فريق طوفان الأقصى

METABOLISM

Modified N.16

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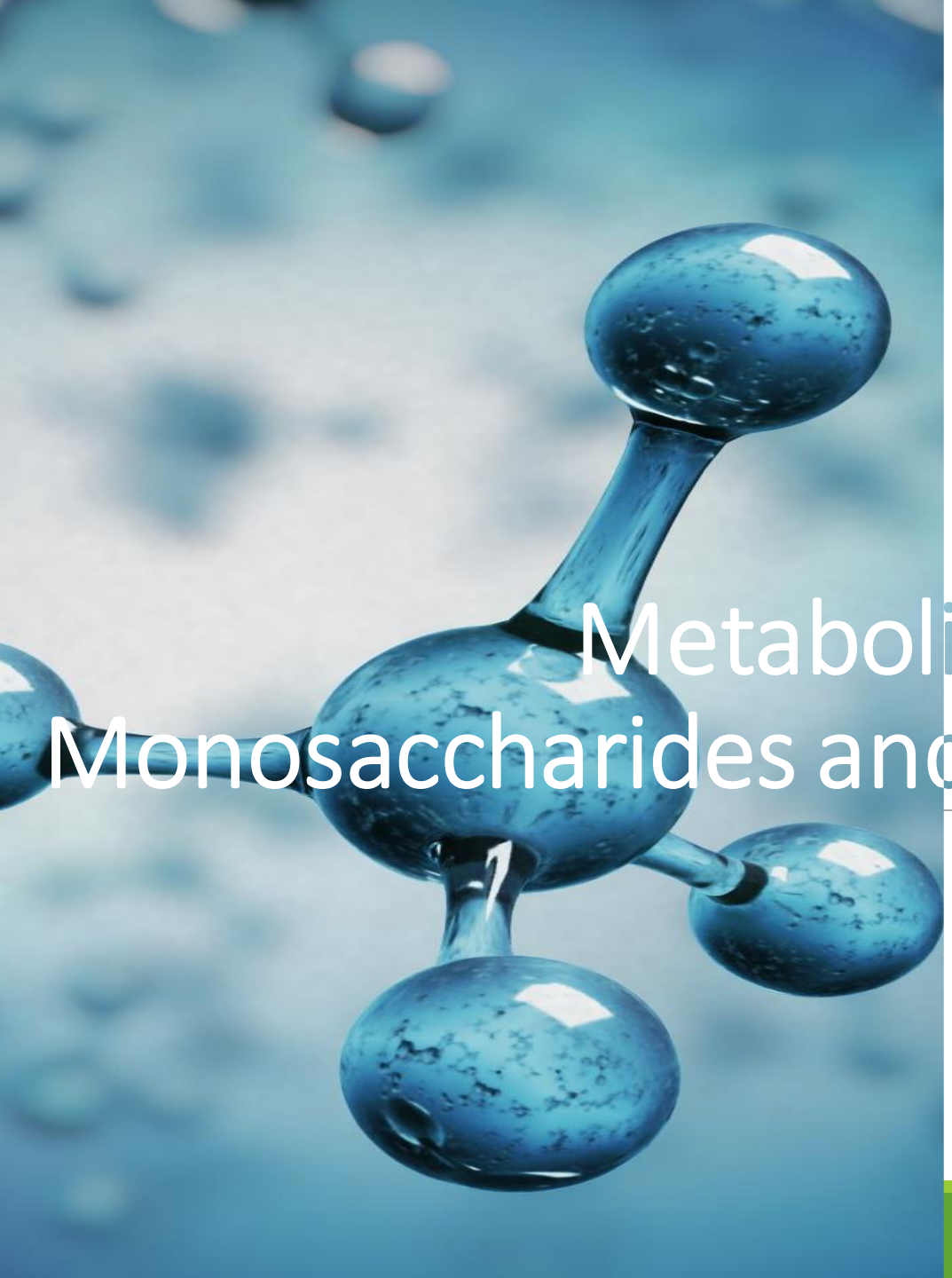


Metabolism of Monosaccharides and Disaccharides

Dr. Diala Abu-Hassan, DDS, PhD

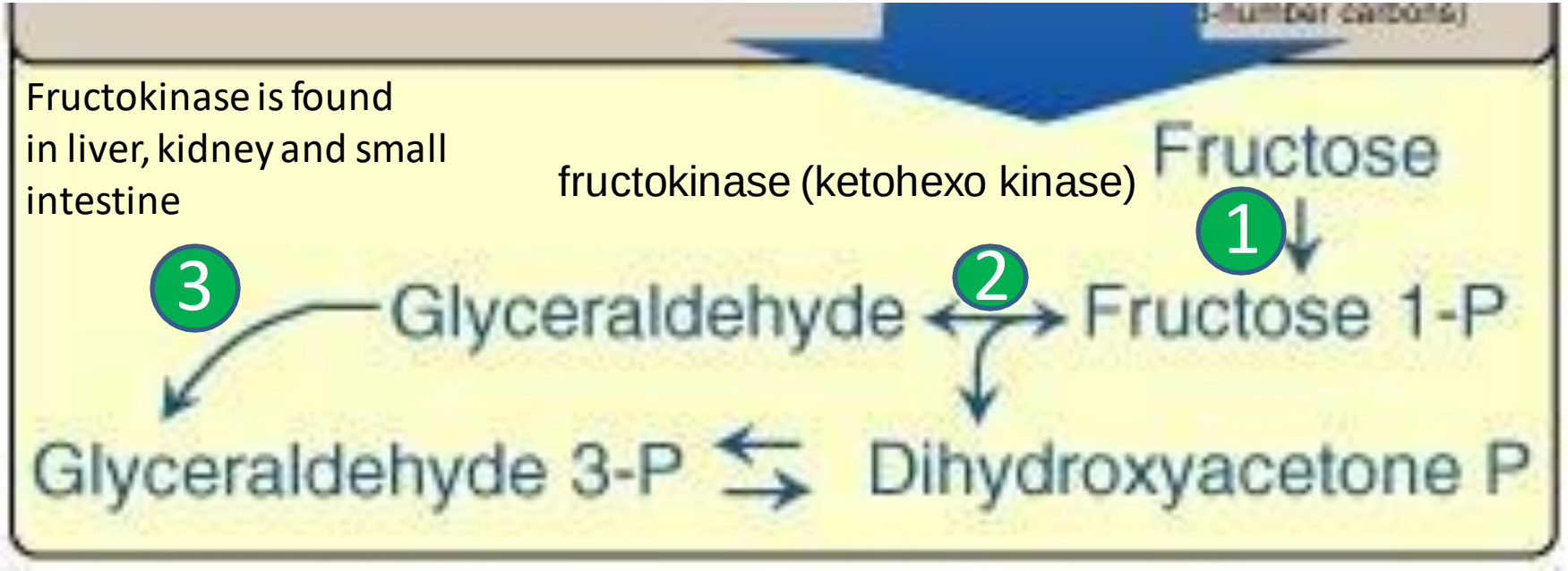
Fructose Metabolism

10% of the daily calorie intake

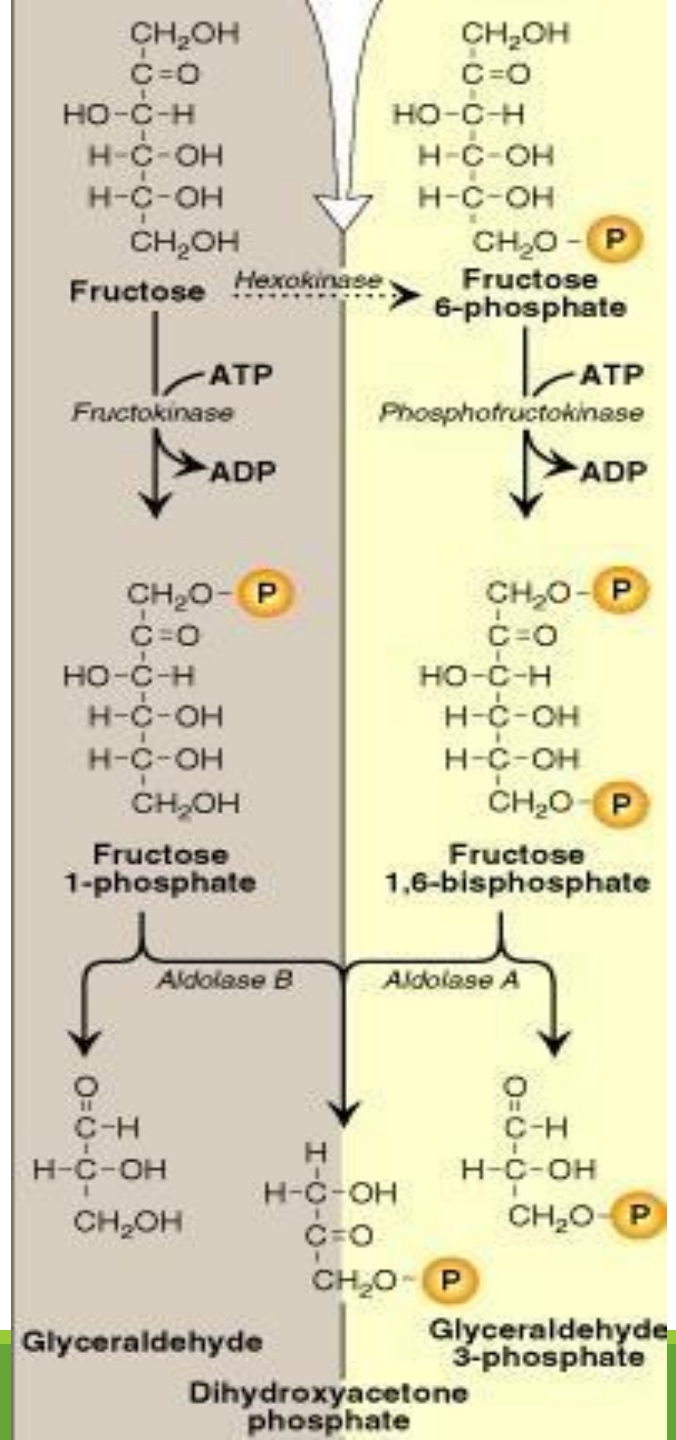
Sources: sucrose, Fruits, honey, high-fructose corn syrup

Entry into cells is not insulin dependent.

Does NOT promote the secretion of insulin

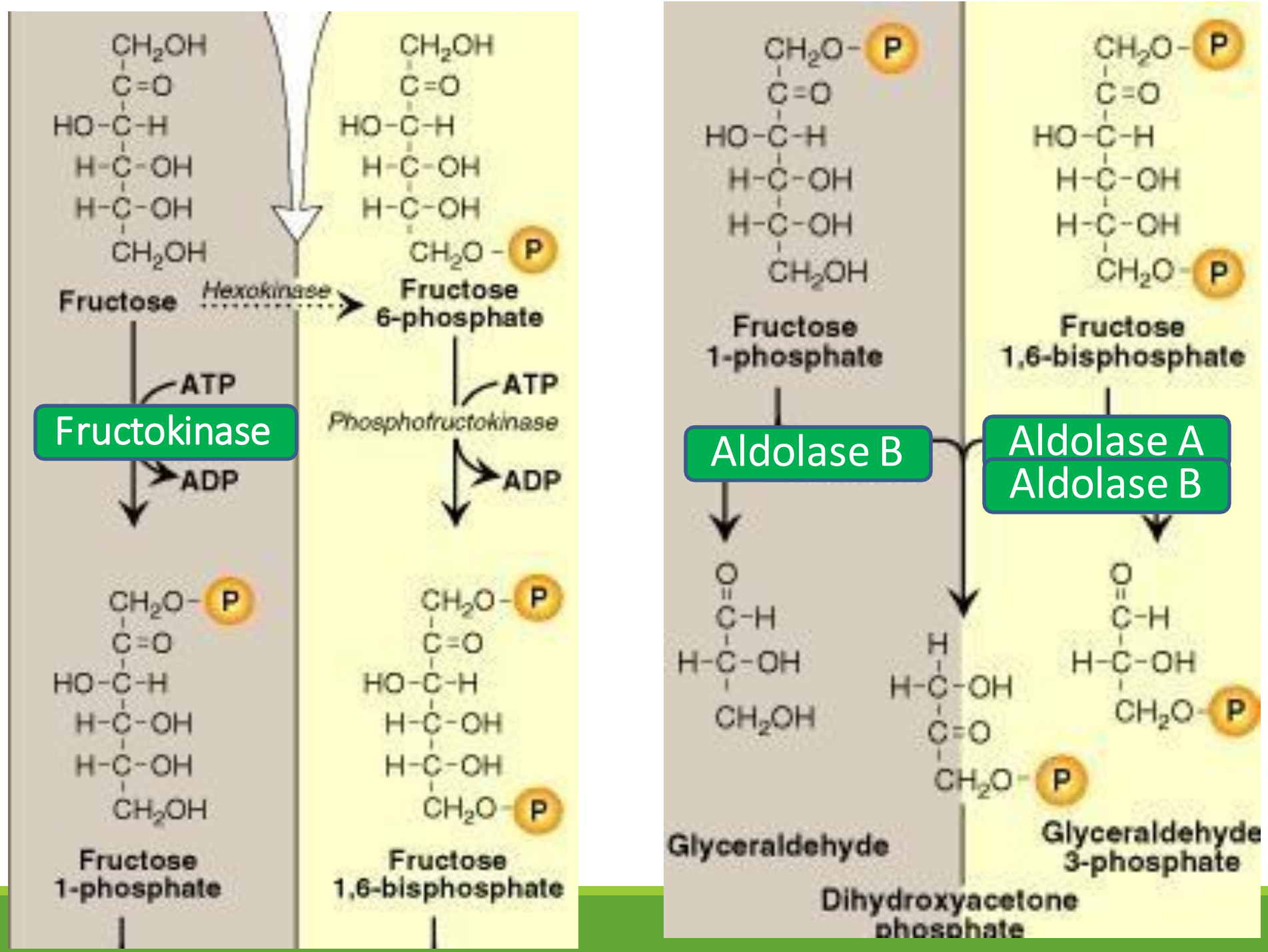


Fructose Metabolism



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 *phosphor fructokinase-1-P* the major rate-limiting step in glycolysis


Fructose
Hexokinase
Fructose 6-phosphate
ATP
Fructokinase
ADP
ATP
Phosphofructokinase
ADP
Fructose 1-phosphate
Fructose 1,6-bisphosphate
Fructose 1-phosphate
Fructose 1,6-bisphosphate
Aldolase B
Aldolase A
Aldolase B
Glyceraldehyde
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate

Quick recap: We previously discussed the degradation of monosaccharides and disaccharides.

- Now, we will shift our focus to the synthesis or building of monosaccharides and disaccharides in specific cases and types

We began discussing fructose, fructose can enter the cells by insulin-independent manner . There's an ongoing debate about its impact on blood sugar levels-glucose-(some people say it increase blood sugar and some say it doesn't have a noticeable effect .when Fructose enter the call it can follow two different pathways

1-fructose can enter it is own specific pathway by fructokinase

2-fructose can enter glycolytic-regular one-by hexokinase

And it has higher affinity toward its own specific pathway why?

-faster because it has lower number of steps/skips the slowest step of glycolysis which is catalyzed by phospho-fructokinase-1

Another difference between the two pathways is that p-fructose--->fructose-1 phosphate by fructokinase can be cleaved into glyceraldehyde and DHAP by Aldolase B whereas in glycolytic pathway fructose 1,6 biphosphate can be cleaved to glyceraldehyde and DHAP by Aldolase A and B

Attachment: https://youtu.be/R3voJC1CBXg?si=lc99SJrW38snrYSv

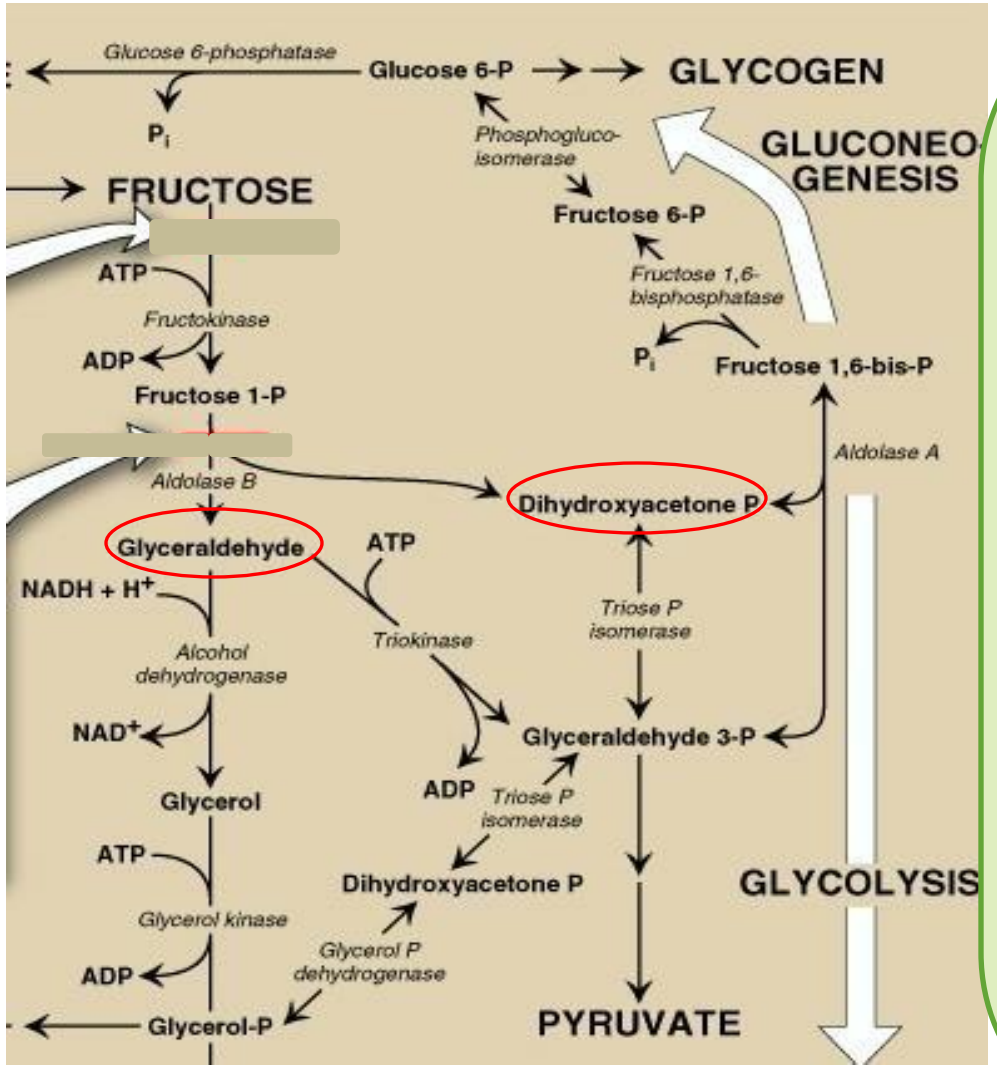
NOTE: Aldolase A is assossiated with glycolysis (this universal and general pathway that happens in all tisuues) so this enzyme is also found in all the tissues

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	

Aldolase b is restricted in those sites

Human expresses three forms of aldolase (we will only be discussing two of them)

Fructose Metabolism and Interaction with other Pathways



- **NOTE:** The specific pathway of fructose generates glyceraldehyde and dihydroxyacetone p (DHAP), serving as an intermediate that links this fructose metabolism pathway to both glycolysis and gluconeogenesis
- It can be converted by Triose P isomerase to GAP 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
- Glycrol p can be used to make triacylglycrol (TAG) **fats**

- **The complement in this slide :** Depending on the condition of the cell , fructose can be used either in glycolysis or glucose production or it is own degredation(in cells that depend on fructose as a source of energy such as sperms this degredation mostly proceed to remnant steps of glycolysis)

Disorders of Fructose Metabolism

- Fructokinase Deficiency ➔ essential fructosuria ➢

NOTE: ➢ autosomal recessive

- Accumulation of fructose ➔ fructosuria .

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

– Benign condition

NOTE: • alternative enzyme available, Hexokinase, which can partially compensate the deficiency, thus, accumulation occurs at low rates

NOTE: considered benign (حميد)or mild not cancer because there is an alternative pathway- glycolytic-

- Aldolase B Deficiency ➔ hereditary fructose intolerance, (Fructose Poisoning)
  - Severe disturbance in liver and kidney metabolism
  - ↑↑↑ Fruc. 1-Phosph. ➔ Decrease in P_i ➔ drop in ATP ➔ ↑↑ AMP ➔ ↑ degradation of AMP
  - Hypoglycemia and lacticacidemia (lactic acidosis)
  - Hyperuricemia
  - Hepatic failure due to reduced hepatic ATP
  - Avoid fructose, sucrose and sorbitol

■ **NOTE:** Specific pathway won't proceed, glycolytic pathway proceeds partially by the A isozyme.

■ **NOTE:** ATP was used in the phosphorylation of fructose

■ **NOTE:** due to hepatic failure and ↓ATP stimulates glycolysis to compensate for the lost atp

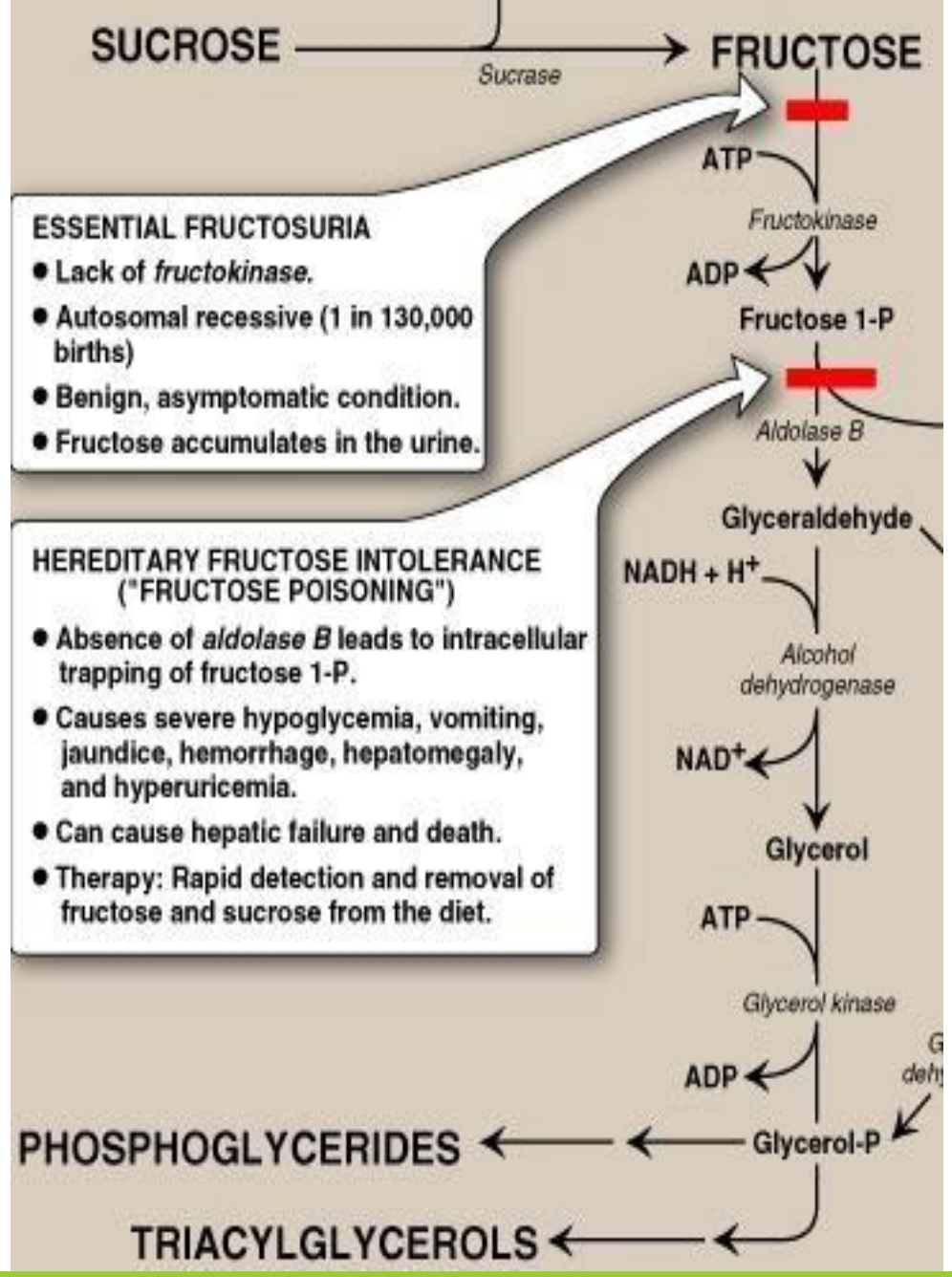
■ **NOTE:** lactic acidose because glycolysis was active for glucose so there will be a lot of pyruvate and pyruvate under these condition may be directed to acytyl coA or lactate in this condetion

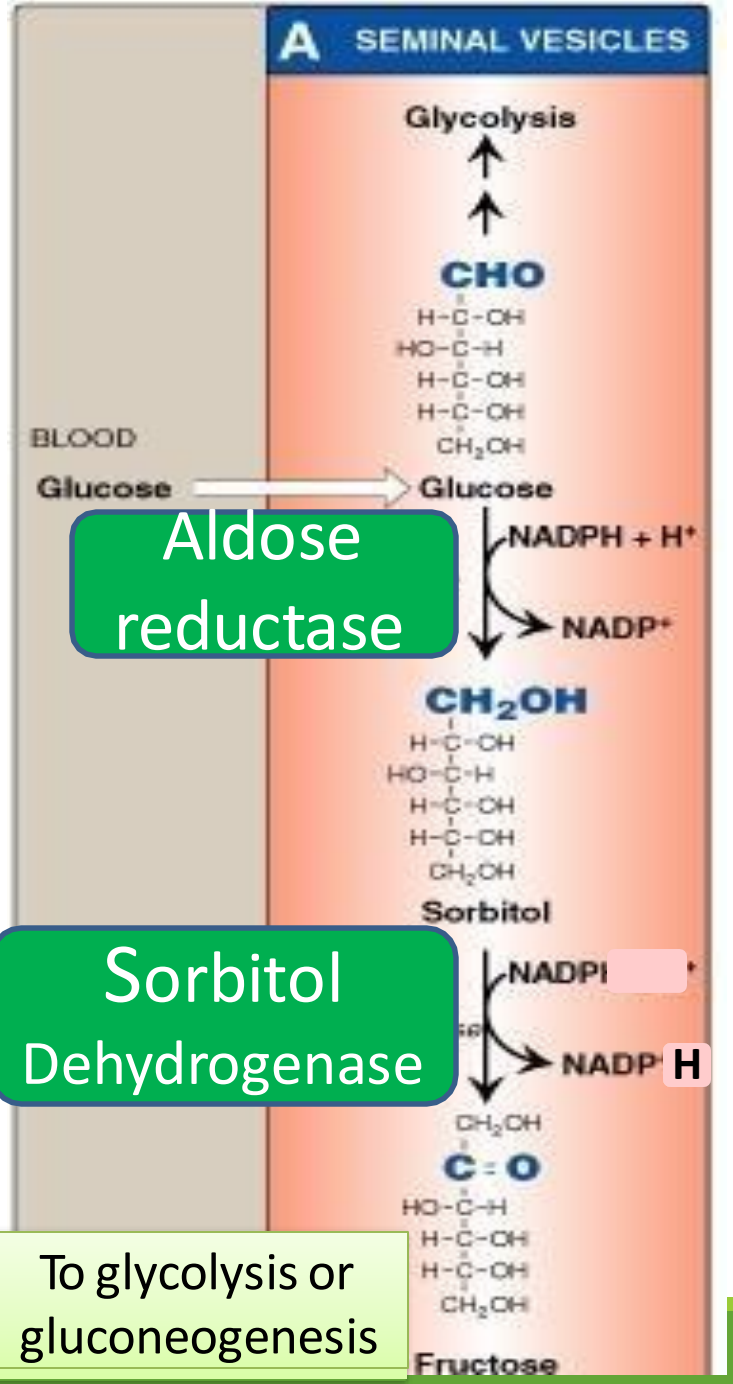
The complement in this slide: accumulation of uric acid in the blood result in hyperuricemia, this would be uptaken or percipitate in synovial fluid of the joints as mono sodium unate crystals which can be identified by the immune system as foreign body inducing inflammantory responce and enlarge in the joint called tophus (cause gout-like symptoms)

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

- When nucleotide get degraded phosphat and sugar can be recycled Nitrogenous bases undergo degeredation primarily due to the presence of nitrogen (it should be balanced because it can serve as sorce of ammonia which is toxic)

Disorders of Fructose Metabolism





Conversion of glucose to fructose via sorbitol

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

Sorbitol Dehydrogenase: Liver, ovaries and seminal vesicles

Fructose : the major energy source for sperm cells

The complement in this slide: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 NADP+).
- 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.

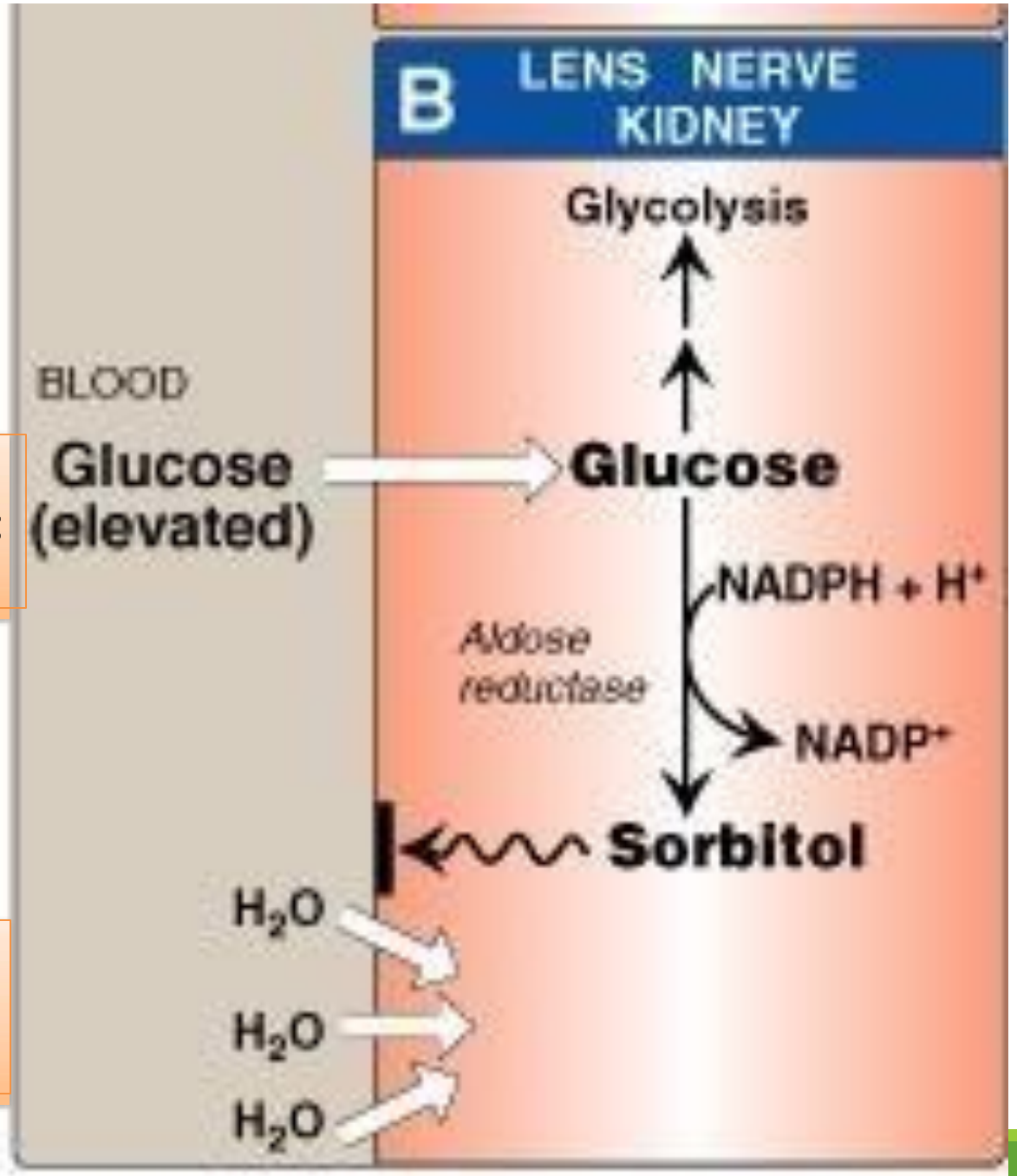
Only these cells may proceed to the second step (conversion of sorbitol into fructose by sorbitol DH), other cells can't (they lack the enzyme). Seminal vesicles and ovaries' cells are very active and depend on fructose as a main source of energy (high metabolic rates, they try to utilize all available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

Fructose: the major energy source for sperm cells.

Conversion of glucose to sorbitol and Diabetic Complications

Glucose entry is insulin independent in these tissues

Water retention and cell swelling leading to diabetic complications



The complement in this slide: 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 (السكرية الشبكية) (remember: retina is a layer of nerve cells).

The complement in this slide: Other complications may occur such as; diabetic foot perphrial specifically , 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.

Cataract in the lense normally it is transparent so if cell death happens in it this will interfere with passage of light and function of the lense

Nueropathy also happen in diabetic patients (the patient will not feel wounds especially in his foot this might lead to gangrene)

(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

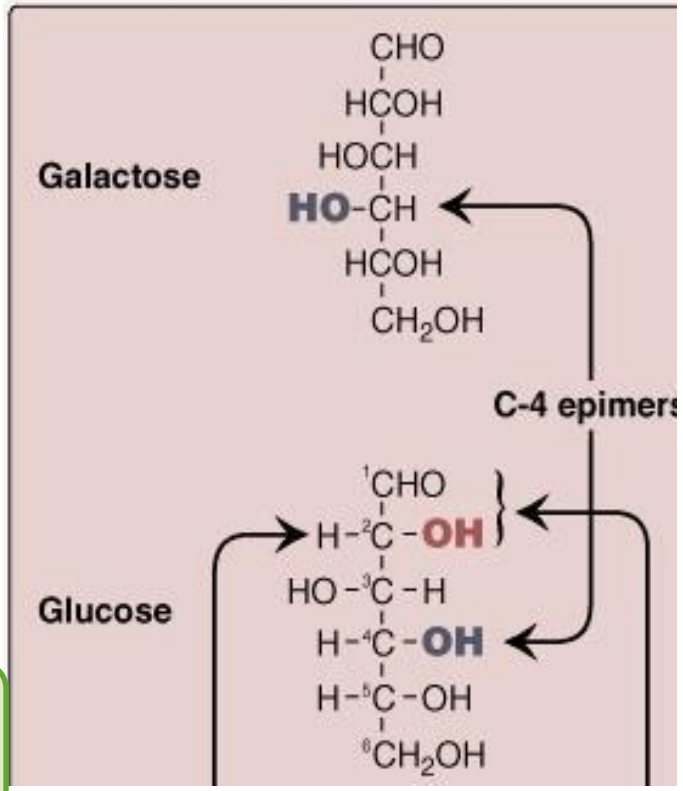
Galactose Metabolism

- **An epimer of glucose**

NOTE: C 4 orientation

- **Sources: component of lactose, lysosomal degradation glycolipids and glycoproteins**

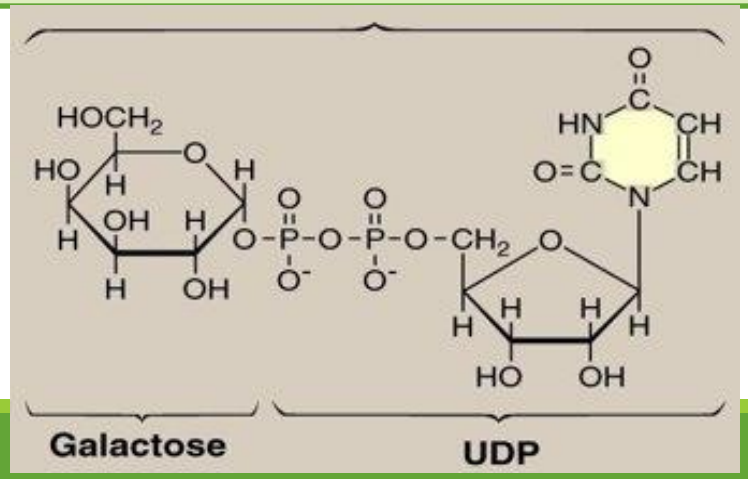
NOTE: The major dietary source of galactose is lactoseo (galactosyl β-1,4-glucose) obtained from milk and milk products and non dietry sources : lysosomal degradation glycolipids and glycoproteins



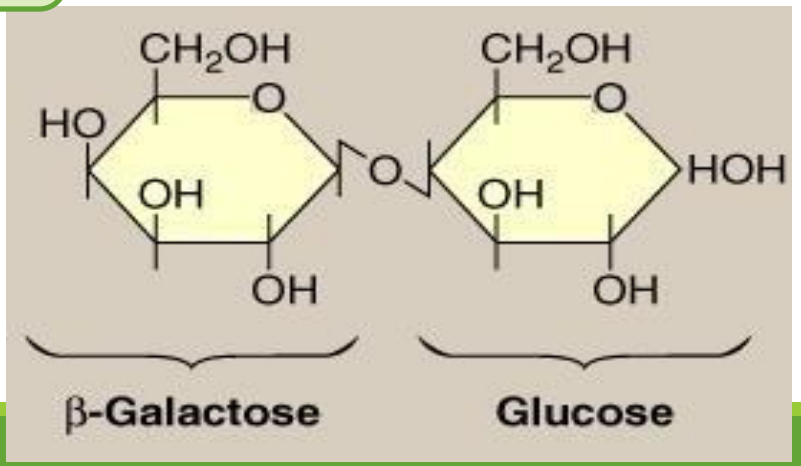
- **Entry to cells is insulin independent**

NOTE: he transport of galactose into cells is not insulin dependent (large amount of galactose won't trigger insulin secretion) same as fructose.

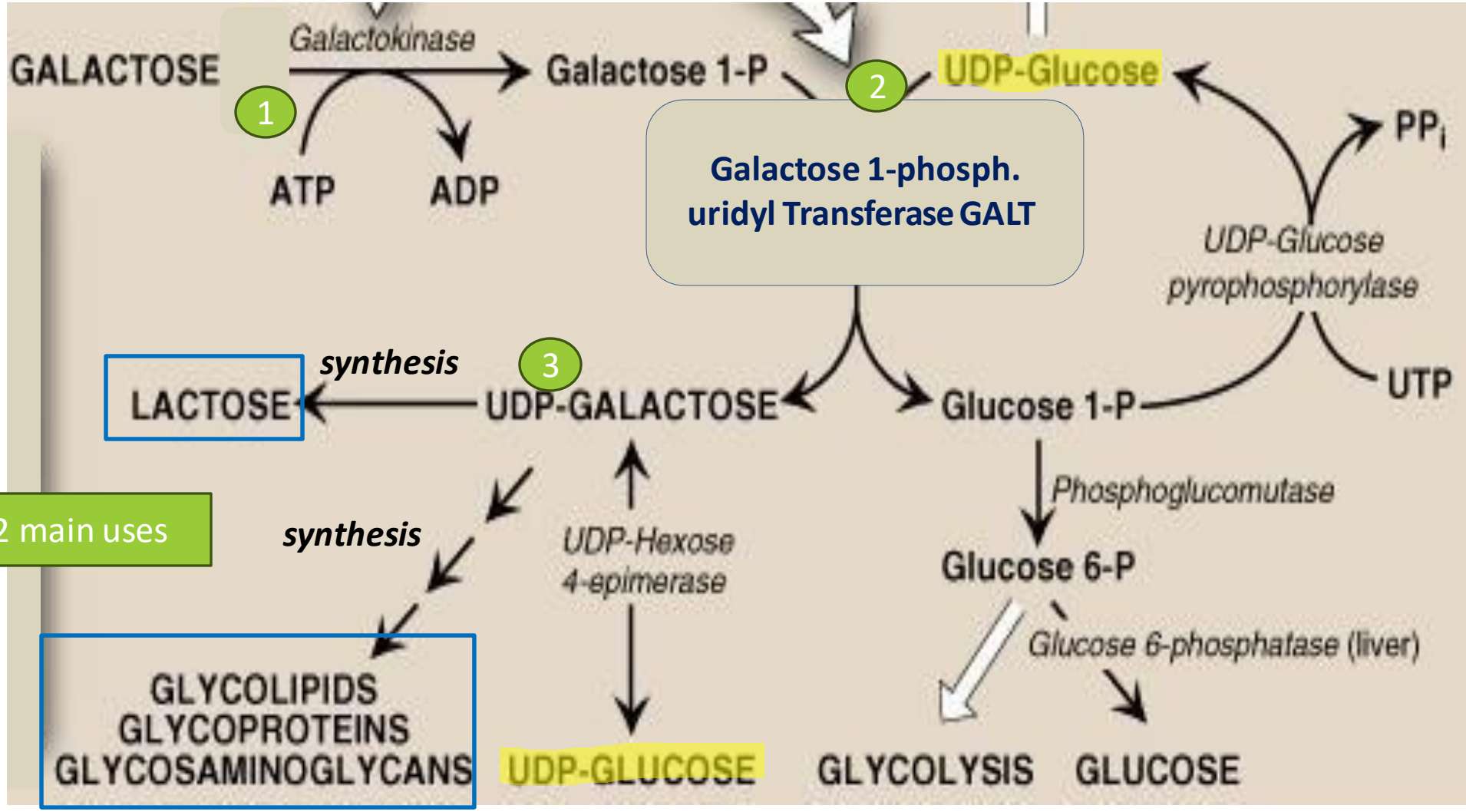
UDP Galactose;
An Intermediate in Galactose Metabolim



Lactose



Galactose metabolism and fates



Glycogen synthesis

- **The complement in this slide:**

1. galactose can be phosphorylated into galactose-1-phosphate through galactokinase and one ATP molecule is consumed.

2. Loaded on UDP molecule . 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 uridylyl transferase (GALT)

.3UDP-galactose could be further used

a) **for the synthesis of sugars like lactose (I mammary glands) or modified lactose(In males and females) -main use-**

b) **Synthesis of GAGs by some modifications (remember that glucose and galactose are responsible for GAGs synthesis (glycosaminoglycans), and sugar components of glycoproteins or peptidoglycans or glycolipids.-main use-**

c) **If there is large a mounts it will be directed into another path converted to UDP-glucose and support glycogen synthesis.**

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

The complement in this slide:

- 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-4epimer, UDP-glucose, by **UDP-hexose 4- epimerase.** This "new" UDP- glucose (produced from the original UDP- galactose) can participate in **glycogenesis**

NOTE:

What happens to Glucose-1-P?

1.It converts to Glucose-6-P by phosphoglucomutase

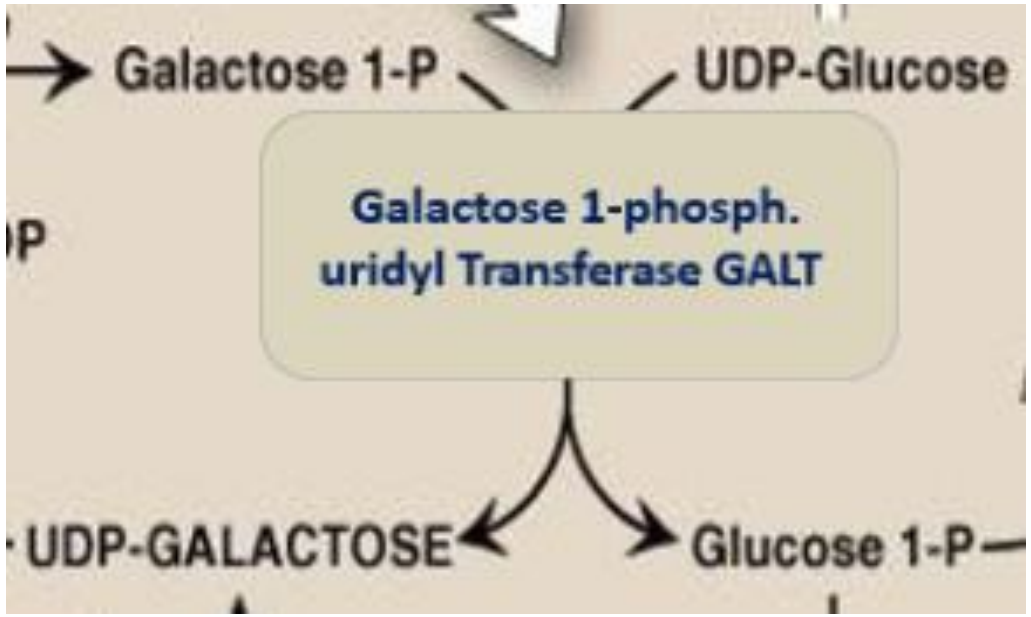
2a. Then dephosphorylation by Glucose-6-Phosphotase in liver generating glucose
or Enters Glycolysis
Or

2b. it reacts with UTP by UDP glucose pyrophosphorylase to produce UDP-glucose again and enters glycogenesis

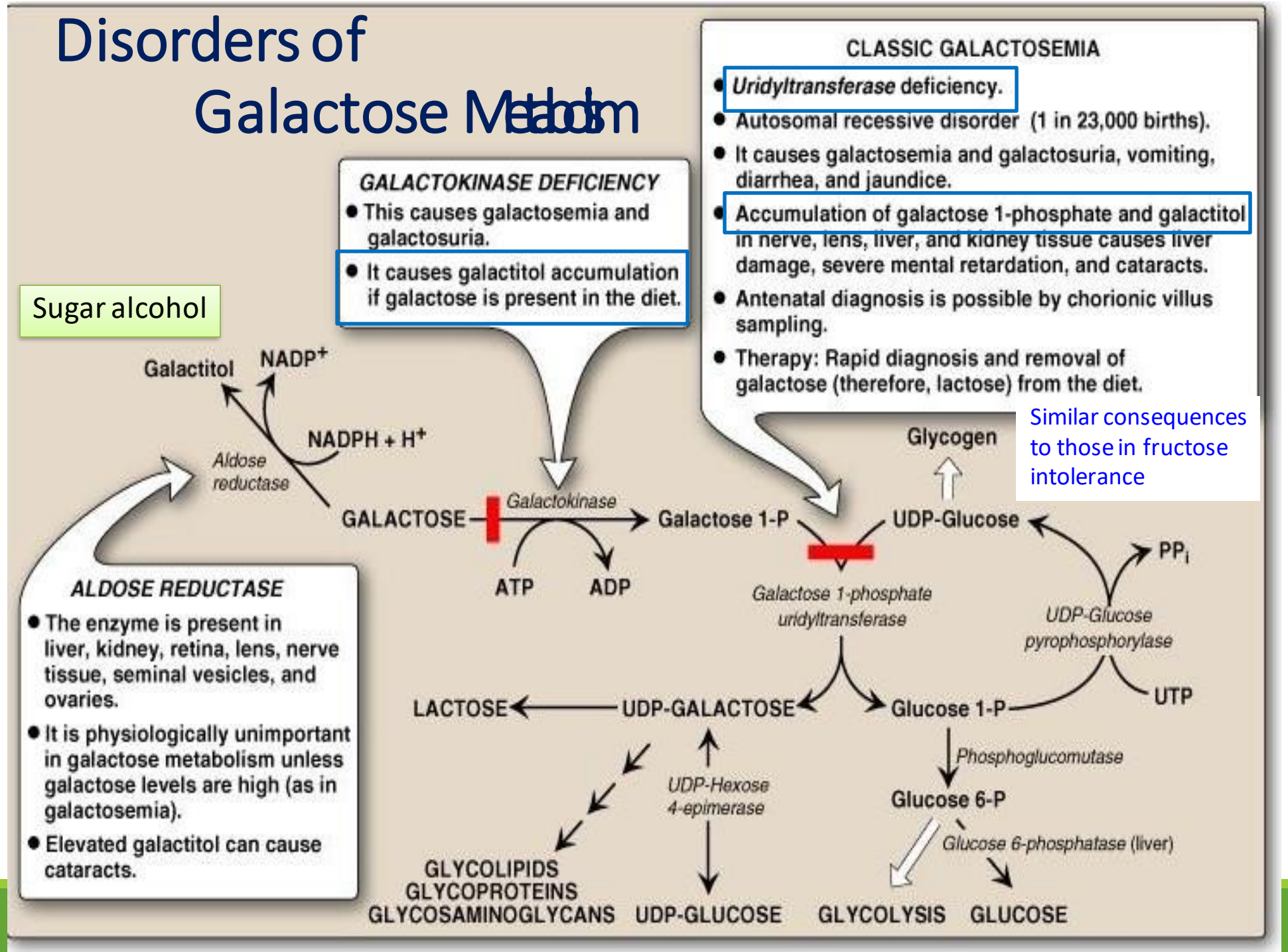
The complement in this slide:

- The UDP in UDP-Galactose is from UDP-Glucose. This step is the interaction point between the two pathways, it connects galactose with glucose. As we know that most of pathways in cell is made for GLUCOSE not galactose.

- The Hexokinase can phosphorylate galactose to produce Galactose-6-p , however, it is not a glycolytic intermediate as fructose-6-P, then it cannot be useful in glycolysis.



Disorders of Galactose Metabolism



Similar consequences to those in fructose intolerance

■ **The complement in this slide:**

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 (which accumulates in the cell and attracts water molecules causing cell to burst) --> mental retardation and cataracts

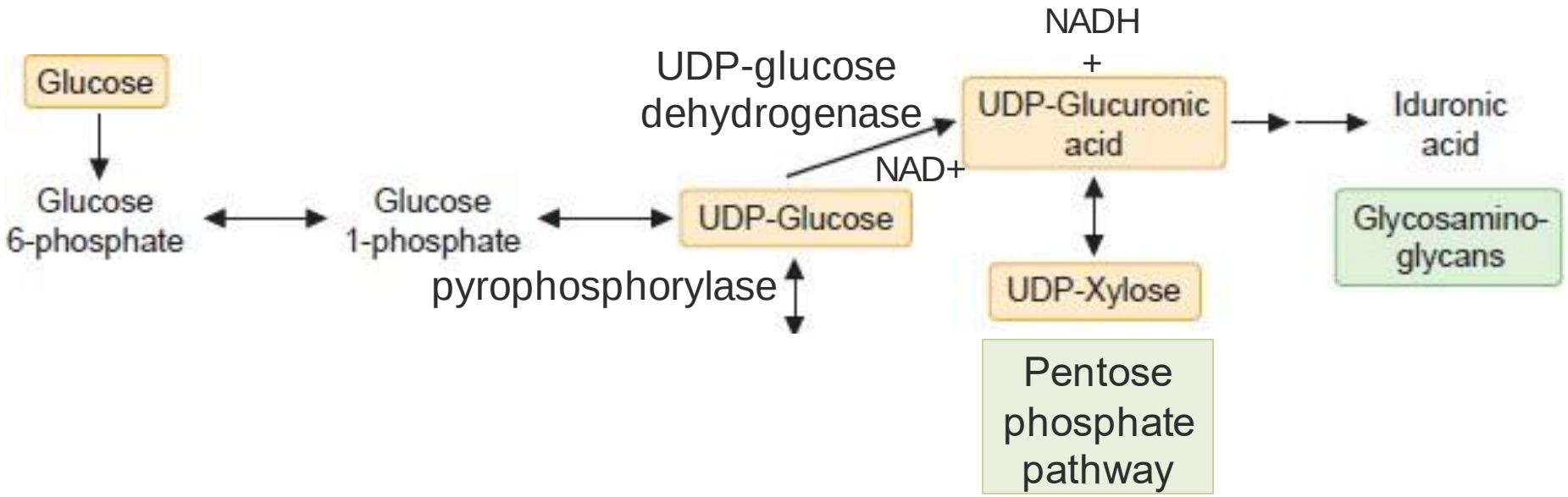
2. **Deficiency of Galactokinase**

The galactose accumolates so the cell increases the reduction of galactose by aldose reductase producing galactitol and oxidation of NADPH.

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** than GALT deficiency 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.**

The complement in this slide:

- 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,..).

- formation of glucose-6-phosphate(apart glycolysis), mutase converts it to glucose-1-phosphate, and uploaded on UDP by pyrophosphorylase then undergoes glycogenesis or another pathway that we will discuss.

- 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** .
- could be converted to **UDP-Xylose which innervate the pentose phosphate pathway** mechanism, but **the most important function synthesis of glycosaminoglycans (GAGs).**

NOTE: GLUCOSE-6-P is a brranching point where it can go glycolysis, glycogenesis , glucuronic acid synthesis...etc

Lactose Synthesis

- Lactose is Galactosyl β (1→4) glucose
- Produced by mammary glands

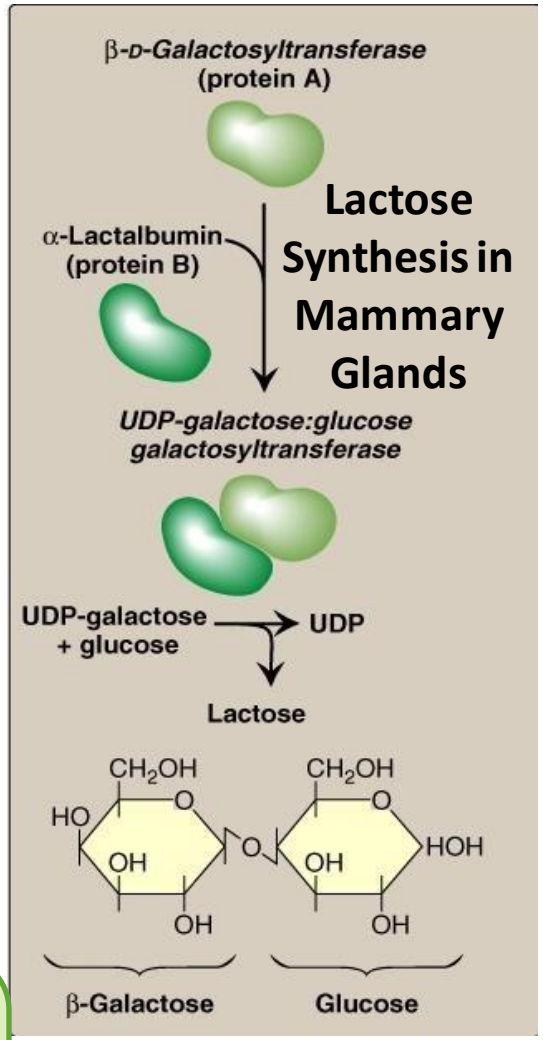
NOTE: or produced for sugar components of glycolipids ,GAGs, glycoproteins …

- Galactosyl β (1→4) glucose is found in glycolipids and glycoproteins

Lactose Synthase

UDP Gal. + Glucose ⟶ Lactose + UDP

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



NOTE:

- **Protein A (enzyme)is responsible for catalysing the reaction**
- **Protein B (not enzyme)is responsible for identifying adding (glucose only) to galactose in mammary glands**

- In glycolipids and N-linked glycoprotein synthesis

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

The complementing this slide: **in places other than mammary glands the protein B is absent so protein A will not distinguish, so it adds glucose or modified glucose rather than glucose only.**

اللهم أنصرهم وثبت اقداهم وسدد رميهم يارب العالمين أنك على كل شيء قدير اللهم غزة وأهل غزة وأراضي وأطفال ورجال غزة .. يارب احميهم بعينك التي لا تنام

أَخِي جاوَزَ الظالمونَ المَدَى
فحَقَّ الجِهَادُ وحَقَّ الفِدَا

فلا بُدَّ أنْ يَسْتَجيبَ القدرْ
إذا الشَّعْبُ يوماً أرادَ الحياةَ

أَنتركُهُم يَغصِبون العُروبَ
ةَ مَجدَ الأُبَوَّةِ والسُّؤدَدَا

ولا بُدَّ للقيدِ أن يَنْكَسِرْ
ولا بُدَّ لِلَّيْلِ أنْ ينجلي

وليسُوا بغيرِ صَليلِ السُّيوف
يُجِيبُونَ صَوتاً لنا أو صدى

تتَبَخَّرَ في جَوِّها واندَثَرْ
ومَن لم يعانقْهُ شَوْقُ الحياةِ

فَجَرِّد حُسَامَكَ من غِمدِه
فليس له بَعدُ أن يُغمَدا

من صَفْعَةِ العَدَمِ المنتصرْ
فويلٌ لمَنْ لم تَشُقْهُ الحياةُ

أَخي أَيُّها العربيُّ الأَبيُّ
أَرَى اليوم مَوعِدَنا لا غَدَا

وحدَّثَني روحُها المُستَتِرْ
كذلك قالتْ ليَ الكائناتُ

أَخي أَقبَلَ الشَّرقُ في أُمَّةٍ
تَرُدُّ الضَّلالَ وتُحيي الهُدَى

وفوقَ الجبالِ وتحتَ الشَّجرْ
ودَمْدَمَتِ الرِّيحُ بَيْنَ الفِجاجِ

أخي إنَّ في القدس أختاً لنا
أعدَّ لها الذابحون المُدى

رَكِبتُ المنى ونَسيتُ الحَذرْ
إذا مَا طَمحْتُ إلى غايةٍ

صبَرنا على غَدرهم قادِرينَ
وكُنَّا لهُم قَدَراً مُرصدا

ولا كُبَّةَ اللَّهَبِ المُستَعِرْ
ولم أتجنَّبْ وُعورَ الشِّعابِ

طلَعنا عليهم طُلوعَ المَنُونِ
فطَارُوا هَبَاءً وصارُوا سُدَى

يَعِشْ أبَدَ الدَّهرِ بَيْنَ الحُفَرْ
ومن لا يحبُّ صُعودَ الجبالِ

أَخي قُم إلى قِبلَةِ المشرِقَينِ
لنَحمِي الكنيسةَ والمسجِدا

لا تدفع ثمن رصاصهم قاطع بضائع الاحتلال

V2:

Slide 11

decrease instead of increase

Slide 15

NADP+ instead of NAD+