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Sheet Slides

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Fructose

- About **10%** of the **daily** calorie intake is supplied by **fructose**.
- Fructose and galactose transport into cells is **not insulin dependent** *(unlike glucose into certain tissues).* Also, in contrast to glucose, fructose does **not promote** the secretion of **insulin**.

Fructose sources:

a- The **major** source of fructose is the disaccharide **sucrose**, which when cleaved in the intestine, releases **fructose** and **glucose**.

b- Fructose is also found as a **free** monosaccharide in many **fruits**, **honey** and in **high-fructose corn syrup**, which is used to sweeten soft drinks.

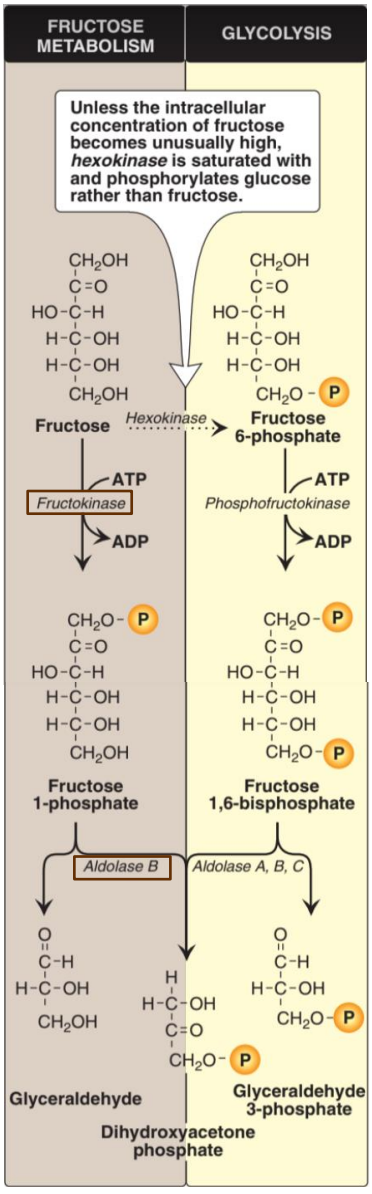
Fructose Metabolism Steps:

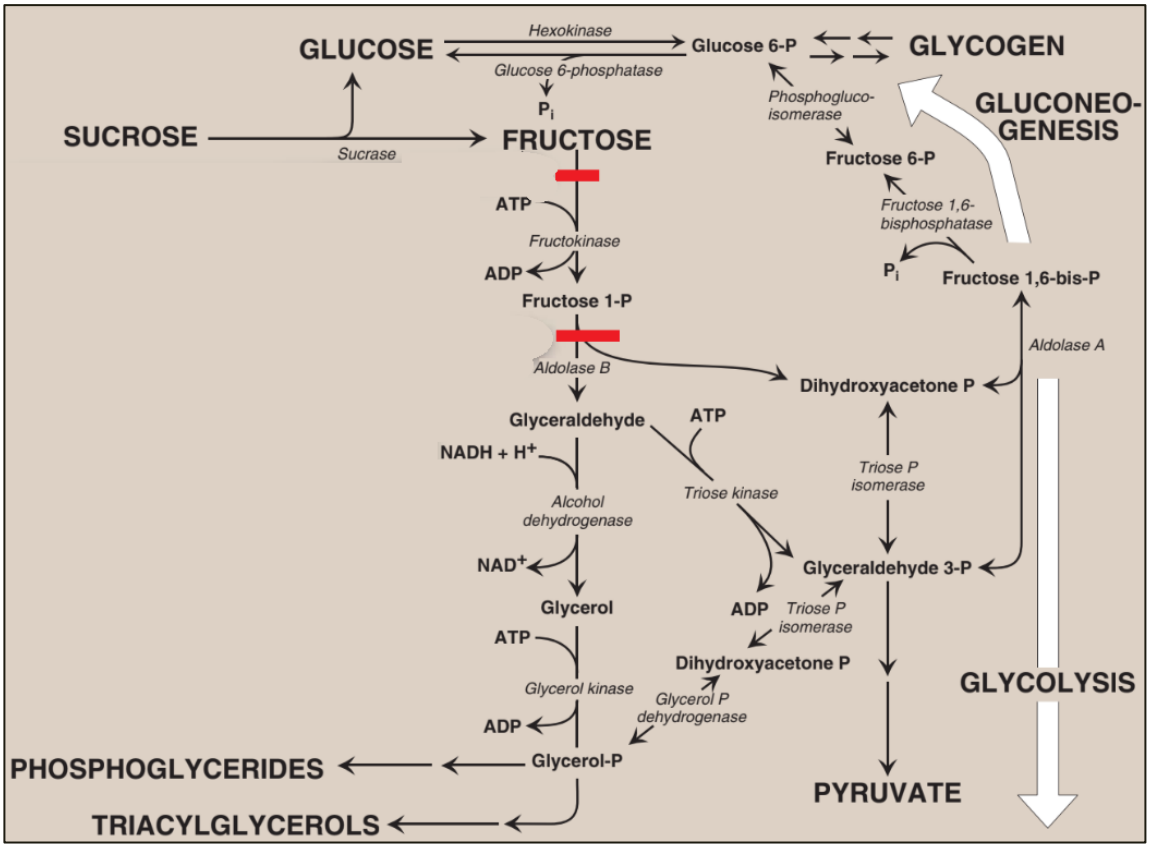
1. Fructose must be **phosphorylated** before it can be further metabolized. This can be accomplished by either **hexokinase** or **fructokinase** *(mainly),* where fructose in phosphorylated into **fructose 1-phosphate** using **ATP** as the phosphate donor.

> ***Note 1:*** ***Fructokinase*** *is present in the* ***liver*** *,* ***kidney****, and the* ***small intestinal*** *mucosa. It has a* ***high*** *affinity to* ***fructose*** *and converts it to* ***fructose 1-phosphate****.*
>
> ***Note 2:*** ***Hexokinases*** *phosphorylate many hexoses such as* ***glucose*** *and* ***fructose****. However, it has a much* ***lower*** *affinity for* ***fructose****. Therefore,* ***Unless*** *the intracellular concentration of fructose becomes unusually high, hexokinase is saturated with and phosphorylates* ***glucose rather*** *than fructose.*

2. Fructose 1-phosphate is cleaved by **Aldolase B** into **dihydroxyacetone phosphate** (DHAP) and **glyceraldehyde**.

   DHAP can directly enter **glycolysis** or **gluconeogenesis**, whereas **glyceraldehyde** can be **metabolized** by a number of pathways, *as illustrated in the next page.*





Humans express three aldolases:

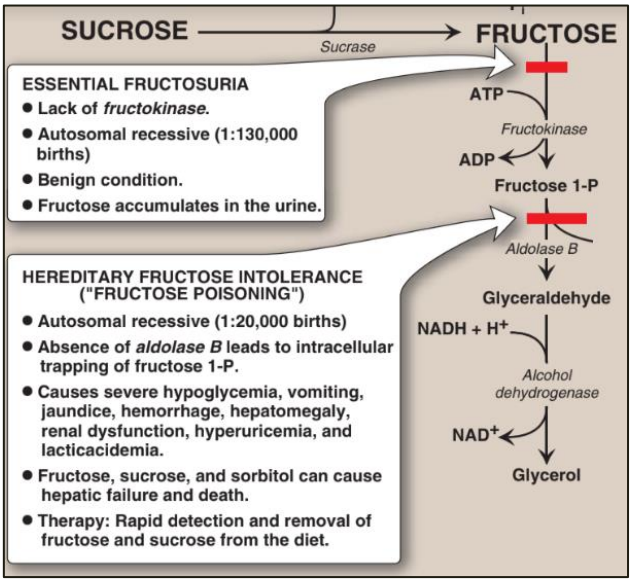
Refer to the figure in the previous page to trace their roles in glycolysis and fructose metabolism.

Aldolase B	Aldolase A	Aldolase C
In the liver, kidney, and small intestine.	Found in most tissues.	In the brain.
Cleaves **both** fructose 1-phosphate and fructose 1,6-bisphosphate.	Cleave fructose 1,6-bisphosphate produced during **glycolysis** *(only)* to DHAP and G3P.	

Extra Note: *The rate of **fructose metabolism** is **more rapid** than that of **glucose**. Because **DHAP** and **glyceraldehyde** formed from fructose 1-phosphate, **bypass phosphofructokinase-1**, the major rate limiting (**slowest**) step in **glycolysis**.*

Disorders of fructose metabolism

1- Fructokinase deficiency. *(Essential Fructosuria)*



- It is a **benign** *(not harmful in effect)*, **asymptomatic** condition.
- It is an **autosomal recessive** disorder which occurs **rarely** (1 in 130,000 births).
- **Fructose** accumulates → **Fructosuria**.
  Fructosuria : Fructose excretion in urine.

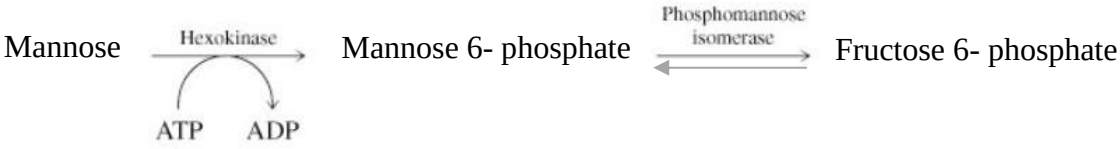
2- Aldolase B deficiency. (Hereditary Fructose Intolerance)

- It is a **severe** disturbance of **liver** and **kidney metabolism.**
- **Fructose 1-phosphate** accumulates:
  - → Resulting in a **drop** in the level of inorganic phosphate (**Pi**)
  - → **Drop** in **ATP** production
  - → As ATP falls, **AMP rises**
  - → The AMP is degraded, causing **hyperuricemia** *(excess of uric acid in the blood)* and **lactic acidosis**.
- It also causes **hypoglycemia** with **vomiting**, **Jaundice** *(yellow discoloration of the skin)*, **hemorrhage**, **hepatomegaly** *(enlarged liver)*, **hepatic failure** and **death.**
- In babies, The first symptoms of HFI appear when a baby is **weaned** from milk.
- **Diagnosis** of HFI is made on the basis of **fructose in the urine**.
- **Treatment**: **Sucrose**, as well as **fructose**, must be **removed** from the diet to prevent liver failure and possible death. Also, **Aldolase B deficiency** is part of the **newborn screening panel** to treat it at early stages if present.

Mannose Metabolism

Mannose, the **C-2 epimer** of **glucose**, can be **converted** into **fructose 6-phosphate** through these steps:

1. **Hexokinase** phosphorylates **mannose**, producing **mannose 6-phosphate**.
2. **Mannose 6-phosphate** is then reversibly **isomerized** to **fructose 6-phosphate** by **phosphomannose isomerase**.



> ***Note:*** *There is **little mannose** in dietary carbohydrates. **Most** intracellular mannose is synthesized from **fructose**.*

Conversion of glucose to fructose via sorbitol

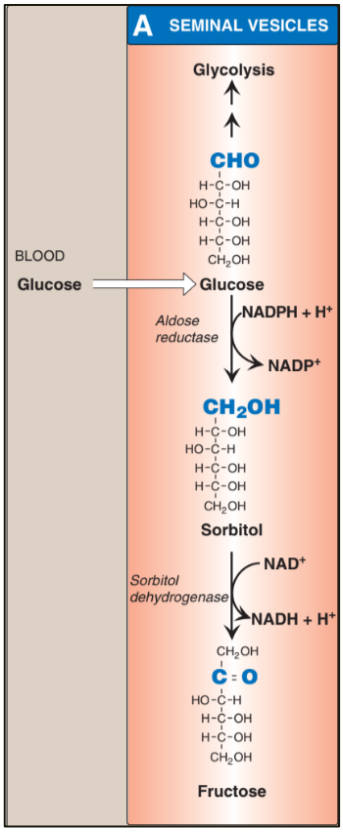
1. **Aldose Reductase** is an enzyme found in **many** tissues, including the **lens**, **retina**, **Schwann cells**, **liver**, **kidney**, **ovaries** and **seminal vesicles**.

   It reduces **glucose**, producing **sorbitol**.

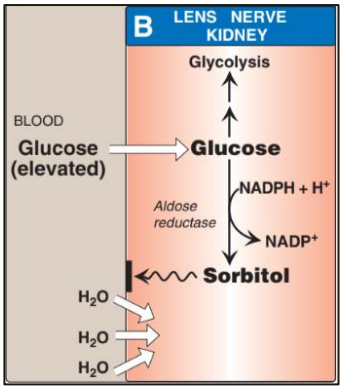
2. **Sorbitol Dehydrogenase** is found in cells of the **liver**, **ovaries**, and **seminal vesicles**.

   It oxidizes the **sorbitol** producing **Fructose**.

- The two-reaction pathway from glucose to fructose in the **seminal vesicles** *(as in the figure to the right)* benefits sperm cells, which use fructose as a **major energy source**.
- The pathway from sorbitol to fructose in the **liver** *(as in the figure in the next page)* provides a mechanism by which any available **sorbitol** is converted into a substrate that can enter **glycolysis** or **gluconeogenesis**.



Sorbitol can accumulate due to either:



a- **Sorbitol dehydrogenase** is low or absent.

b- In the case of **uncontrolled diabetes** where large amounts of **glucose** enter the cells during **hyperglycemia**, which is then converted into **sorbitol** through **aldose reductase** causing a significant increase in the amount of sorbitol.

Sorbitol accumulation causes **strong osmotic effects** and, therefore, **water retention** and **swelling**. This phenomenon Also, can be attributed to the pathologic alterations associated with diabetes such as **cataract** formation.

Galactose

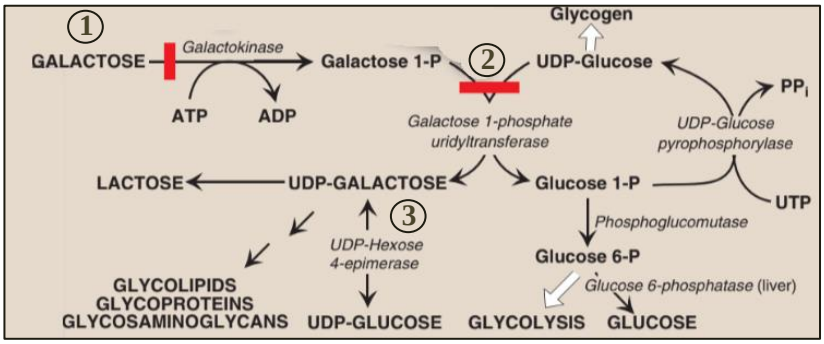
- Galactose is the **C-4 epimer** of **glucose**.
- Like fructose, the transport of galactose into cells is **not insulin dependent**.

Galactose Sources:

a- The **major** dietary source of galactose is **lactose** obtained from milk and milk products.

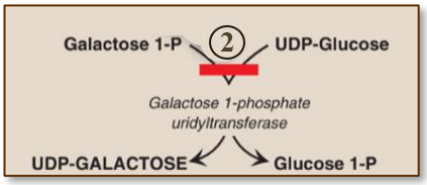
b- Some galactose can also be obtained by lysosomal degradation of complex carbohydrates, such as **glycoproteins** and **glycolipids**.

Galactose Metabolism Steps:



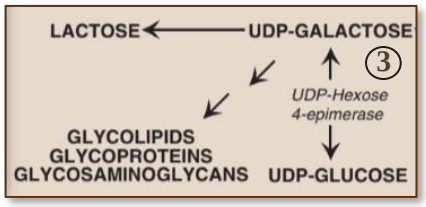
1. Like fructose, galactose must be phosphorylated before it can be further metabolized. **Galactokinase** phosphorylates **galactose** into **galactose 1-phosphate**, using **ATP** as the phosphate donor.

2. Then, galactose 1-phosphate uridylyl-transferase (**GALT**) catalyzes an **exchange reaction** in which **UDP-glucose** reacts with **galactose 1-phosphate**, producing **UDP-galactose** and **glucose 1-phosphate**.

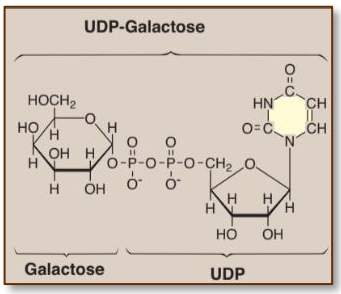


3. **UDP-galactose** is converted reversibly to **UDP-glucose**, by **UDP-hexose 4-epimerase**.

   Each can participate in many biosynthetic reactions:



   a- **UDP-glucose** can enter the mainstream of **glucose metabolism**. It also participates in **glycogenesis** as well as in the **GALT** reaction.



   b- **UDP-galactose** serves as the **donor** of galactose in a number of synthetic pathways, including synthesis of **lactose**, **glycoproteins**, **glycolipids**, and **glycosaminoglycans**.

> ***Note:*** *If galactose is **not provided** by the diet (for example, when it cannot be **released** from **lactose** as a result of a lack of **β-galactosidase** in people who are **lactose intolerant**), all tissue requirements for **UDP-galactose** can be met by the action of **UDP-hexose 4-epimerase** on **UDP-glucose**, which is **efficiently** produced from **glucose 1-phosphate**.*

Disorders of galactose metabolism

1. **Deficiency in galactose 1-phosphate uridylyl-transferase "GALT"** ***(Classic galactosemia).***

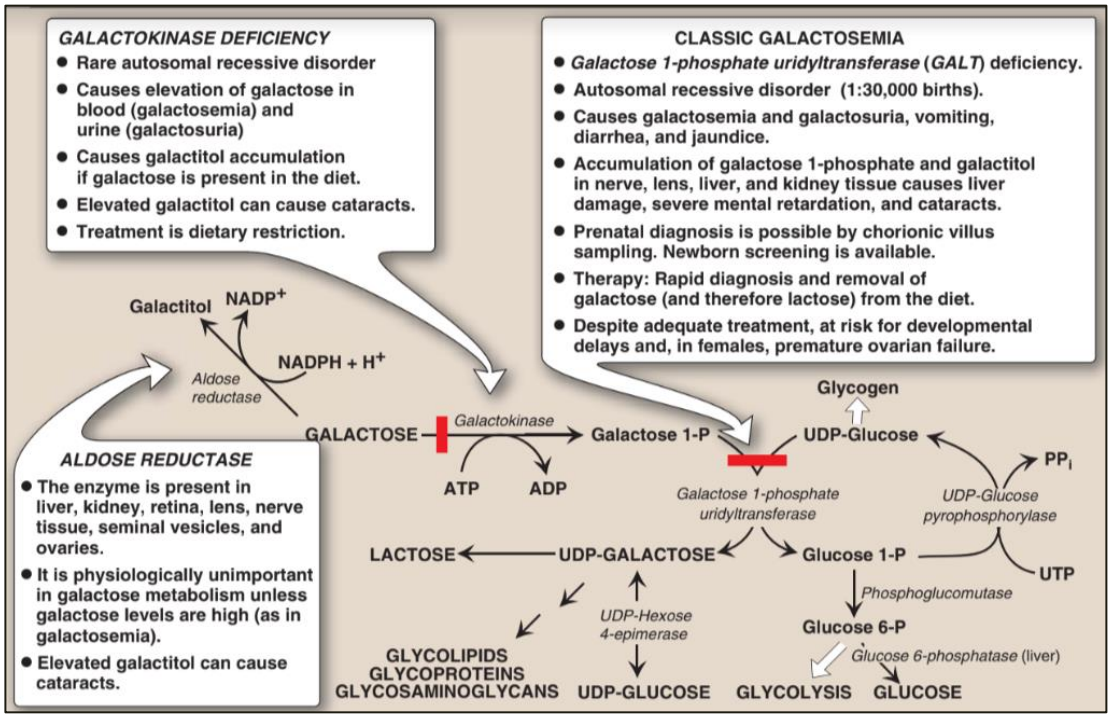
   In this disorder, **galactose 1-phosphate** and **galactose accumulate**.

2. **Deficiency in Galactokinase**

   It also causes **accumulation** of **Galactose**, but a **less severe galactosemia**.

When the galactose levels are **high** due to the **accumulation** as in **both** disorders above, **Aldose reductase** converts the **galactose** into **galactitol**. Elevated galactitol levels then can **contribute** to **cataract**. **Treatment** requires removal of **galactose** and **lactose** from the diet.

> ***Note:*** *Physiologic consequences are similar to those found in **hereditary fructose intolerance** but a **broader** spectrum of **tissues** is affected.*
>
> ***Recall:*** *1. **Aldose reductase** converts **Galactose** → **Galactitol**, and **Glucose** → **Sorbitol**.*
> *2. **GALT and Aldose B deficiency** are both part of the **newborn screening panel**.*



Lactose Synthesis

- Lactose is a **disaccharide** that consists of a molecule of **β-galactose** attached by a **β (1→4)** linkage to **glucose**. Therefore, **lactose** is galactosyl β (1→4)-glucose.
- Galactosyl β (1→4)-glucose is found in **glycolipids** and **glycoproteins**.
- **Lactose sources**: **Milk** and other **dairy products**.
- **Lactase** is an enzyme which **degrades** lactose, it is located in the brush border of the small **intestine**. It is **not** found in the **serum**.

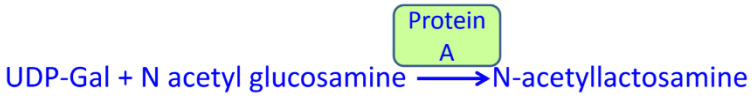
Lactose synthesizes

Lactose synthase is a complex of **2 proteins**:

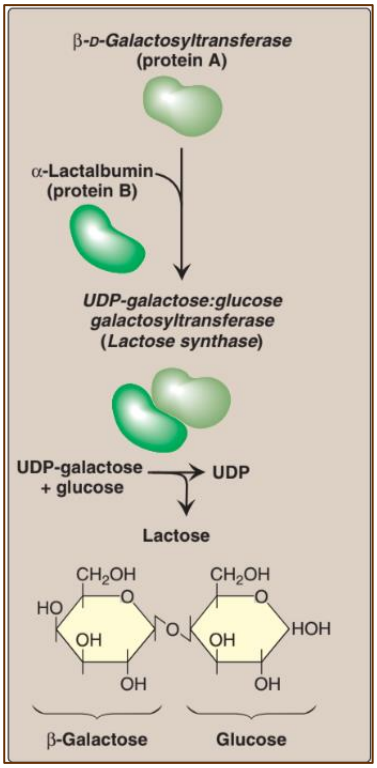
1. **Protein B** *(found in the lactating mammary gland)*
2. **Protein A: Galactosyl-transferase**

Protein A is found in a number of body tissues.

Alone, it has role in **glycolipids synthesis**:



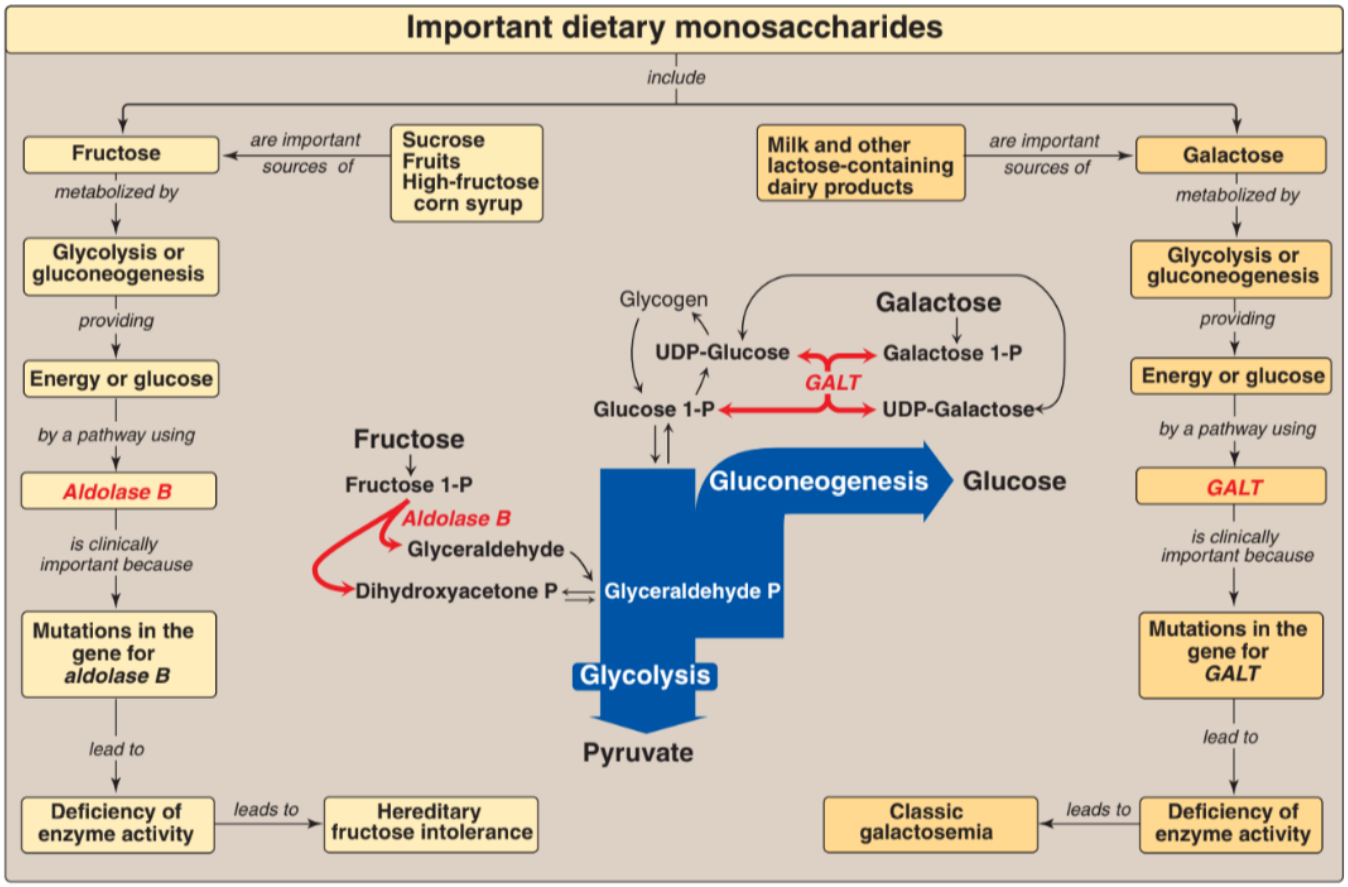
It **transfers galactose** from **UDP-galactose** to **N-acetyl-glucosamine**, producing **N-acetyl-lactosamine** which is a component of **many glycoproteins**.



Protein B forms a **complex** *(called Lactose synthase)* with **protein A** changing the specificity of protein A so that it binds to **glucose** not **N-acetyl-glucosamine** producing **lactose**, rather than producing N-acetyl-lactosamine.

As illustrated, **Lactose Synthase** *(complex of protein A and B)* transfers **galactose** from **UDP-galactose** to **glucose**, releasing UDP and forming galactosyl β (1→4)-glucose (**Lactose**).

Summary of the metabolism of fructose and galactose



Questions from Lippincott Biochemistry Book

1. Following the **intravenous injection** of **lactose** into a rat, **none** of the lactose is metabolized. However, **ingestion** of lactose leads to **rapid** metabolism of this disaccharide. The difference in these observations is a result of:

   A. The presence of lactase in the serum.
   B. The absence of hepatic galactokinase.
   C. The absence of maltase in the serum.
   D. The presence of lactase in the intestine.

2. A female with **classic galactosemia** due to GALT deficiency is able to produce lactose in breast milk because:

   A. Free galactose is the acceptor of glucose transferred by lactose synthase in the synthesis of lactose.
   B. The enzyme deficient in galactosemia is activated by a hormone.
   C. Hexokinase can efficiently phosphorylate dietary galactose to galactose 1-phosphate.
   D. Galactose can be produced from fructose by isomerization.
   E. Galactose can be produced from a glucose metabolite by epimerization.

3. 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. Tests on the baby's urine were positive for reducing sugar but negative for glucose. The infant most likely suffers from:

   A. Aldolase B deficiency.
   B. Fructokinase deficiency.
   C. Galactokinase deficiency.
   D. β-galactosidase deficiency.

I was highly dependent on the book in this sheet.

Best Wishes ♥

Key answer: D, E, A.