King Saud University
College of Sciences
Biochemistry Department

الأيض (١)
Metabolism (1)
BCH 340

Lecture 7: Metabolism of fructose and galactose

Intended learning outcomes (ILOs)

By the end of this lecture, students will be able to:

- Describe the biochemical pathways through which fructose and galactose is metabolized in the body.
- Differentiate fructose and galactose metabolism from glucose metabolism.
- Explaining the consequences of disorders of fructose and galactose metabolism.

Metabolism of fructose

- Fructose is a monosaccharide found naturally in fruits, honey, and some vegetables.
- The condensation of one molecule of fructose with glucose (with the loss of a water molecule) results in the formation of sucrose.
- Unlike glucose, which can be taken up by many cells in the body, fructose is almost exclusively metabolized in the liver.
  - Other tissues like the small intestine, kidney, and adipose tissue also possess fructose metabolizing enzymes.

Remember:

- Fructose is absorbed in the small intestine via facilitated diffusion using glucose transporter proteins, primarily GLUT5. It doesn't require insulin for uptake.

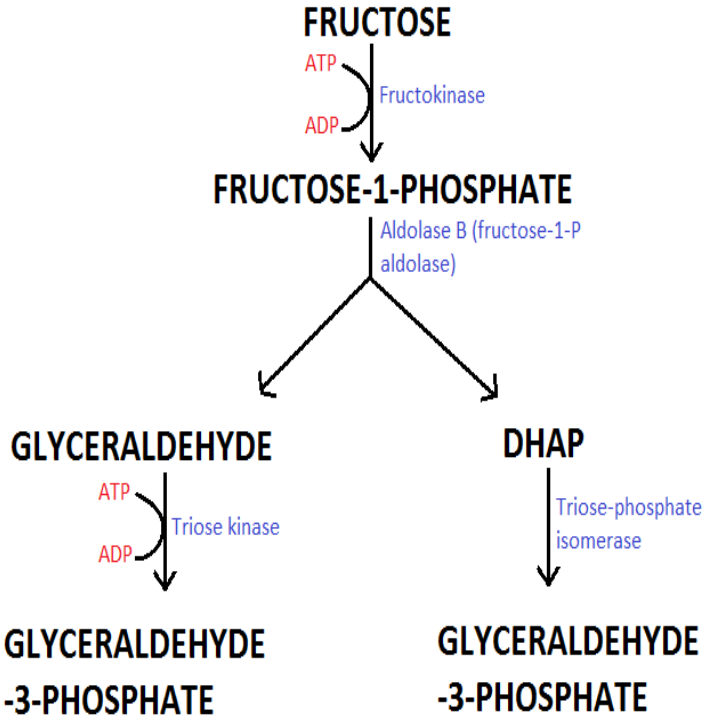
Metabolism of fructose (cont.)

Conversion to fructose-1-phosphate:

- Once absorbed, fructose is phosphorylated by fructokinase into fructose-1-phosphate.
- This step is irreversible and unique to fructose metabolism.

Splitting into glyceraldehyde and dihydroxyacetone phosphate:

- Fructose-1-phosphate is then (irreversibly) split into glyceraldehyde and dihydroxyacetone phosphate (DHAP) by the enzyme aldolase B (also called fructose-1-phosphate aldolase).

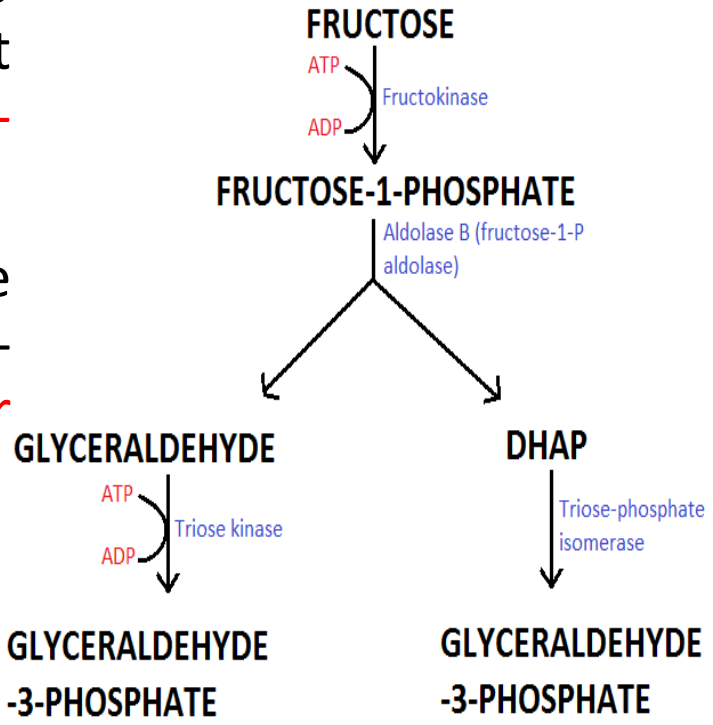


Metabolism of fructose (cont.)

- The utilization of fructose by fructokinase then aldolase bypass the steps of glucokinase and PFK-1 activated by insulin.

Glycolysis:

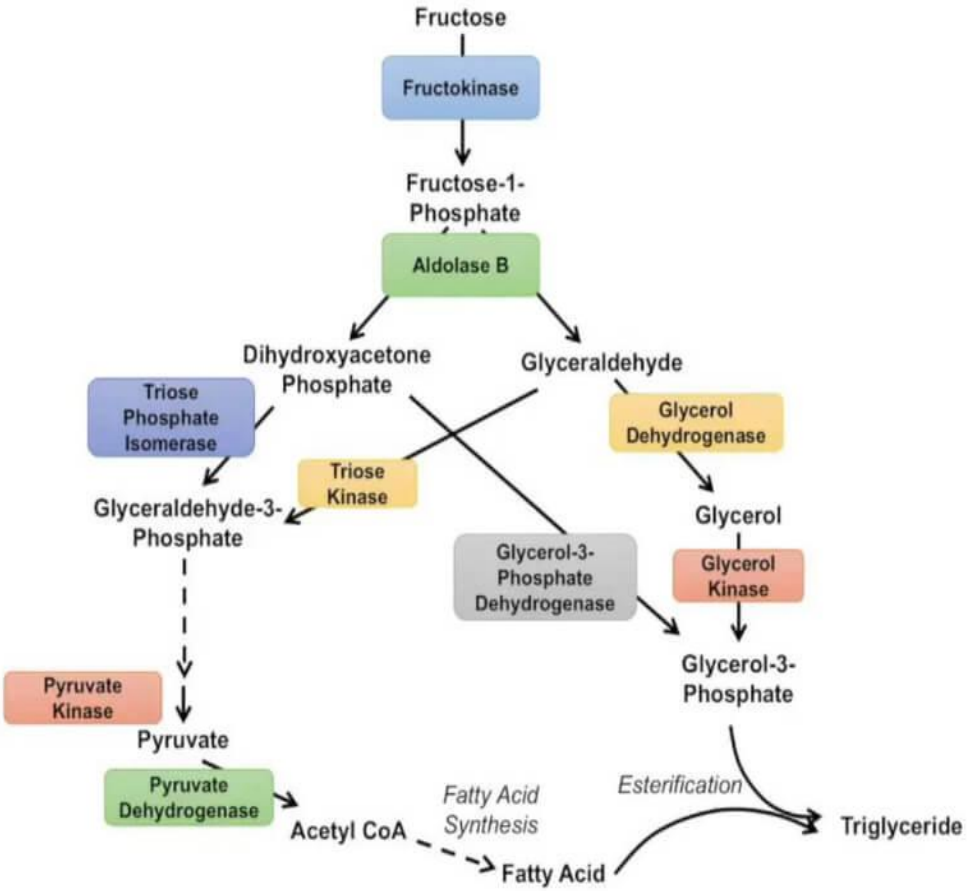
- Glyceraldehyde is converted into glyceraldehyde-3-phosphate, a step that ultimately leads to the entry of fructose-derived carbons into glycolysis.
- DHAP, on the other hand, can be converted to glyceraldehyde-3-phosphate as well, allowing it to enter glycolysis at a later step.



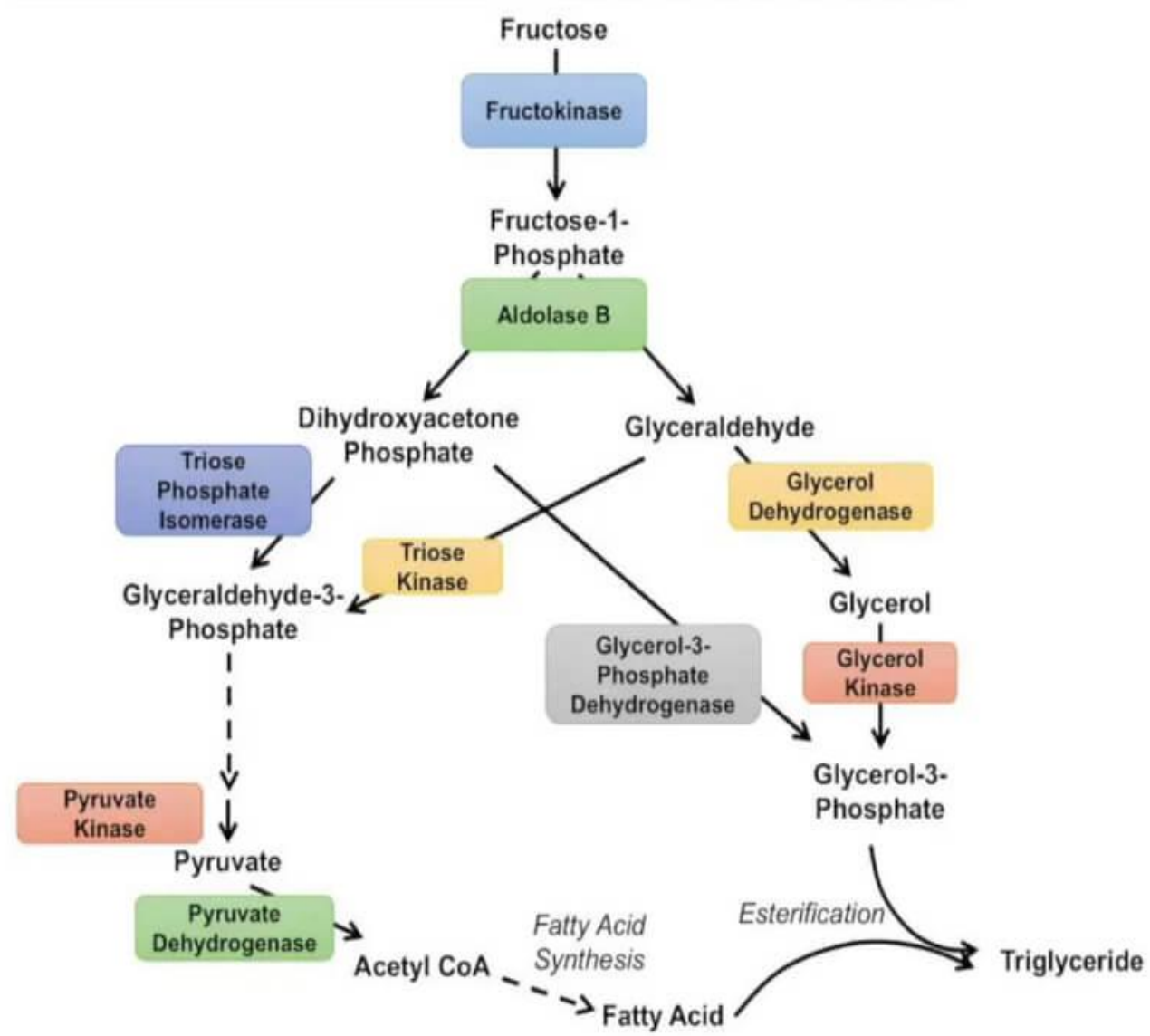
Metabolism of fructose (cont.)

Triglyceride synthesis:

- When fructose is consumed in excess of the body's immediate energy needs, the liver converts it into fatty acids through a process called *de novo* lipogenesis (DNL).
- These fatty acids can then be esterified with glycerol to form triglycerides, which are stored in adipose tissue.



Metabolism of fructose



Metabolism of fructose in muscles

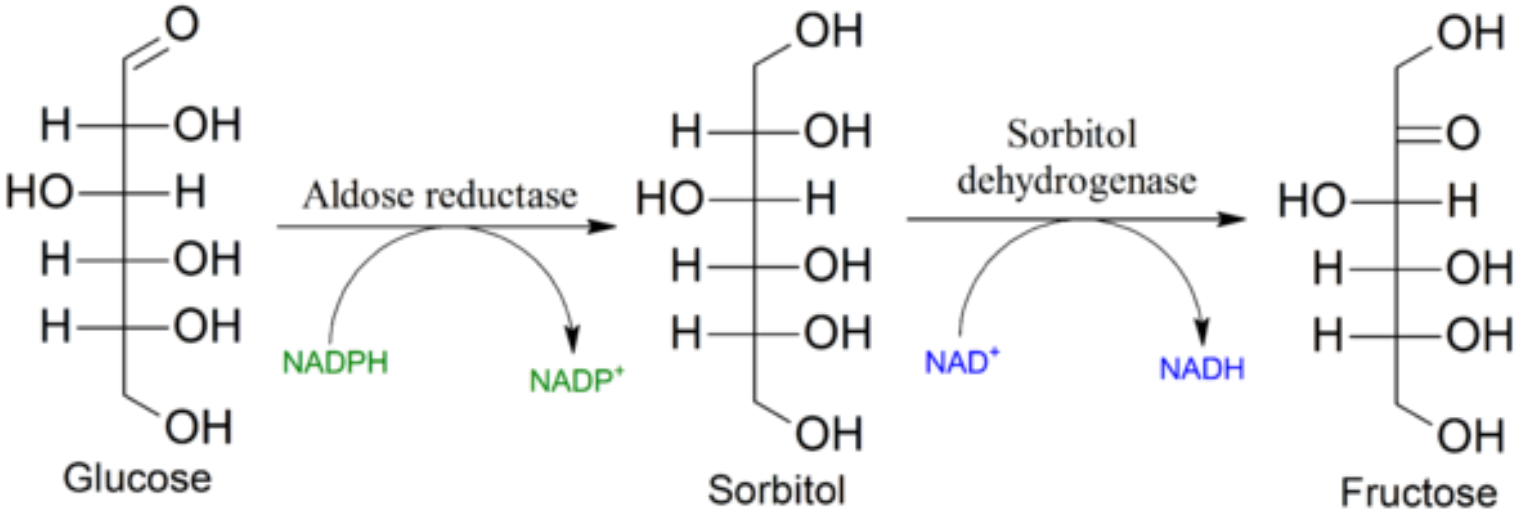
- Unlike glucose, which can be directly taken up and metabolized by muscle cells, fructose has to undergo some initial processing in the liver before it can be utilized by muscles.
- Muscle cells DO NOT contain fructokinase. Instead, they only contain hexokinase, which can only phosphorylate fructose to fructose-6-phosphate.
- Hexokinase generally has low affinity for fructose. Therefore, muscles primarily metabolize glucose for energy through glycolysis and the citric acid cycle.

Metabolism of fructose in muscles (cont.)

- Additionally, muscle cells have lower levels of aldolase B compared to liver cells, which limits their capacity to metabolize fructose efficiently.
- This limited capacity, along with the preference for glucose metabolism, makes fructose a less significant energy source for muscle cells compared to glucose.

Metabolism of fructose in tests

- Fructose metabolism in the testes plays a crucial role in sperm production (spermatogenesis) and male fertility.
- Fructose is produced and metabolized in the seminal vesicles (testes) via the polyol pathway (sorbitol pathway)

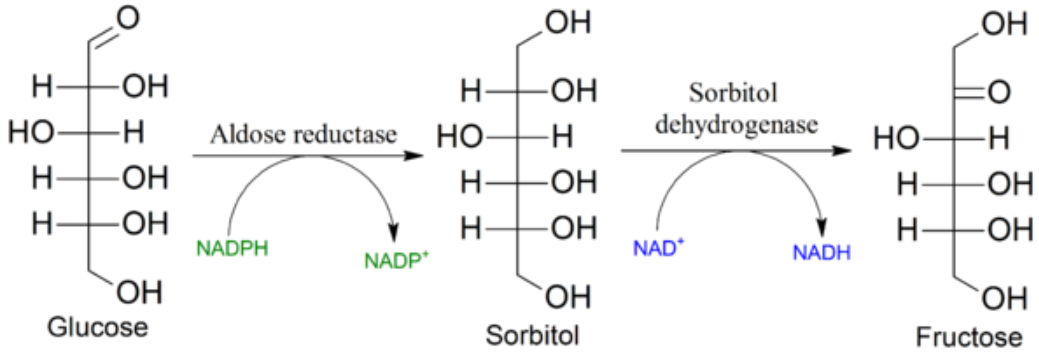


Metabolism of fructose in tests (cont.)

Sorbitol pathway:

- The enzyme aldolase reductase converts glucose to sorbitol, using NADPH as a cofactor.
- Sorbitol is then converted to fructose by sorbitol dehydrogenase.
- Fructose can then be metabolized via the glycolytic pathway in sperm to make ATP (sperms utilize fructose as an energy source for motility and viability).

- Deficiency of fructose correlates with male infertility.



Metabolism of fructose (cont.)

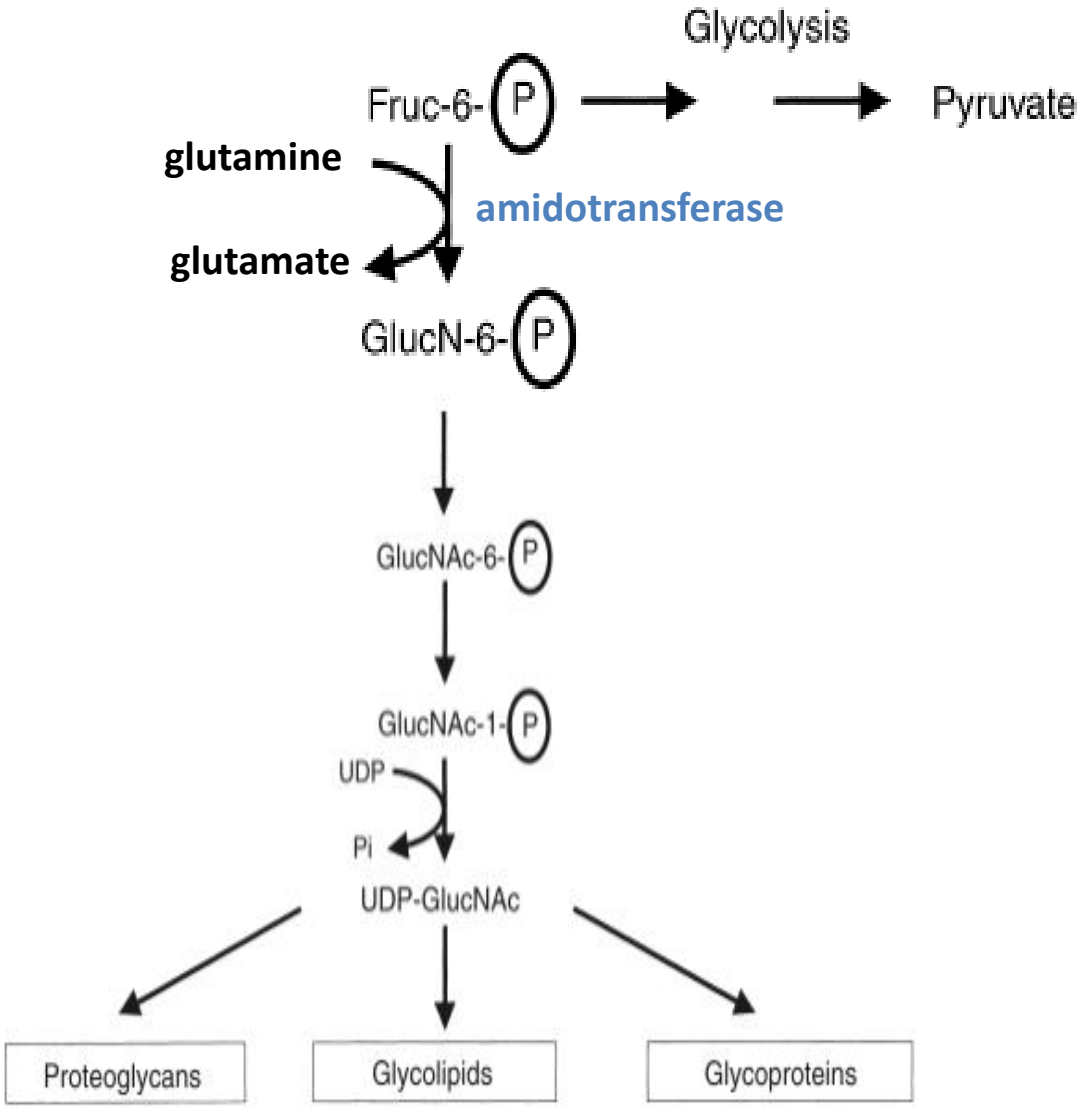
Role of fructose in the synthesis of amino sugars:

- The conversion of fructose-6-phosphate to glucosamine-6-phosphate involves several steps. It is an important process in the synthesis of amino sugars and glycoproteins.

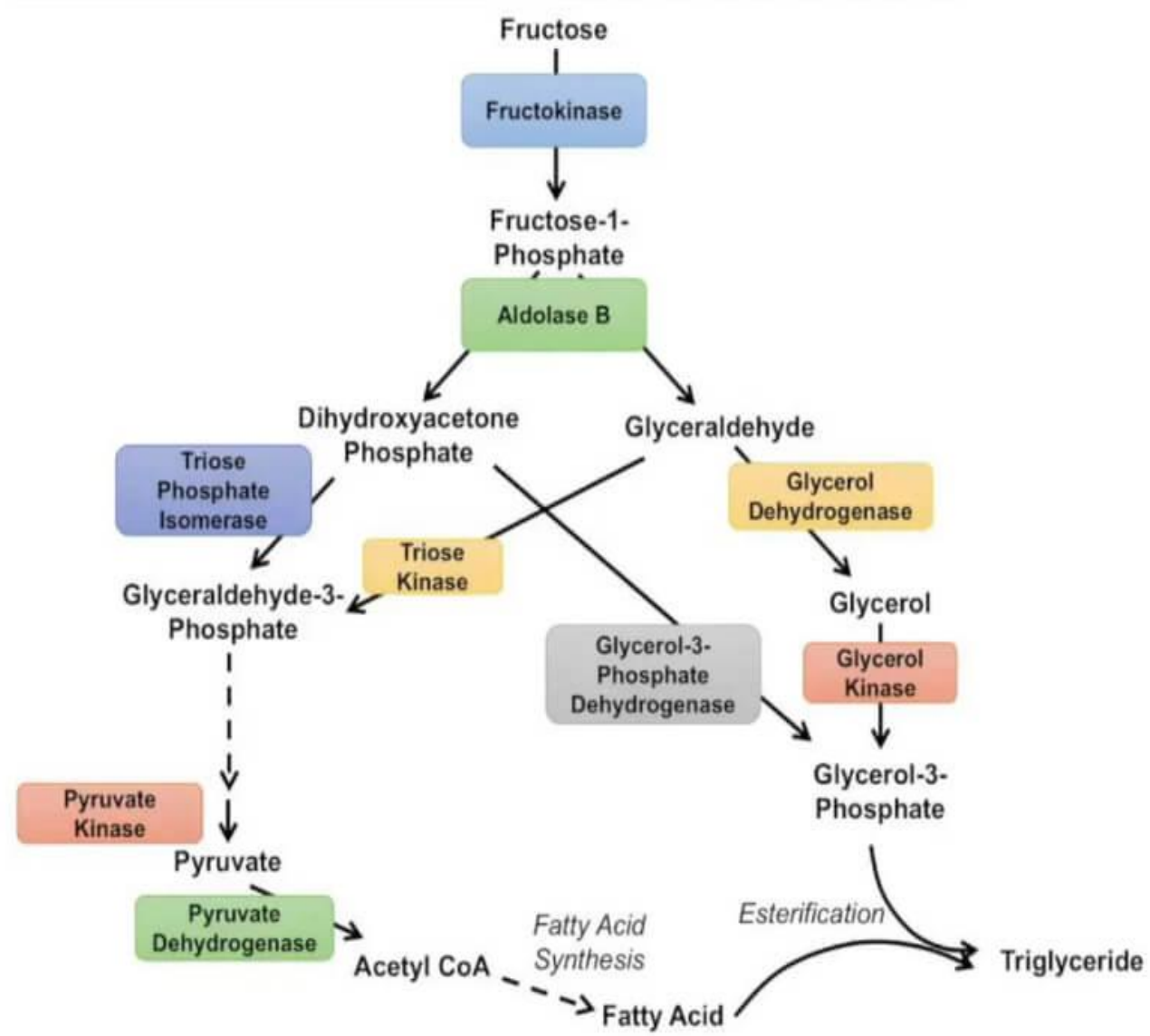
- Fructose-6-phosphate is isomerized to glucosamine-6-phosphate by the enzyme glutamine:fructose-6-phosphate amidotransferase.
  - This step involves the transfer of an amino group from glutamine to the C-2 position of fructose-6-phosphate, resulting in the formation of glucosamine-6-phosphate.

- Glucosamine-6-phosphate (precursor for amino sugar) can then undergo further modifications in various pathways.
  - Including glycosylation, which plays critical roles in cell signaling, protein stability, and cell-cell interactions.

Role of fructose in the synthesis of amino sugars



Metabolism of fructose



Disorders of fructose metabolism

Essential fructosuria:

- Cause: this disorder is caused by a deficiency in the enzyme fructokinase, which is responsible for the first step in fructose metabolism.
- Effect: this deficiency leads to the accumulation of fructose in the blood and the excess loss in urine because it cannot be converted into a usable form by the body.
- Symptoms: gastrointestinal discomfort or symptoms such as bloating, gas, or diarrhea after consuming fructose-rich foods.
- Treatment: this disorder doesn't cause any significant health problems, and most people with this condition can lead normal lives without requiring specific treatment.

Disorders of fructose metabolism (cont.)

Hereditary fructose intolerance:

- Cause: deficiency of aldolase B enzyme activity resulting in the accumulation of fructose-1-phosphate.
- Effect: affected individuals cannot properly metabolize fructose. The accumulation of fructose-1-phosphate in the liver leads to:
  - Liver and kidney dysfunction, the extent of which is proportional to the degree of fructose consumption.
  - Hypoglycemia.
  - Impaired gluconeogenesis and glycogenolysis in the liver.
- Symptoms: may include nausea, vomiting, abdominal pain, hypoglycemia, and liver dysfunction.
- Treatment: Strict avoidance of fructose, sucrose, and sorbitol in the diet.

Metabolism of galactose

- Galactose is a monosaccharide that is commonly found in dairy products. It is one of the two components (along with glucose) of lactose, the sugar found in milk.
- Galactose is metabolized in the body primarily through the galactose metabolic pathway (Leloir pathway), which involves several enzymatic steps in which galactose is converted into glucose-6-phosphate, a molecule that can:
  - Enter glycolysis for energy production.
  - Used as an intermediate for other metabolic processes.

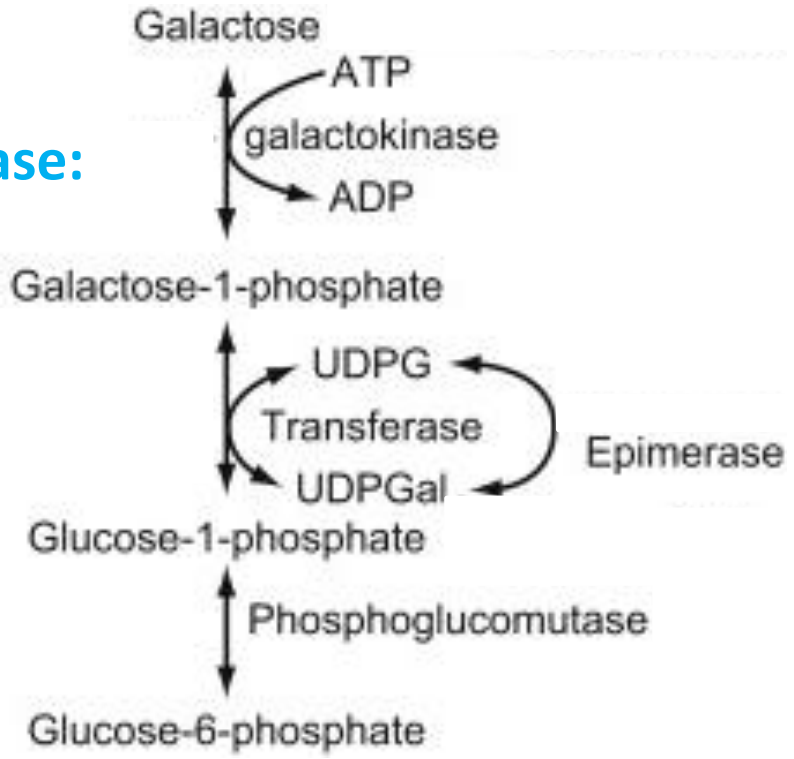
Metabolism of galactose (cont.)

Galactokinase:

- The first step in galactose metabolism is the conversion of galactose to galactose-1-phosphate, which is catalyzed by the enzyme galactokinase. This reaction requires the utilization of ATP.

Galactose-1-phosphate uridylyltransferase:

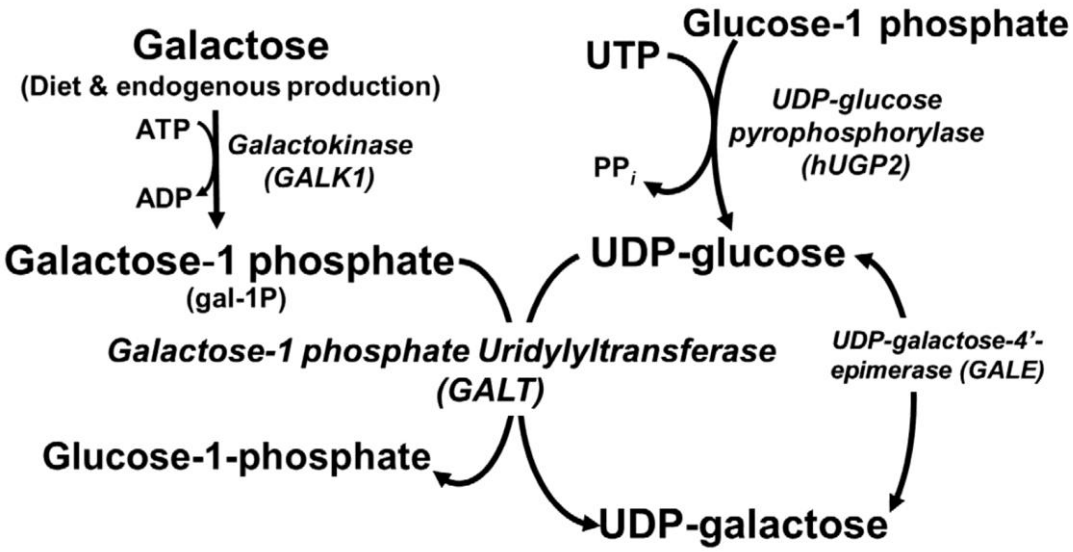
- The enzyme GALT catalyzes the conversion of galactose-1-phosphate + UDP-glucose to glucose-1-phosphate + UDP-galactose.



Metabolism of galactose (cont.)

UDP-glucose 4-epimerase:

- UDP-galactose is then converted to UDP-glucose by the enzyme UDP-glucose 4-epimerase.
  - This enzyme catalyzes epimerization reaction, allowing for the interconversion between galactose and glucose.

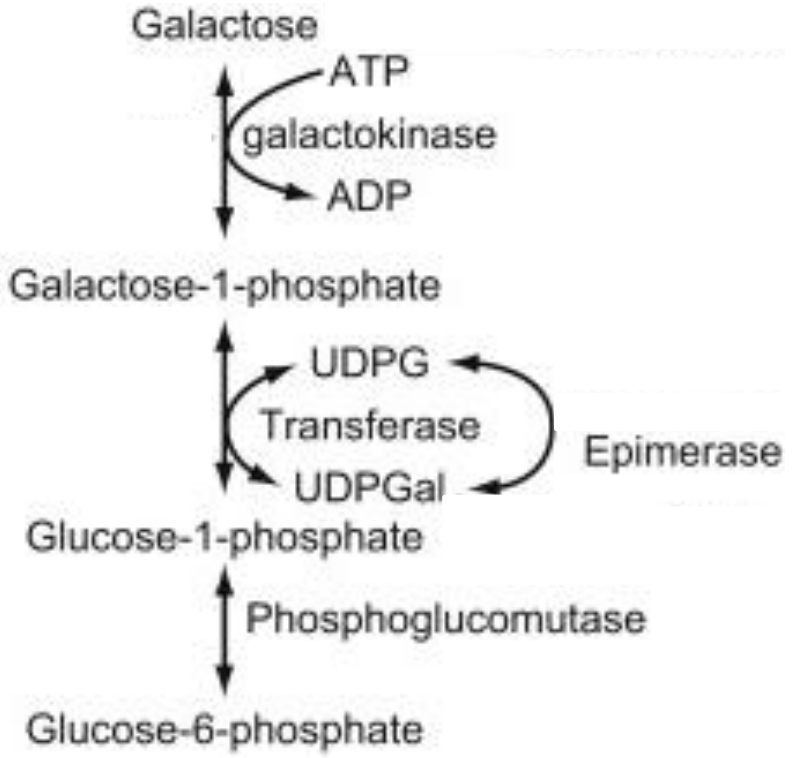


Metabolism of galactose (cont.)

Phosphoglucomutase:

- The enzyme phosphoglucomutase catalyze the conversion of glucose-1-phosphate to glucose-6-phosphate.

- **Glucose-6-phosphate can then:**
  - Enter glycolysis to be metabolized further to produce energy.
  - Be used for other metabolic processes in the body.



Disorders of galactose metabolism

Galactosemia:

- Galactosemia is a rare genetic disorder in which the body is unable to effectively metabolize dietary galactose.

- Cause: this condition is caused by mutations in genes that are responsible for the breakdown of galactose into glucose.
  - As a result, galactose and its metabolites can accumulate in the body, leading to various health problems. The severity of galactosemia can vary widely depending on the specific enzyme deficiency and the degree of impairment.

- Symptoms: they may include jaundice, poor feeding, vomiting, diarrhea, lethargy, and failure to thrive.
  - If left untreated, galactosemia can lead to liver damage, kidney problems, cataracts, intellectual disability, and developmental delays.

Assignments

Q1: Discuss the impact of consuming a diet high in fructose on metabolic health, including the effects on lipogenesis and insulin resistance.

Q2: Compare the regulation of galactose and glucose metabolism. Why is the utilization of galactose as a metabolic fuel less efficient than glucose?

Disorders of galactose metabolism