INBORN ERRORS OF CARBOHYDRATE METABOLISM

DR. A. TARAB
DEPT. OF BIOCHEMISTRY
HKMU
• Carbohydrates account for a major portion of the human diet and are metabolized into three principal monosaccharides: galactose, fructose and glucose.

• The failure to effectively use these molecules accounts for the majority of the inborn errors of human carbohydrates metabolism.
Galactose

1. **Galactosemia**, the inability to metabolize galactose, is the most common monogenic disorder of carbohydrate metabolism, affecting 1 in every 55,000 newborns.

- When galactose in the body is not broken down, it accumulates in tissues.
- The most common signs are **failure to thrive**, hepatic insufficiency, cataracts, and developmental delay.
• Long term disabilities include poor growth, **mental retardation**, and ovarian failure in females

• Galactosemia is caused by **mutations** in the **gene** that makes the **enzyme galactose-1-phosphate uridyltransferase**

• 2. A milder form of galactosemia, called **Galactokinase deficiency**, is caused a lack of the enzyme **uridine diphosphate galactose-4-epimerase** which breaks down a byproduct of galactose
(1) \[ \beta-D\text{-galactose} \overset{\text{galactose mutarotase}}{\rightleftharpoons} \alpha-D\text{-galactose} \]

(2) \[ \alpha-D\text{-galactose} \overset{\text{ATP, ADP}}{\rightarrow} \text{galactose 1-phosphate} \]

(3) \[ \text{galactose 1-phosphate} + \text{UDP-glucose} \overset{\text{uridylyltransferase}}{\rightarrow} \text{UDP-galactose} + \text{glucose 1-phosphate} \]

(4) \[ \text{UDP-galactose} \overset{\text{UDP-galactose 4-epimerase}}{\rightarrow} \text{UDP-glucose} \]
• This type of galactosemia is associated with cataracts, but does not cause growth failure, mental retardation, or hepatic disease.
• Dietary reduction of galactose is also the treatment but not as severe as in patients with classical galactosemia.
• This deficiency can be systemic or limited to red blood cells and leukocytes.
• Screening is performed by measuring GAL-1-P urydil transferase activity
• Early identification affords prompt treatment, which consists largely of eliminating dietary galactose
Fructose

• Three autosomal recessive disorders involve the inability to metabolize fructose.

• 1. The most common is caused by mutations in the gene encoding hepatic fructokinase, an enzyme which is normally present in the liver, pancreatic islets and kidney cortex, that catalyzes the first step in the metabolism of dietary fructose.

• Inactivation of the hepatic fructokinase results in asymptomatic fructosuria.
2. Hereditary fructose intolerance (HFI) results in poor feeding, failure to thrive, hepatic and renal insufficiency, and death.

HFI is caused by a deficiency of fructose 1,6-biphosphate aldolase in the liver, kidney cortex and small intestine.

Infants and adults are asymptomatic unless they ingest fructose or sucrose.
• The disorder is characterized by severe hypoglycemia and vomiting following fructose intake.
• Prolonged intake of fructose by infants with this defect leads to vomiting, poor feeding, jaundice, hepatomegaly, hemorrhage and eventually hepatic failure and death.
• The hypoglycemia that result following fructose uptake is caused by fructose-1-phosphate inhibition of glycogenolysis.
• 3. Hereditary fructose-1,6-bisphosphatase deficiency results in severely impaired hepatic gluconeogenesis and leads to episodes of hypoglycemia, apnea, hyperventillation, ketosis and lactic acidosis

• These symptoms can take on a lethal course in neonates

• If patients are adequately supported beyond childhood, growth and development appear to be normal
Glucose

1. **Diabetes mellitus type 1** is a genetic disorder caused by reduced or absent levels of **insulin**, a hormone that regulates the metabolism of **glucose**.

2. **Glucose 6-Phosphate dehydrogenase deficiency** is an **X-linked recessive hereditary disease** characterised by abnormally low levels of **glucose-6-phosphate dehydrogenase** (abbreviated **G6PD** or **G6PDH**).
• **G6PD** is a metabolic enzyme involved in the *pentose phosphate pathway*, especially important in *red blood cell* metabolism

• G6PD deficiency is the most common human enzyme defect

• Individuals with the disease may exhibit nonimmune *hemolytic anemia* in response to a number of causes, most commonly *infection* or exposure to certain medications or chemicals
Glucose-6-phosphate Dehydrogenase

NADPH + H⁺

NADP⁺

6-Phosphogluconolactonase

H₂O + H⁺

6-phosphogluconate

Glucose-6-phosphate

6-phosphogluconolactone
• 4-year old boy diagnosed with glucose-6-phosphate dehydrogenase deficiency showing jaundice in the sclera
• Most individuals with G6PD deficiency are asymptomatic.
• G6PD deficiency is an inherited 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 200 million individuals worldwide

• This deficiency has the highest prevelance 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 more than 400 different mutations in the gene coding for G6PD
• Only some of these mutations cause clinical symptoms
Lactose

• The ability to metabolize lactose depends on an intestinal enzyme called lactase
• In most mammals, production of lactase diminishes after infants are weaned from maternal milk
• However, 5% to 90% of the human population possess an advantageous autosomal mutation in which lactase production persists after infancy
• The geographic distribution of lactase persistence is concordant with areas of high milk intake
• Lactase non-persistence is common in tropical and subtropical countries
• Individuals with lactase non-persistency may experience nausea, bloating and diarrhea after ingesting dairy
Glycogen

- Carbohydrates are most commonly stored as glycogen in humans
- Consequently, enzyme deficiencies that leads to impaired synthesis or degradation of glycogen are also considered disorders of carbohydrates metabolism
- The two organs most commonly affected are the liver and the skeletal muscle
• **Glycogen storage diseases** that affect the liver typically cause **hepatomegaly** and **hypoglycemia**, relating to impaired mobilization of glucose for release to the blood during fasting

• Those that affect skeletal muscle cause exercise intolerance, progressive weakness and cramping result from inability to increase glucose entry into glycolysis during exercise
• A small amount of glycogen is continuously degraded by the lysosomal enzyme, α(1→4)-glucosidase (acid maltase)
• The purpose of this pathway is unknown
• However, a deficiency of this enzyme causes accumulation of glycogen in vacuoles in cytosol, resulting in the serious glycogen storage disease type II (Pompe disease)
Glycogen-engorged lysosome

• This electron micrograph shows skeletal muscle from an infant with type II glycogen-storage disease (Pompe disease)
<table>
<thead>
<tr>
<th>Glycogen Storage Disease</th>
<th>Symptoms, in addition to glycogen accumulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong>, liver deficiency of <strong>Glucose-6-phosphatase</strong> (von Gierke's disease)</td>
<td><strong>hypoglycemia</strong> (low blood glucose) when fasting, liver enlargement.</td>
</tr>
<tr>
<td><strong>Type IV</strong>, deficiency of <strong>branching enzyme</strong> in various organs, including liver (Andersen's disease)</td>
<td><strong>liver dysfunction</strong> and early death.</td>
</tr>
<tr>
<td><strong>Type V</strong>, muscle deficiency of <strong>Glycogen Phosphorylase</strong> (McArdle's disease)</td>
<td><strong>muscle cramps</strong> with exercise.</td>
</tr>
<tr>
<td><strong>Type VII</strong>, muscle deficiency of <strong>Phosphofructokinase</strong>.</td>
<td><strong>inability to exercise.</strong></td>
</tr>
</tbody>
</table>