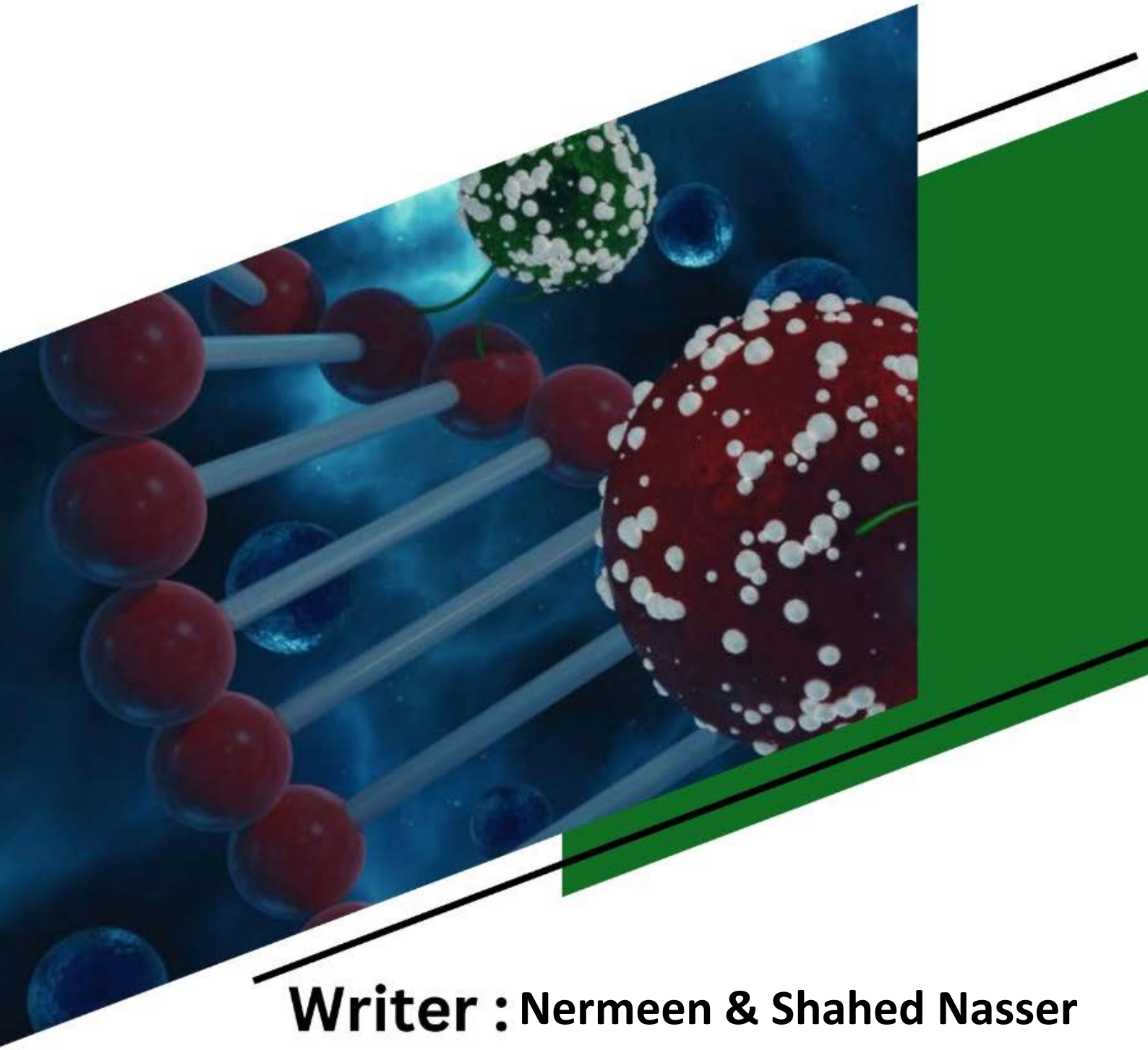
Doctor 021

METABOLISM

Sheet no. 16



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Corrector :

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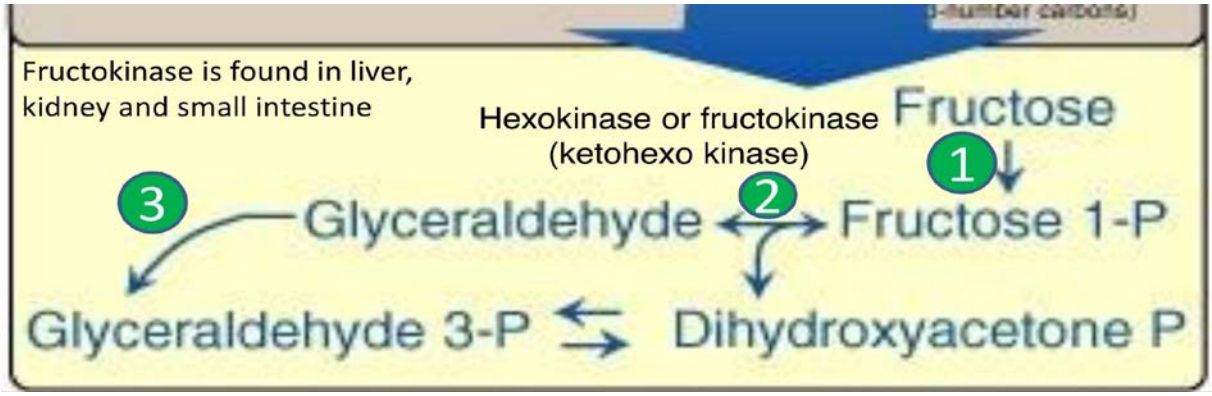
METABOLISM OF MONOSACCHARIDES AND DISACCHARIDES:

I. FRUCTOSE METABOLISM:

- **10% of the daily calorie intake.**
- **Sources of fructose: sucrose, fruits, honey, high-fructose corn syrup (found as free fructose in these sources, except for sucrose).**
- **Entry into cells is not insulin dependent (for both galactose and fructose, unlike glucose).**
- **Does NOT promote the secretion of insulin.**
- **Fructokinase is found in liver, kidney and small intestine.**



- Fructose is a substrate for hexokinase that can phosphorylate it into fructose-6-phosphate, hence, we can proceed in glycolysis skipping the isomerization step.
- Fructokinase is a specific enzyme for fructose phosphorylation, which phosphorylates fructose to fructose-1-phosphate.
- **Hexokinase affinity to fructose is low.**
- **The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose-1-phosphate bypass phosphofructokinase-1 the major rate-limiting step in glycolysis** (this sentence is in the slides as **"phosphor fructokinase-1-P the major rate-limiting step in glycolysis"**, which I believe it was misspelled).

(take a closer look at the details of the following figure, we will go into them thoroughly)

Starting with the left part:

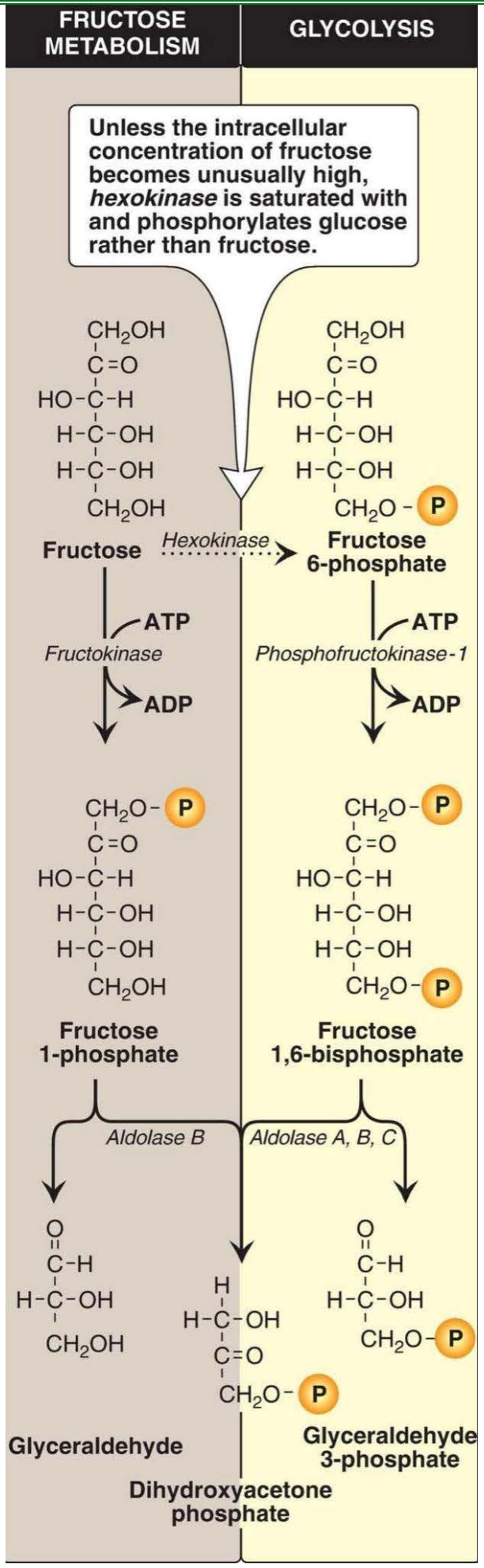
- Fructose is phosphorylated by its specific enzyme, fructokinase, into fructose-1-phosphate.
  Side note: the phosphate donor is ATP.
- Fuctose-1-phosphate is cleaved by aldolase **B** into dihydroxyacetone phosphate and glyceraldehyde (note that there is only one phosphate group and it appears in the DHAP because of its position (close to ketone) in fructose-1-phosphate).
- DHAP can be used in glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by a number of pathways.

While in the right part:

- Fructose is phosphorylated by hexokinase (less specific to fructose) into fructose-6-phosphate.
- The remaining steps are the already known (I assume) steps of glycolysis.
- Fructose-6-phosphate→ fructose-1,6-bisphosphate (*Enzyme*: PFK-1).
- Fructose-1,6-bisphosphate→ GAP, DHAP (*Enzyme*: aldolase **A, B, C**).
- NOTE that 2 ATP molecules are consumed.

➢ Aldolase A is found in most tissues, while aldolase B is restricted to liver, kidneys, and small intestine.

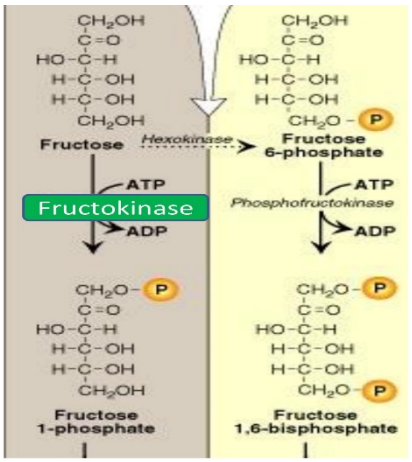
➢ Aldolase A acts on fructose-1,6-bisphosphate as a substrate, aldolase B acts on both fructose-1,6-bisphosphate and fructose-1-P, which makes it specific for fructose metabolism.

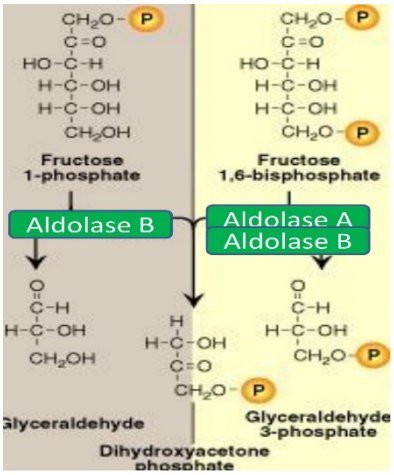


HUAMNS EXPRESS THREE FORMS OF ALDOLASE:

(the doctor focused on only two of them A, B (the table is just a recap of what I've already mentioned, cheer up))

Aldolase B	Aldolase A
Liver, kidney, small intestine	**In most tissues**
Substrates: **Fruc.-1-phosphate & Fruc.-1,6-bisphosphate**	**Substrate:** **Fruc.-1,6-bisphosphate NOT Fruc.-1-phosphate**
↓activity→ fructose intolerance	

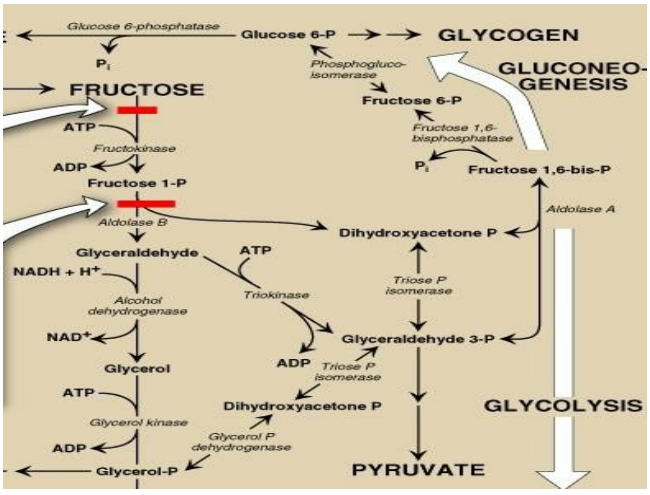




FRUCTOSE METABOLISM AND INTERACTION WITH OTHER PATHWAYS

DHAP is the connection point:

- It can be converted by Triose P isomerase to GAP and continue in glycolysis.
- Lipid metabolism: glyceraldehyde→ GAP (triokinase, ATP) → DHAP (triose P isomerase).



- Gluconeogenesis: glycerol→ glycerol-P (glycerol kinase, ATP) → DHAP (glycerol P dehydrogenase, alcohol is converted into ketone) → reverse steps of glycolysis.

➢ Depending on the condition of the cell, fructose can be used either in glycolysis or glucose production or its own degradation (in cells that depend on fructose as a source of energy such as sperms, this degradation mostly proceed to remnant steps of glycolysis).

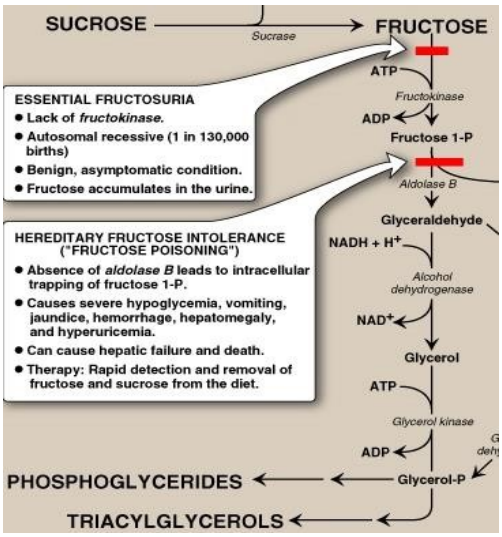
DISORDERS OF FRUCTOSE METABOLISM

➢ **Fructokinase deficiency→ essential fructosuria (autosomal recessive).**

- **Accumulation of fructose→ fructosuria.**

  Side note: fructosuria is characterized by the presence of fructose in the urine after ingesting fructose.

- **Benign condition (alternative enzyme is available, Hexokinase, which can partially compensate the deficiency, thus, accumulation occurs at low rates).**



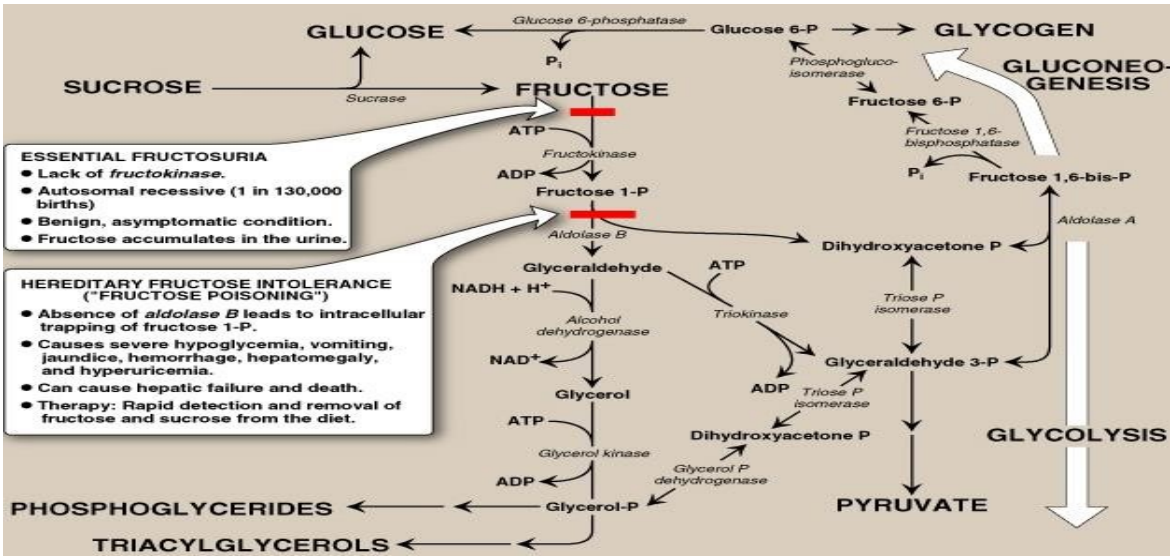
➢ **Aldolase B deficiency→ hereditary fructose intolerance, (Fructose Poisoning).**

- **Specific pathway won't proceed, glycolytic pathway proceeds partially by the A isozyme.**
- **Severe disturbance in liver and kidney metabolism.**
- **↑↑↑Fruc.-1-Phoph. → drop in P_i→ drop in ATP (used in the phosphorylation of fructose)→ ↑↑AMP→ ↑degradation of AMP.**
- **Hypoglycemia (due to hepatic failure and ↓ATP (stimulates glycolysis)) and lactic acidemia (lactic acidosis).**
- **Hyperuricemia (accumulation of uric acid in the blood, may cause gout-like symptoms).**

  Side note: increased AMP conc. stimulates the degradation of nucleotides (mainly purines, ATP and GTP) which results in the production of uric acid.

- **Hepatic failure due to reduced hepatic ATP.**
- **Prevent fructose, sucrose and sorbitol.**

Recap fructose metabolism:

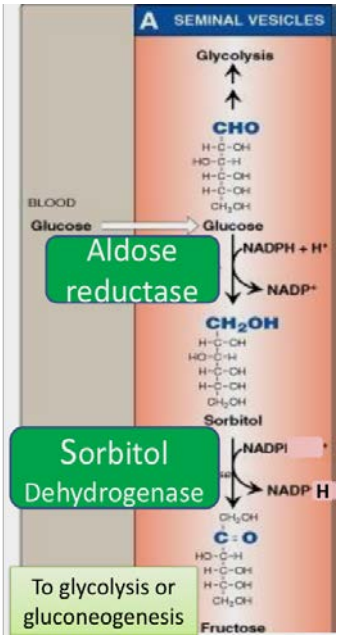


CONVERSION OF GLUCOSE TO FRUCTOSE VIA SORBITOL

Aldose Reductase:

(Works on aldoses and converts them to alcohols)

Found in many tissues; Lens, retina, schwan cells, liver, kidney, ovaries, and seminal vesicle.



When glucose enters to one of these tissues, it might be converted into sorbitol by aldose reductase (reducing glucose and oxidizing NADPH, remark that high NADPH/$NADP^+$ ratio is needed in the cells). Sorbitol is then oxidized by sorbitol dehydrogenase to fructose (reducing NAD^+).
Note that the final product is also fructose.

Side note: glucose can be converted into sorbose (ketohexose) which is further reduced into a polyalcohol (sorbitol).

Sorbitol Dehydrogenase: found in Liver, ovaries and seminal vesicles.

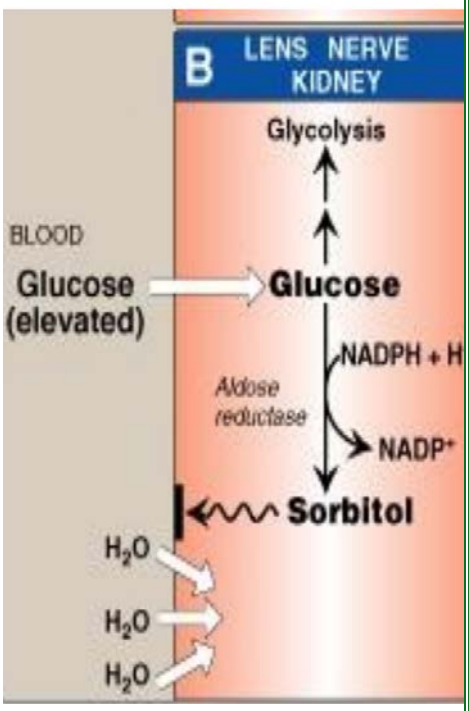
Only these cells may proceed to the second step (conversion of sorbitol into fructose by sorbitol DH), other cells can't (they lack the enzyme). Seminal vesicles and ovaries' cells are very active and depend on fructose as a main source of energy (high metabolic rates, they try to utilize all available energy resources).

Fructose: the major energy source for sperm cells.

CONVERSION OF GLUCOSE TO SORBITOL AND DIABETIC COMPLICATIONS

Side note: diabetes is when your body lacks insulin or has resistance against it.

Because insulin is not required for the entry of glucose into cells of the retina, lens, kidneys, and peripheral nerves, large amounts of glucose may enter these cells during times of hyperglycemia (for example, in uncontrolled diabetes). Elevated intracellular glucose concentrations and an adequate supply of reduced NADPH cause *aldose reductase* to produce a significant increase in the amount of sorbitol, which cannot pass efficiently through cell membranes and, therefore, remains trapped as a sugar alcohol. As a result, sorbitol accumulates in these cells, causing strong osmotic effects and cell swelling due to water influx and retention leading to diabetes complications. So, the diabetic patients will suffer from diabetic retinopathy (الشبكية السكرية) (remember: retina is a layer of nerve cells).



Other complications may occur such as; diabetic foot, when high blood sugar damages the nerves and blood vessels in the feet, may lead to a loss of feeling in the feet and gangrene, and problems in the kidneys due to high amounts of glucose.

(My friends there is glut in these tissues like the other ones, so, please don't forget that. Also, they have this extra ugly mechanism that leads to the entrance of glucose in large amounts without control, regardless, whether there's insulin or not).

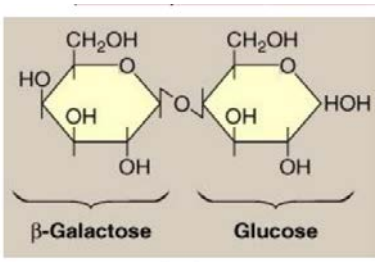
Note: this mechanism is inactive unless in the case of hyperglycemia (in diabetic patients), due to this elevation in glucose levels, it enters the cells

insulin-independently. Km of aldolase reductase is high, hence, only active at high glucose concentrations (sorbitol pathway is not active in normal conditions).

-We could benefit from sorbitol impermeability in the production of artificial sweeteners (no absorption due to the absence of sorbitol transporter), frequently used by diabetic patients.

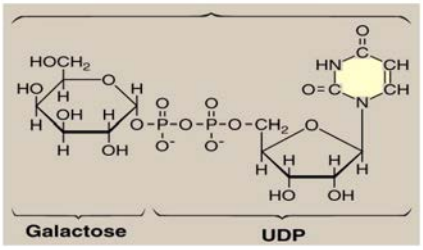
GALACTOSE METABOLISM

The major dietary source of galactose is lactose (galactosyl β-1,4-glucose) obtained from milk and milk products. Galactose can also be obtained by lysosomal degradation of glycoproteins and glycolipids. Like fructose (and mannose), the transport of galactose into cells is not insulin dependent (large amount of galactose won't trigger insulin secretion).



Lactose

- **An epimer of glucose**
- **Sources: component of lactose, lysosomal degradation glycolipids and glycoproteins**
- **Entry to cells is insulin independent**
- **UDP Galactose; an Intermediate in Galactose Metabolism**

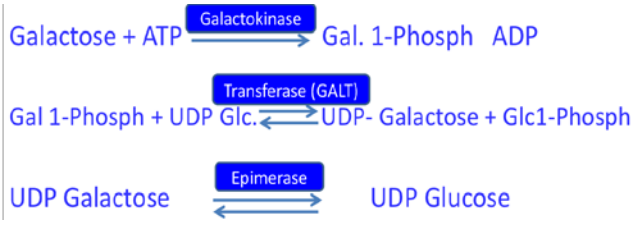


Let's talk about this beautiful pathway: galactose can be phosphorylated into galactose-1-phosphate through galactokinase (not Hexokinase) and one ATP molecule is consumed. Galactose-1-phosphate cannot enter the glycolytic pathway unless it is first converted to (UDP)-galactose. This occurs in an exchange reaction, in which UDP-glucose reacts with galactose-1-phosphate, producing UDP-galactose and glucose-1-phosphate catalyzed by galactose-1-phosphate uridylyltransferase (GALT).

(Don't forget to memorize enzymes' names my fellows)

-You must have figured out that galactose differs from fructose because it is not an intermediate in glycolysis so it will participate in different way which you will know instantly.

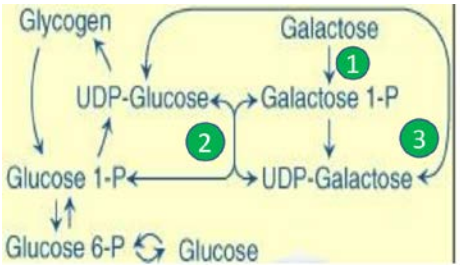
For UDP-galactose to enter the mainstream of glucose metabolism, it must first be isomerized to its C-4



epimer, UDP-glucose, by UDP-hexose 4- epimerase. This "new" UDP-glucose (produced from the original UDP- galactose) can participate in biosynthetic reactions (for example, glycogenesis, glycolysis…) as well as in the GALT reaction.

(Remember that epimerase is an isomerase)

UDP-galactose can serve as the donor of galactose units in a number of synthetic pathways, including synthesis of lactose which is essential in breast feeding. This mechanism could happen in also males but for other purposes.



Side note from the doctor: when we drink milk the lactose will be immediately degraded into galactose and glucose but lactose is essential for mammary glands that's why we have such mechanisms.

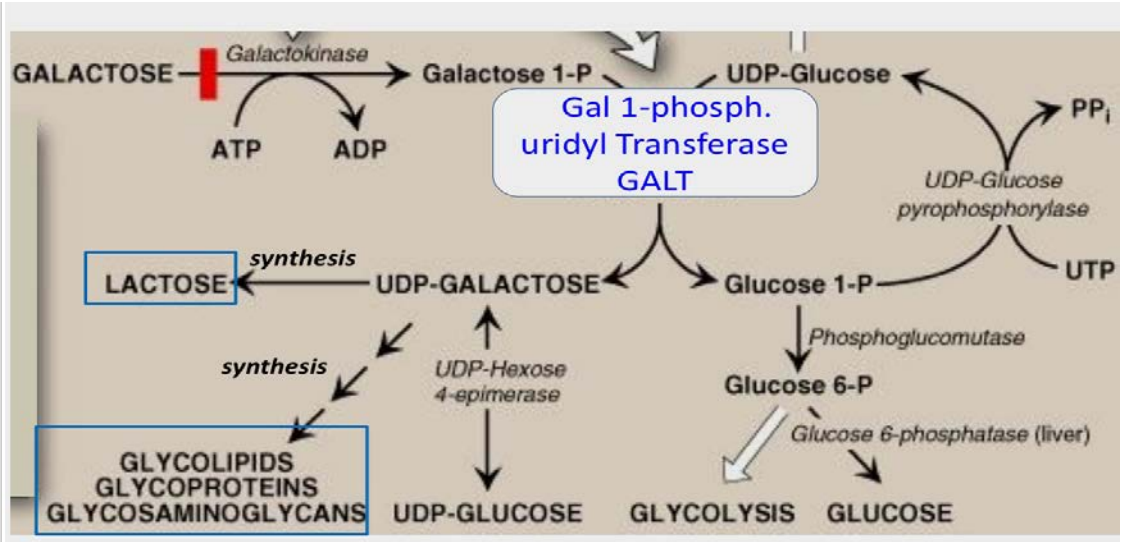
Also, this UDP-galactose could be further used for the synthesis of sugars and GAGs by some modifications (remember that glucose and galactose are responsible for GAGs synthesis (glycosaminoglycans)), hence, it may help in the synthesis of glycoproteins or peptidoglycans as simple sugar. If the body doesn't need lactose or galactose, it will be converted to UDP-glucose and support glycogen synthesis.

Galactose is not usually used as an energy-source but is used for other metabolic pathways.

(Don't neglect the pictures they are important my lovely fellows)

GALACTOSE METABOLISM AND FATES

This figure summarizes everything enjoy ☺



DISORDERS OF GALACTOSE METABOLISM

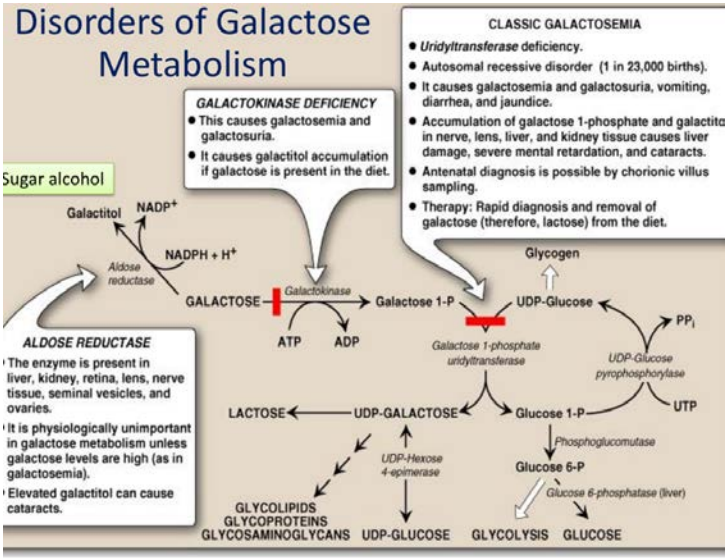
1. Deficiency of GALT… classic Galactosemia

- **Accumulation of Galactose-1-Phosphate and galactose**

Energy will be consumed and galactose phosphorylation will stop, that's why galactose accumulates, ending up with more ADP and AMP in comparison with ATP (which is used for nothing).

GALT deficiency leads to low ATP formation (similar to fructose poisoning).

- **Similar consequences to those in fructose intolerance**
- **Galactose …… Galactitol production**



2. Deficiency of Galactokinase

The accumulated galactose (will not enter to the glycolysis like the fructose) is shunted into side pathways such as that of galactitol production. Deficiencies in galactokinase and the epimerase result in less severe disorders of galactose metabolism because we will not consume energy.

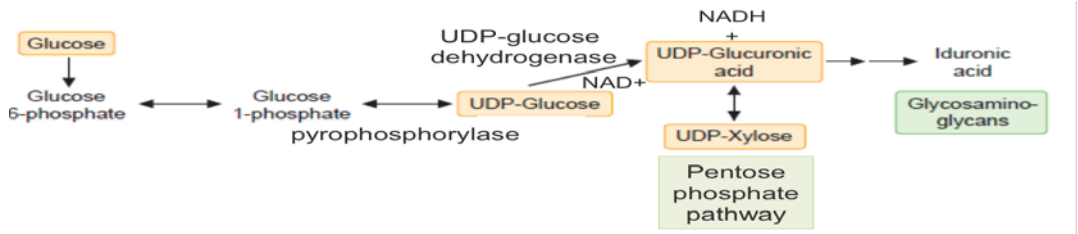
- **Accumulation of Galactose ……Galactitol**

METABOLISM OF GLUCURONIC ACID

- **Is a quantitatively minor route of glucose metabolism**
- **It provides biosynthetic precursors and interconverts some less common sugars to ones that can be metabolized.**

Glucuronic acid is a derivative of glucose it is going to be synthesized under well fed state, to supply most of our cells with GAG (glycosaminoglycan). Like the pentose phosphate pathway (discussed later), it provides biosynthetic precursors and interconverts some less common sugars to ones that can be metabolized. We have high concentrations of glucose so it will enter to the cells and participate in different glucose metabolism (glycolysis, glycogen synthesis,..). The first steps are identical to those of glycogen synthesis, formation of glucose-6-phosphate, its isomerization to

glucose-1-phosphate, and activation of glucose-1-phosphate to form UDP-glucose. UDP-glucose is then oxidized to UDP-glucuronic acid by NAD^+ and UDP-glucose dehydrogenase then the UDP glucuronic acid is utilized in biosynthetic reactions to form an ether, ester or an amide, could be converted to UDP-Xylose which innervate the pentose phosphate pathway mechanism, but the most important function synthesis of glycosaminoglycans (GAGs).

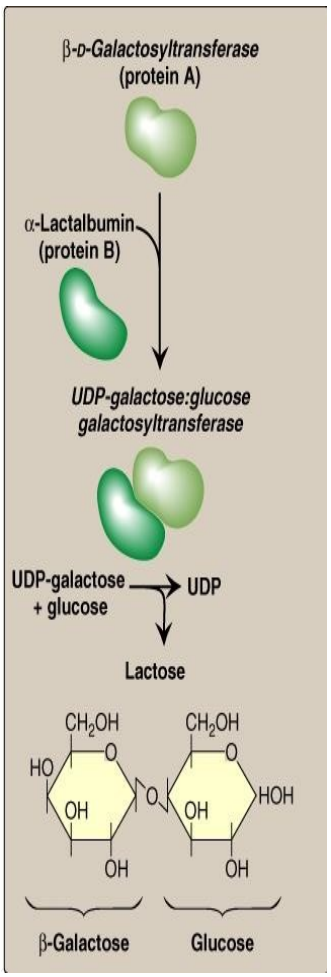


LACTOSE SYNTHESIS

- **Lactose is galactosyl β (1→4) glucose.**
- Lactose is milk sugar (as a component of breast milk), mainly composed of glucose and galactose.
- **Produced by mammary glands.**
- **Galactosyl β (1→4) glucose is found in glycolipids and glycoproteins.**

- **Lactose synthase: complex of 2 proteins: Galactosyl transferase (protein A) and α-lactalbumin (Protein B).**
  Only in mammary glands, its synthesis is stimulated by prolactin.

  Galactosyl transferase→ for transfer and connection.
- The substrates of the enzyme are glucose & UDP-galactose.



- **In glycolipids and N-linked glycoprotein synthesis (modified lactose).**

UDP-Gal + N acetyl glucosamine $\xrightarrow{\text{Protein A}}$ N-acetyllactosamine

- Protein B is only active in mammary glands.
- The combination of both protein A & B works in the mammary glands.
- UDP is released as a byproduct.

يَفنَى العِبادُ ولا تَفنَى صَنائِعُهُم

فاختَر لِنَفسِكَ ما يَحلو بِهِ الأَثَرُ