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Biochemistry 2

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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Hey everyone, I hope your spirits are high 😊 just wanted to assure you that this lecture is one of the easiest. I hope you won't find any difficulties studying it. Everything in the slides is included.

Metabolism of monosaccharides and disaccharides

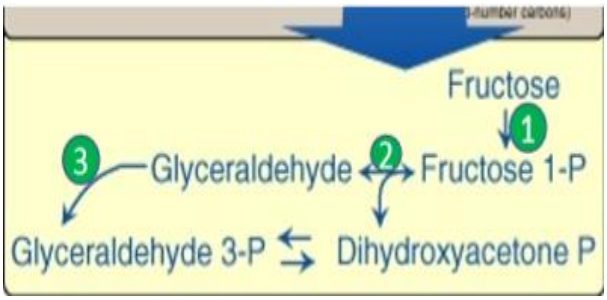
Glucose is the most common monosaccharide consumed by humans. However, two other monosaccharides, fructose and galactose, are found in significant amounts in our diet (primarily in disaccharides) and make important contributions to energy metabolism. So, it's worth our time to consider their metabolism.

❖ Fructose:

- **Fructose** (سكر الفواكه) is a hexose sugar similar to glucose but with a carbonyl (ketone) group on carbon #2 instead of carbon #1.
- Our daily intake of fructose from food is considered high (around 10%) which is more than 50 g/day. These sources include: sucrose (glucose + fructose), fruit, honey, and high-fructose corn syrup (food sweetener used in soft drinks).
- Entry into the cell is insulin independent which is why it's used by many diabetic patients as a substituent for other sugars.
- Unlike glucose, it doesn't induce insulin secretion.
- Transported into intestinal cells by Glut 5.

❖ Mechanism of fructose metabolism:

1. **Phosphorylation of fructose** at carbon #1, using ATP as a phosphate donor to produce fructose 1-phosphate. This step is mediated by the enzyme **fructokinase.**



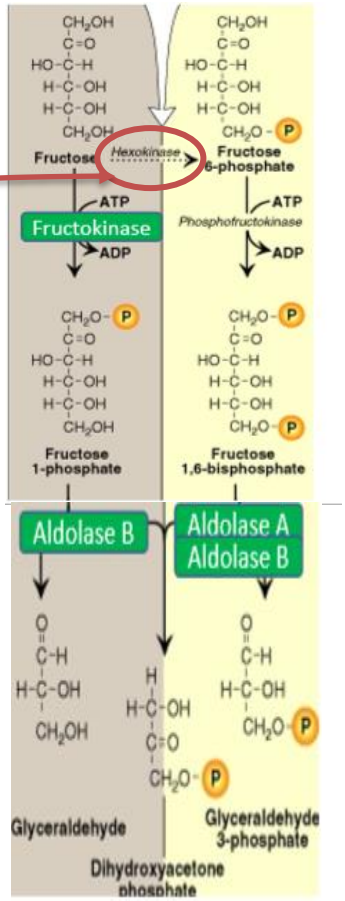
Hexokinase can also phosphorylate fructose, but it's not the main catalyst; it has low affinity for fructose (high Km). So, only when there is a high concentration of fructose can hexokinase do its job.

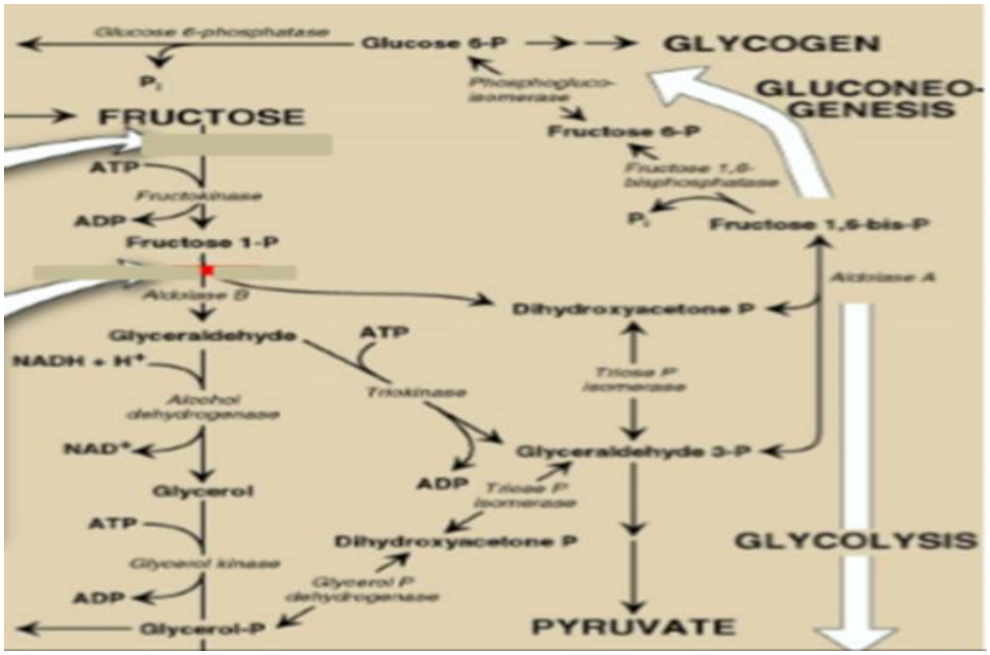
2. **Cleavage of fructose 1-phosphate** (between carbon 3 and 4) to produce glyceraldehyde and dihydroxyacetone phosphate (DHAP), via the enzyme **aldolase B**.

DHAP can directly enter glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by a number of pathways, one of which is phosphorylation to glyceraldehyde 3-phosphate which can enter glycolysis.

Notice: the dotted line here indicates that this is a **minor pathway**; where fructose is phosphorylated by hexokinase to produce fructose 6-phosphate which proceeds in the glycolytic pathway.

This pathway is relatively slower than the main one, because fructose 6-phosphate will go through the rate limiting step catalyzed by phosphofructokinase.





Now, what are aldolases?

Aldolases are a group of isozymes (A, B, C) which can cleave fructose 1,6-bisphosphate that is produced during glycolysis. However, only aldolase B can cleave fructose 1-phosphate. So, **Aldolase B is mandatory for fructose metabolism.**

	Aldolase A	Aldolase B
Tissue distribution	Almost all tissues	Liver, kidneys, small intestines
substrate	Fructose 1,6-bisphosphate	Fructose 1-phosphate and Fructose 1.6-bisphosphate

❖ **Enzyme deficiencies:**

1. Fructokinase deficiency: when fructokinase is deficient, there will be no phosphorylation of fructose → the whole metabolism pathway is halted → accumulation of fructose→ fructose will diffuse through the cell membrane therefore it will be excreted in the urine; a condition called **Fructosuria.**

However, it's considered a benign condition (doesn't cause severe disturbances).

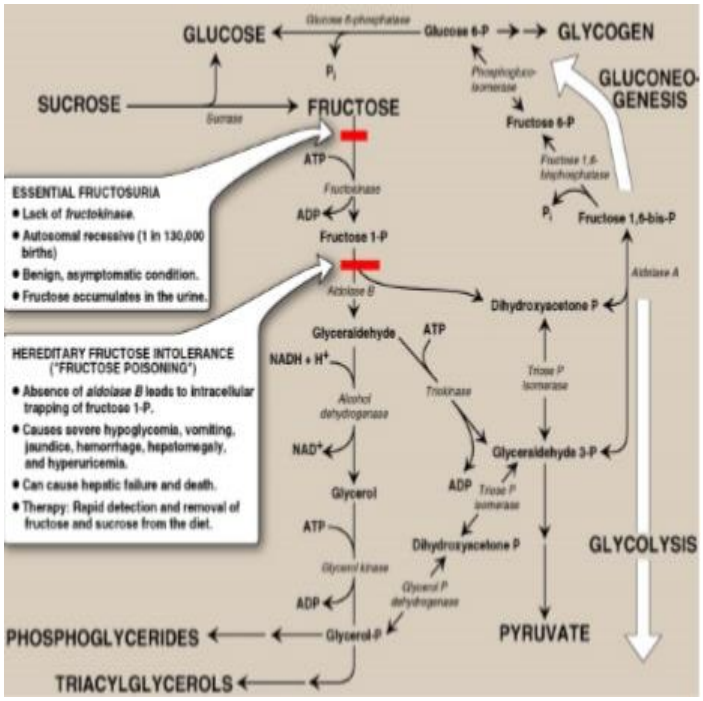
Fructosuria is a rare condition and is considered autosomal recessive (needs two abnormal alleles).

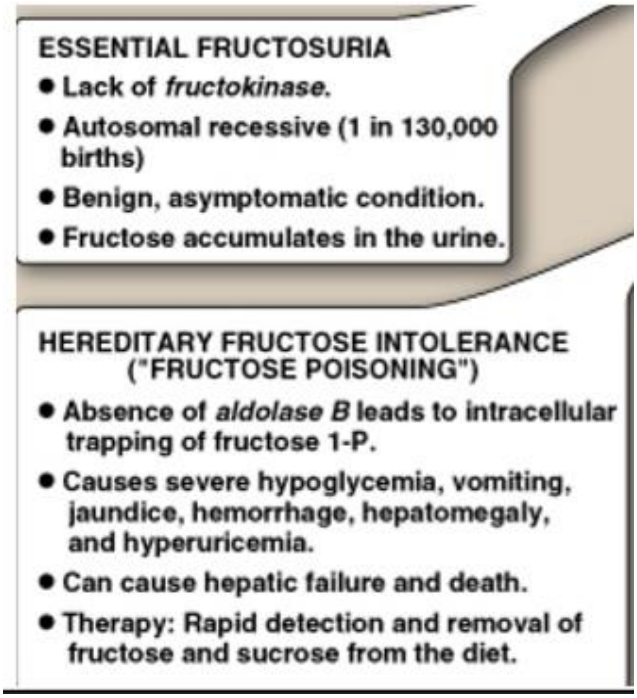
2. Aldolase B deficiency: hereditary fructose intolerance (HFI)→ fructose poisoning

Causes accumulation of fructose 1-phosphate, trapping the phosphate groups in the cells, this causes a drop in organic phosphate, which is required for ATP synthesis→ impaired ATP synthesis.

- **Consequences of impaired ATP synthesis caused by aldolase B deficiency:**
  a. Increasing AMP levels causing continuous elimination of AMP.
  b. Impaired gluconeogenesis (causing hypoglycemia); gluconeogenesis needs ATP
  c. Lactic acidosis.
  d. Inhibiting glycogenolysis.
  e. Hepatic failure.

✓ After the child weans from milk and starts eating other food that may contain sucrose or fructose, symptoms of HFI can be observed.
✓ Ingesting fructose → fructose poisoning.
✓ This condition is more serious; it causes severe disturbance for liver and kidney metabolism (tissues containing aldolase B).
✓ With HFI, sucrose, as well as fructose and sorbitol (an alcohol sugar used in gums), must be removed from the diet to prevent liver failure and possible death.
Why sorbitol? See next topic 😊
✓ Early detection of aldolase deficiency is done via a newborn screening panel; detecting diseases pre-symptomatically in newborns, or if a family member was diagnosed with this disease, it is recommended for the other family members to check up for it.





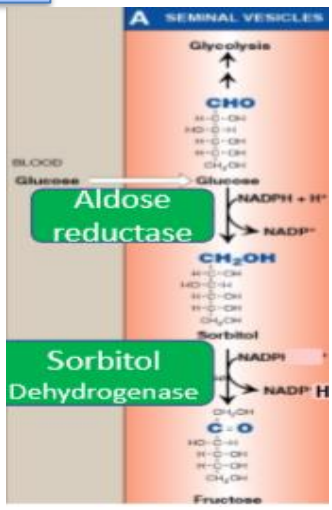
❖ Conversion of glucose to fructose via sorbitol

Most sugars are rapidly phosphorylated following their entry into cells. Therefore, they are trapped within the cells, because organic phosphates cannot freely cross membranes without specific transporters. An alternate mechanism for metabolizing a monosaccharide is to convert it to a polyol (sugar alcohol) by the reduction of an aldehyde group, thereby producing an additional hydroxyl group.

Due to the similarity between glucose and fructose, it is easy for interconversion to happen via sorbitol. (that's why people with hereditary fructose intolerance should stay away from sorbitol).

Glucose is reduced to sorbitol, then sorbitol is oxidized to fructose

1. **Glucose reduction by the enzyme aldose reductase**
   - Aldose reductase in blood reduces the aldehyde group in glucose to give sorbitol (six-carbon molecule with 6 -OH groups).
   - Aldolase reductase is found in: lens, retina, schwann cells, liver, kidneys, ovaries and seminal vesicles.
2. **Sorbitol oxidation by the enzyme sorbitol dehydrogenase**
   - Sorbitol is oxidized at carbon #2 by sorbitol dehydrogenase to give a ketohexose which is fructose.

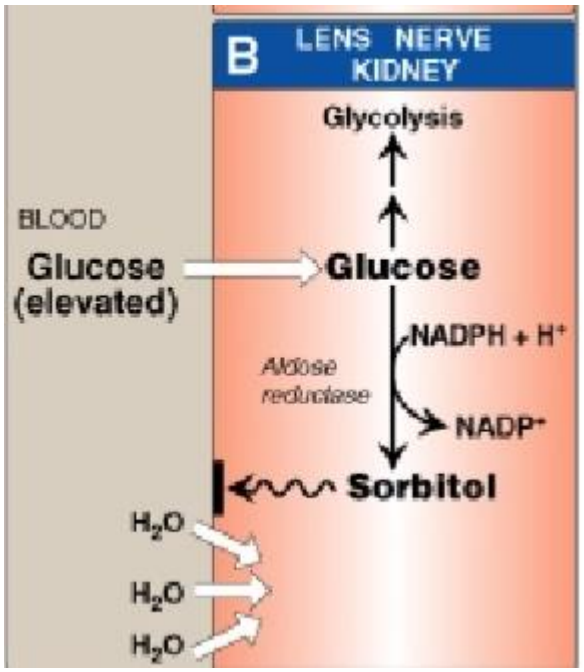


- Sorbitol dehydrogenase is found in: ovaries, liver, seminal vesicles.

In **semen,** fructose is the main energy source for sperm cells.

The pathway from sorbitol to fructose **in the liver** provides a mechanism by which any available sorbitol is converted into a substrate that can enter glycolysis or gluconeogenesis.

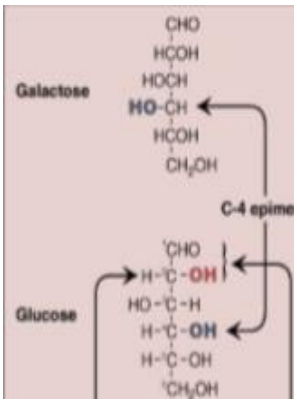
Tissues that express aldose reductase but not sorbitol dehydrogenase (lens, retina, schwann cells, and kidneys) do not convert sorbitol into fructose; these tissues don't need insulin for glucose entrance*. So in the case of high glucose levels, part of the glucose is reduced to sorbitol, but sorbitol cannot be converted to fructose, so it will accumulate in the cells of the lens, and this leads to an increase in the osmotic pressure causing entrance of water molecules to the lens. This mechanism is thought to be associated with cataract; one of diabetes' complications.



*these tissues contain GLUT1 and GLUT3 glucose transporters which are insulin independent. Remember: GLUT4 was the one mediated by insulin.

❖ Galactose

Galactose is an epimer of glucose at carbon # 4 (in glucose -OH group is on the right and in galactose it's on the left).



Sources of galactose:

1. Lactose -milk sugar- is the major source of galactose, it's hydrolyzed in the small intestines producing glucose and galactose.
2. Glycolipids and glycoproteins

Like fructose, the entry of galactose into cells is not insulin dependent. This is the main reason why with diabetes, we are mostly concerned about glucose.

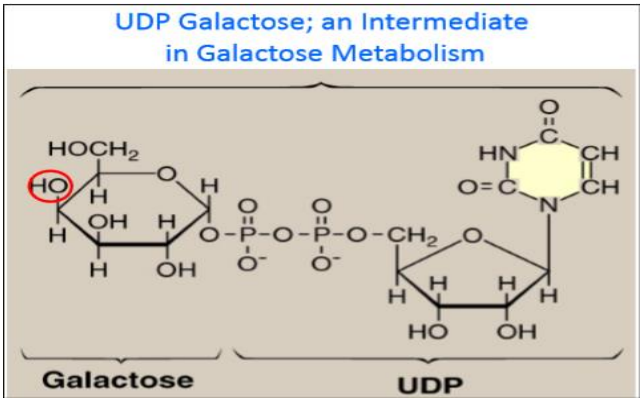
❖ Mechanism of galactose metabolism

1. Galactose is phosphorylated to galactose 1-phosphate by galactokinase enzyme.

   Galactose + ATP → galactose 1-phosphate + ADP

2. An exchange reaction happens between galactose 1-phosphate and UDP-glucose to produce UDP-galactose and glucose 1-phosphate by a transferase enzyme (galactose 1-phosphate uridyl transferase; GALT)

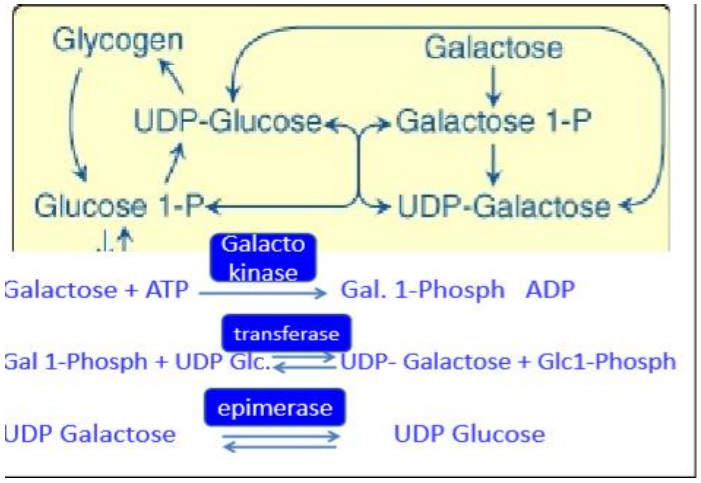
   Galactose 1-phosphate + UDP-glucose → glucose 1-phosphate + UDP-galactose

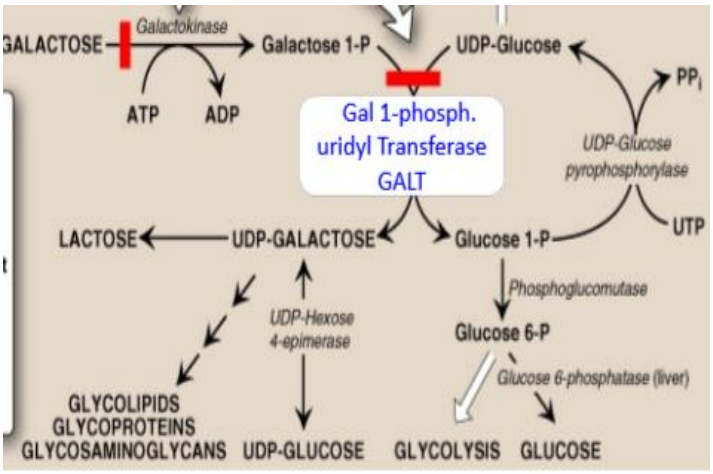


From this step we can proceed to different pathways:

a. We can use UDP-galactose to synthesize lactose, glycolipids or glycoproteins.
b. Glucose 1-phosphate can be converted to UDP-glucose.
c. UDP-glucose can be used in glycogenesis.
d. Glycogen can be degraded to glucose 1-posphate.
e. Glucose 1-phosphate can be easily isomerized to glucose 6-phosphate, which can be converted to glucose or used in glycolysis.
f. Isomerization between UDP-glucose and UDP-galactose by an epimerase enzyme.

Notice that glucose can be converted to galactose **only when bound to UDP.





❖ **Enzyme deficiencies:**

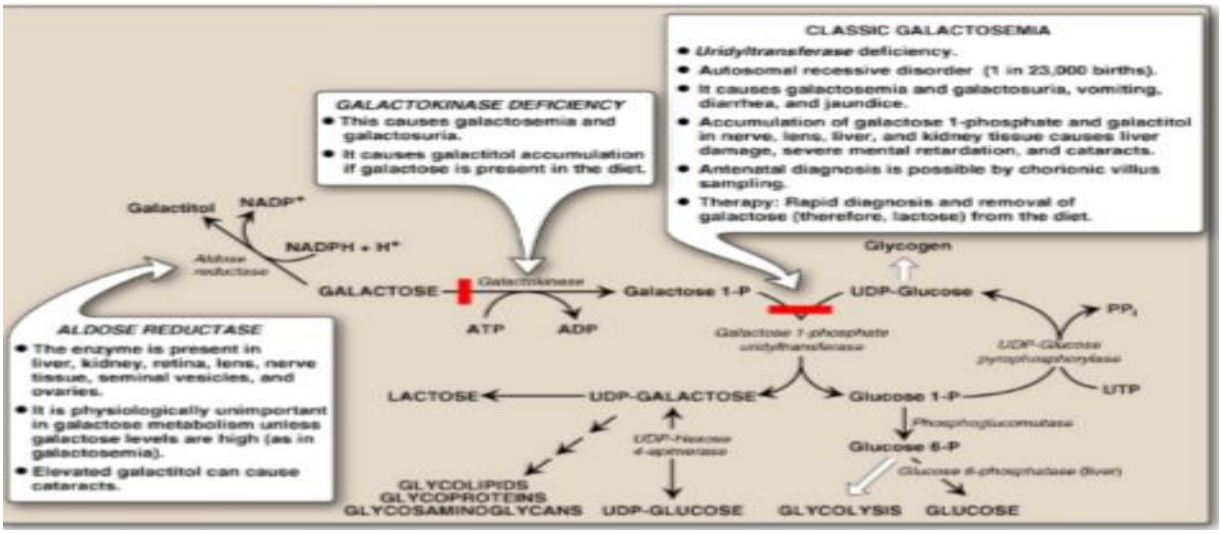
1. Galactose 1-phosphate uridyl transferase (GALT) deficiency: **classic galactosemia**; there will be no exchange reaction, therefore galactose 1-phosphate will accumulate.

Physiologic consequences are similar to those found in hereditary fructose intolerance, but a broader spectrum of tissues is affected.

2. Galactokinase deficiency: accumulation of galactose causing less severe galactosemia.

- The accumulated galactose is moved into side pathways such as that of galactitol production.
- Accumulation of galactitol → cataract.
- Treatment requires removal of galactose and lactose from the diet.

Unlike fructose intolerance, galactose enzyme deficiency's symptoms will appear early in newborns; because it's the building block for the main sugar in milk.

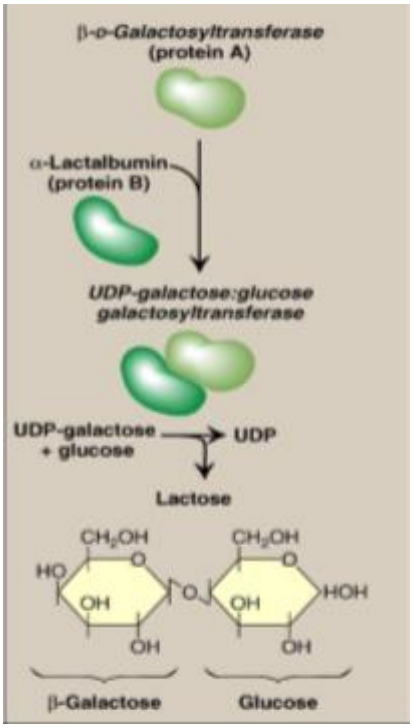


❖ Lactose synthesis

- Lactose (milk sugar) is a disaccharide that consists of a molecule of β-galactose attached by a (β1→4) linkage to glucose**. (galactosyl β-1,4-glucose)**
- Lactose is synthesized by lactose synthase in the mammary glands for breast-feeding. This enzyme transfers galactose from UDP-galactose to glucose, releasing UDP.

UDP-galactose + glucose → lactose + UDP

So, what is the structure of lactose synthase?



It's a complex of two proteins:

Protein A: Galactosyl transferase, found in mammary glands and other tissues.

Protein B: α-lactalbumin, found only in **mammary glands.** Its synthesis is stimulated by the hormone prolactin (prolactin stimulates production of milk).

This enzyme is important in adding **galactose to free glucose.**

In glycolipid and glycoprotein synthesis, only protein A is needed in tissues other than mammary glands.

UDP-galactose + N-acetylglucosamine → N-acetyllactosamine

❖ Mannose conversion to fructose,6-phosphate

- ✓ Mannose is a hexose sugar, not abundant in diets, but is found primarily in glycoproteins.
- ✓ It's another epimer of glucose at carbon #2.
- ✓ Hexokinase phosphorylates mannose, producing mannose 6-phosphate, which in turn, is isomerized to fructose 6-phosphate by phosphomannose isomerase.

Metabolism of alcohol

How do we prepare a carboxylic acid from a primary alcohol?

Simply by oxidation in two steps; the first produces aldehyde and the second produces carboxylic acid. This is exactly what happens in the body:

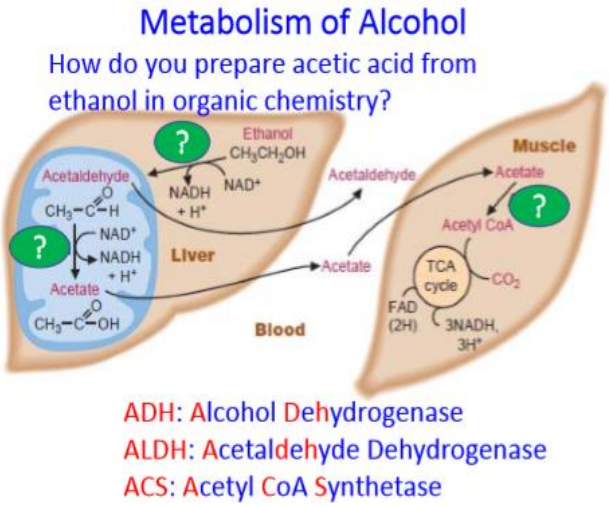
1. Ethanol is oxidized to acetaldehyde by alcohol dehydrogenase.
2. Acetaldehyde is oxidized to acetate by acetaldehyde dehydrogenase.

Acetate is then released to the blood, reaching the muscles -for example-, there it reacts with CoA to produce acetylCoA (by the enzyme acetylCoA synthetase), after that it can enter different pathways of metabolism.

In the case of excessive alcohol intake, frequent oxidation of ethanol and acetaldehyde produces large amounts of NADH. This in turn will inhibit fatty acid oxidation, gluconeogenesis and leads to lactic acidosis.

1 gram of ethanol gives 7kcal of energy (close to lipids)

Whereas, 1 gram of carbohydrates gives 4kcal of energy.



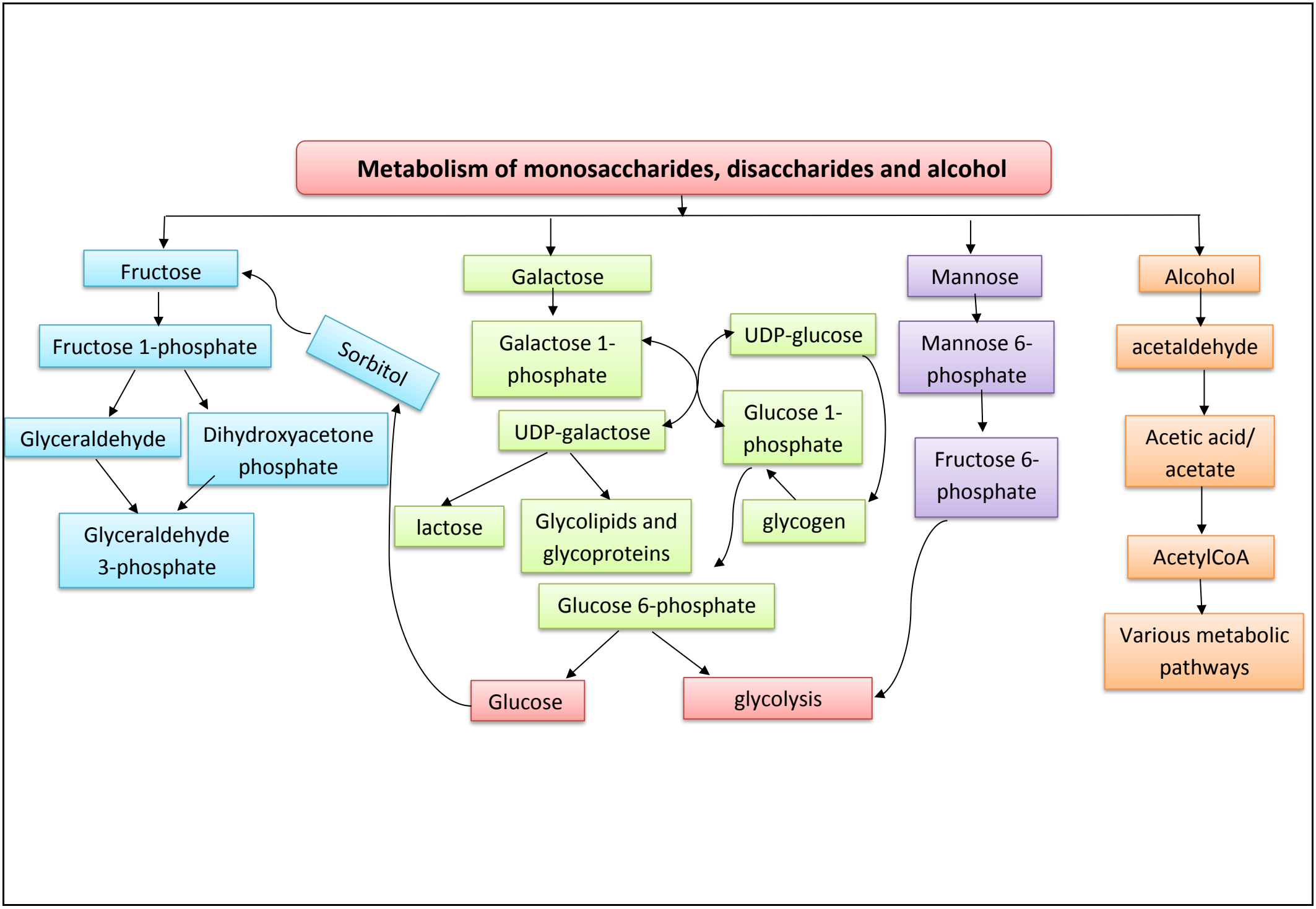
معلومة عالهامش ٨٨ :

The difference between a synthase and a synthetase is **the need for ATP**; **synthase** is an ATP independent enzyme, whereas **synthetase** is ATP dependent.
E.g. AcetylCoA synthetase forms a thioester bond between acetate and CoA, which is a high energy bond, so we need ATP.

That was all guys, thank you for bearing.

I've included a summary in the next page to give you an overlook at the metabolic pathways mentioned earlier.

Good luck


Metabolism of monosaccharides, disaccharides and alcohol
Fructose
Fructose 1-phosphate
Glyceraldehyde
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
Sorbitol
Galactose
Galactose 1-phosphate
UDP-glucose
UDP-galactose
Glucose 1-phosphate
lactose
Glycolipids and glycoproteins
glycogen
Glucose 6-phosphate
Glucose
glycolysis
Mannose
Mannose 6-phosphate
Fructose 6-phosphate
Alcohol
acetaldehyde
Acetic acid/ acetate
AcetylCoA
Various metabolic pathways