pyruvate converted to lactic acid (lactate dehydrogenase)
• Symptoms:
  • neurodegeneration, muscle spasticity and, in the neonatal onset form, early death
Defects in mitochondrial ATP production:

• Leigh syndrome:
  • mutations in the PDH complex
  • the electron transport chain
  • ATP synthase.
Inherited defects in oxidative phosphorylation

- mtDNA has a mutation rate ~ten times greater than that of nuclear DNA
- Mutations in mtDNA are responsible for several diseases, including some cases of mitochondrial myopathies
Pentose phosphate pathway

- **GLUCOSE 6-P DEHYDROGENASE DEFICIENCY**
- hemolytic anemia caused by the inability to detoxify oxidizing agents.
- the highest prevalence in the Middle East, tropical Africa and Asia, and parts of the Mediterranean.

*Figure 13.10*
Pathways of glucose 6-phosphate metabolism in the erythrocyte. HMP = hexose monophosphate pathway.

*Figure 13.11*
Heinz bodies in erythrocytes of a patient with G6PD deficiency.