

# METABOLISM

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



MID – Lecture 16

## Metabolism of Monosaccharides & Disaccharides Pt. 2

وَإِن تَتَوَلَّوْا يَسْتَبَدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَلَكُمْ

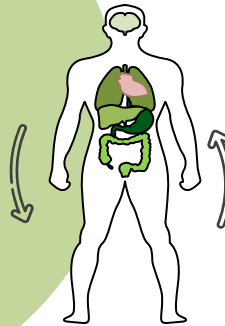
اللهم استعملنا ولا تستبدلنا

Written by:

- Raya Al Weshah
- Isra'a Mohammad

Reviewed by:

- Deema Nasrallah



Quiz on the previous lecture:

[QUIZ LINK](#)

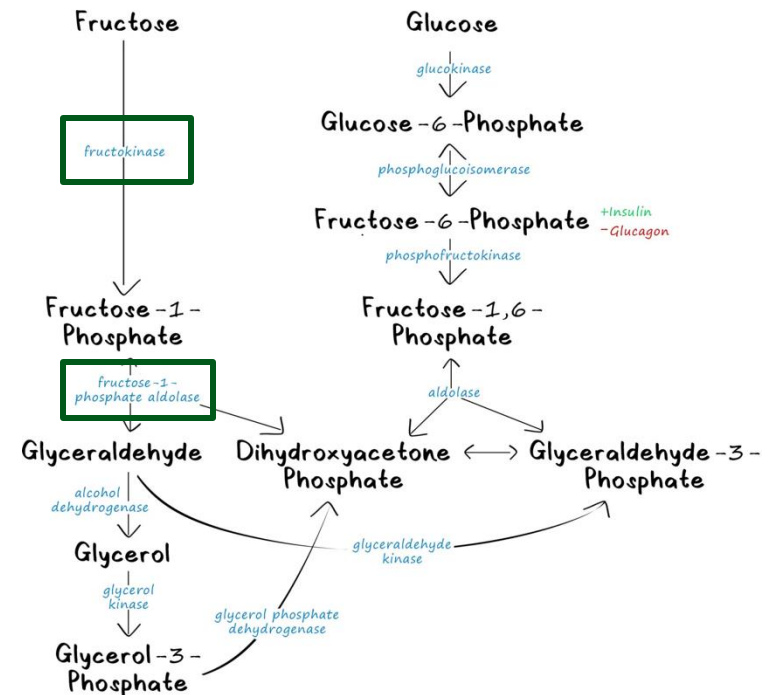
A collage of items representing health and fitness. On the left, two black dumbbells are positioned vertically. At the bottom, a yellow measuring tape is coiled. The top half of the image features a variety of fresh produce: a red onion, a carrot, a cucumber, a yellow apple, a white bowl containing green leafy vegetables and two cherry tomatoes, and a whole potato on the right side.

# **Metabolism of Monosaccharides and Disaccharides**

**Dr. Diala Abu-Hassan, DDS, PhD**

# Recap

As previously mentioned, fructose may either be metabolized through a specific pathway, or a non-specific pathway. We discussed that the specific pathway is better because it skips the rate-limiting step (fructose 1,6-bisphosphate formation), thus saving time. The two important enzymes in the specific pathway of fructose metabolism are fructokinase and aldolase B. Fructokinase phosphorylates fructose into fructose 1-phosphate. Aldolase B catalyzes the cleavage of fructose-1-phosphate into two three-carbon intermediates, DHAP & glyceraldehyde.



Now that you're all caught up, don't forget to say **بِسْمِ اللَّهِ** before you start :)

# Disorders of Fructose Metabolism

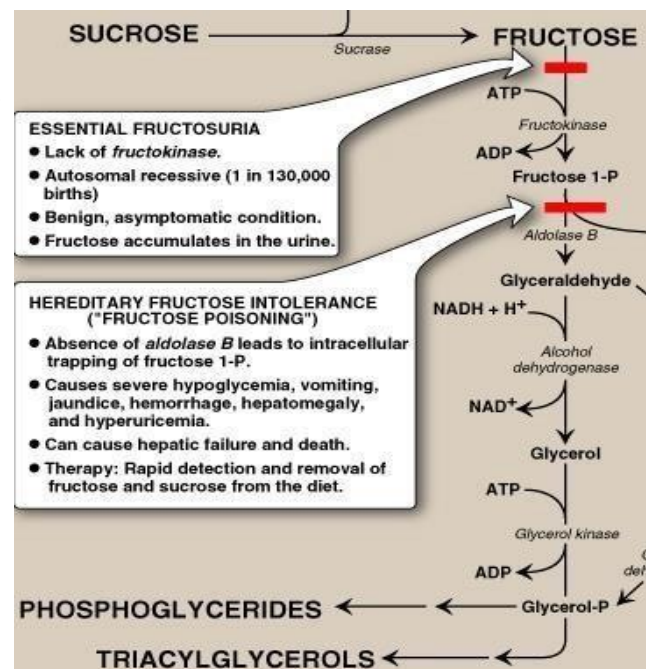
- Fructokinase Deficiency → essential fructosuria Fructose appears in urine.

- Accumulation of fructose → fructosuria
- Benign condition → We can use the alternative pathway.

Some accumulation of fructose could occur → excreted in urine but it is not a big problem especially if the person reduced fructose in their diet.

- Aldolase Deficiency → hereditary fructose intolerance, (Fructose Poisoning)

- Severe disturbance in liver and kidney metabolism
- ↑↑↑ Fruc. 1-Phosph. → drop 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 → Sources of fructose



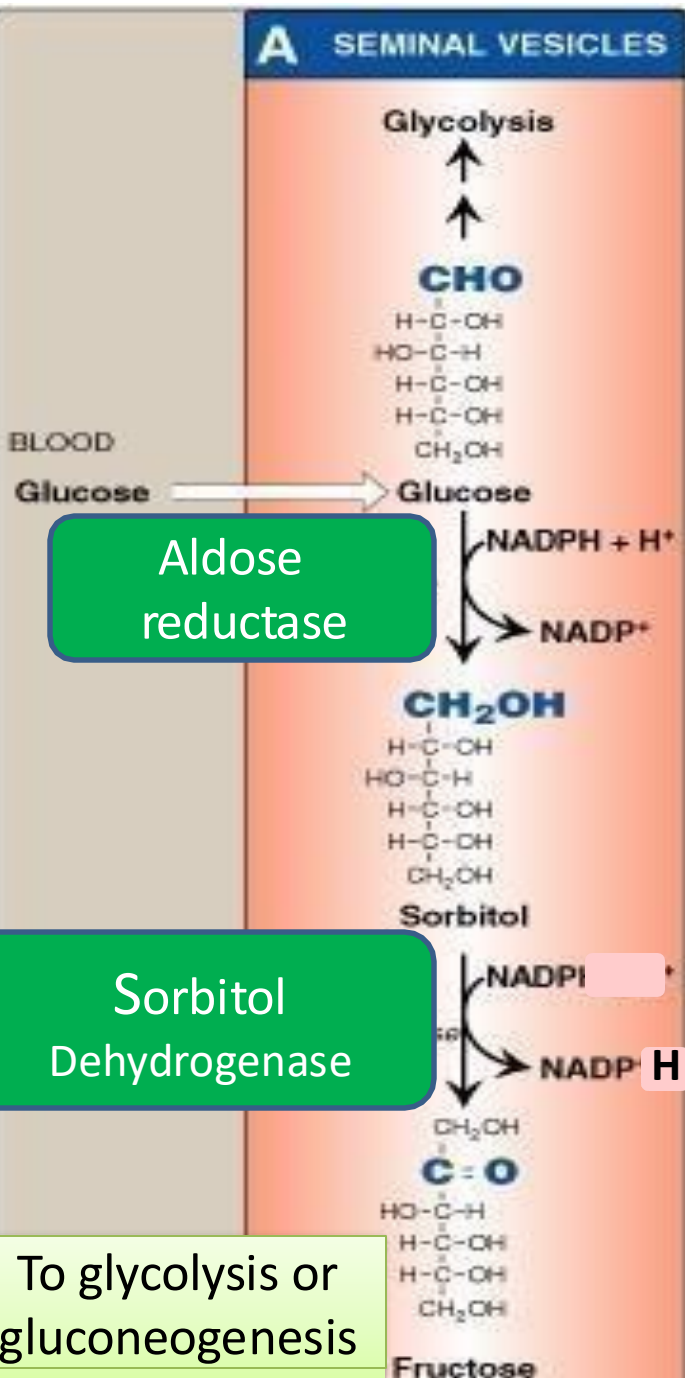
Explained in the next slide... :)

## Aldolase B Deficiency:

In the non-specific pathway, an aldolase B deficiency is not that devastating because aldolase A is present, and can cleave fructose-1,6-bisphosphate into DHAP and G3P, which can carry on to perform glycolysis. However, in the specific pathway where only aldolase B exists, a deficit in aldolase B causes fructose 1-phosphate to accumulate in the cell. Therefore, more ATP molecules are being broken down to supply inorganic phosphate with no subsequent outcomes. As a result, glycolysis is increasingly activated to compensate for the lost energy used for this phosphorylation. This causes **hypoglycemia and lacticacidemia**, which are both products of the increased [pyruvate], resulting in lactic acidosis.

Due to increased utilization of ATP, [AMP] will increase. AMP is a nucleotide, and adenine is a purine. We will learn later that the degradation of purines results in uric acid. AMP's accumulation in the cell leads to the activation of its degradation, causing **hyperuricemia**. Similarly, gout patients also have high [uric acid], due to either increased production, or decreased degradation. **Hepatic failure:** the liver is a dynamic organ that needs energy; a decrease in hepatic ATP decreases gluconeogenesis and protein synthesis.

# Conversion of glucose to fructose via sorbitol



## Aldose Reductase:

Found in many tissues; Lens, retina, Schwann cells, liver, kidney, ovaries, and seminal vesicles

These cells have **aldose reductase**, an enzyme that reduces aldoses. When glucose enters, it can proceed to glycolysis, pentose phosphate pathway, as well as other pathways. It can also activate aldose reductase in these tissue to reduce glucose to sorbitol, a polyalcohol, oxidizing NADPH to NADP+ in the process.

## Sorbitol Dehydrogenase:

Liver, ovaries, and seminal vesicles

Fructose: the major energy source for sperm cells

These cells also have **sorbitol dehydrogenase**, an enzyme that oxidizes sorbitol to fructose (formed a carbonyl at carbon #2). These cells can directly convert glucose → fructose directly via sorbitol.

Recall: Isomerization mentioned previously was between phosphorylated glucose and phosphorylated fructose.

# Conversion of glucose to sorbitol & Diabetic Complications

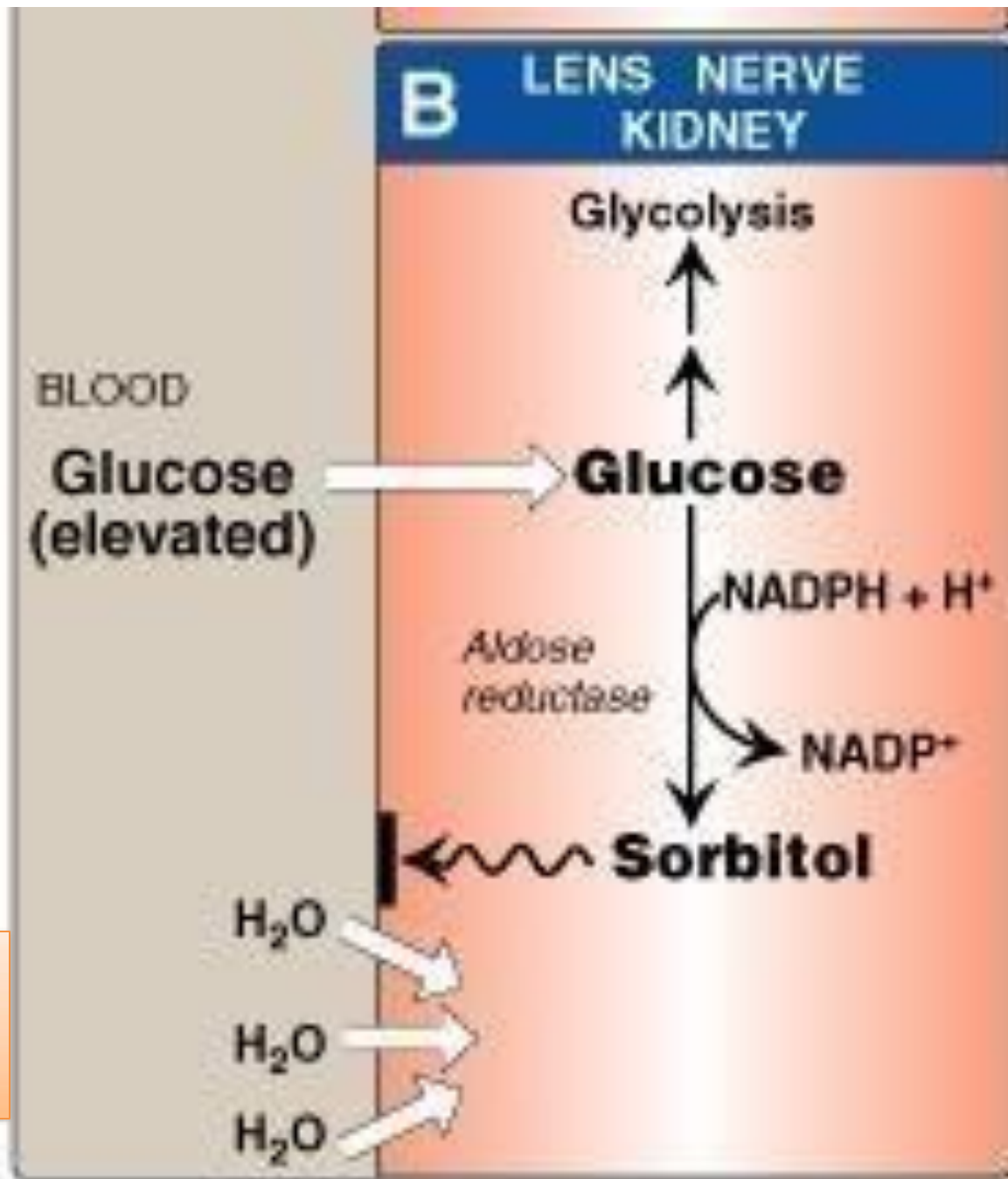
Whether the patient isn't adhering to their treatment, diet isn't working, or even undiagnosed.

In uncontrolled diabetic patients, glucose levels are always high (chronic hyperglycemia). These high levels stimulate the entry of glucose via an insulin independent manner.

Glucose entry is insulin independent in these tissues

Water retention and cell swelling leading to diabetic complications

Explained in the next slide... :)





[ ]: concentration

Type 1 diabetic patients have an insulin deficiency, and type 2 diabetic patients are resistant to insulin. So, it doesn't make sense that insulin production is increased, nor does the increase of GLUTs, making insulin-independent transport the ideal solution. Once glucose enters the cell, it proceeds to glycolysis and other pathways. However, because it's present in high [ ]s, it will activate its reduction to sorbitol. Therefore, [sorbitol] will increase, and since polyalcohols don't have transporters, it will accumulate in the cell, increasing the osmotic pressure and causing retention of water and an increase in the cell's size, accordingly.

This is why diabetic patients (especially uncontrolled diabetic patients) go through complications, such as retinopathy, nephropathy, diabetic foot. Because of diabetic foot, injuries in diabetic's feet go unnoticed (due to nerve damage). This ignorance could progress to an infection, and in some cases, gangrene, leaving the patient with no choice but to amputate their limbs (toe, foot, lower leg, etc.)

Sorbitol is produced in non-diabetics; however, this pathway is stimulated by very high [ ]s of glucose. Remember that glucose is used in many pathway in the cell: glycolysis, pentose phosphate pathway, glucuronate acid synthesis, glycogen synthesis, etc. The production sorbitol is stimulated only when there is a **big amount** of sugar in the blood (the kind present only in diabetic patients).

اللَّهُمَّ أَسْأَلُكَ نَفْسِي إِلَيْكَ، وَقَوَّضْتُ أَمْرِي إِلَيْكَ، وَأَلْجَأْتُ ظَهْرِي إِلَيْكَ، رَغْبَةً وَرَهْبَةً إِلَيْكَ، لَا مَلْجَأَ وَلَا مَنجَىٰ مِنْكَ إِلَّا إِلَيْكَ، آمَنْتُ بِكِتَابِكَ الَّذِي أَنْزَلْتَ، وَبِرَسُولِكَ الَّذِي أَرْسَلْتَ

# Galactose Metabolism

- Epimer of glucose + diastereomers
- Sources: component of lactose, lysosomal degradation glycolipids and glycoproteins
- Entry to cells is insulin independent
- UDP Galactose; an intermediate in galactose metabolism

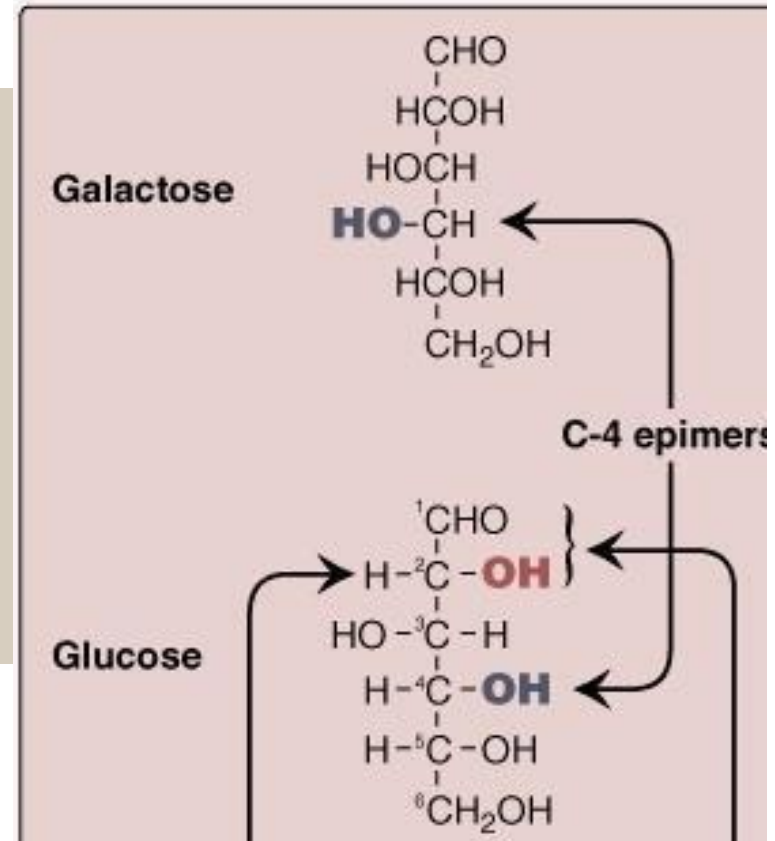
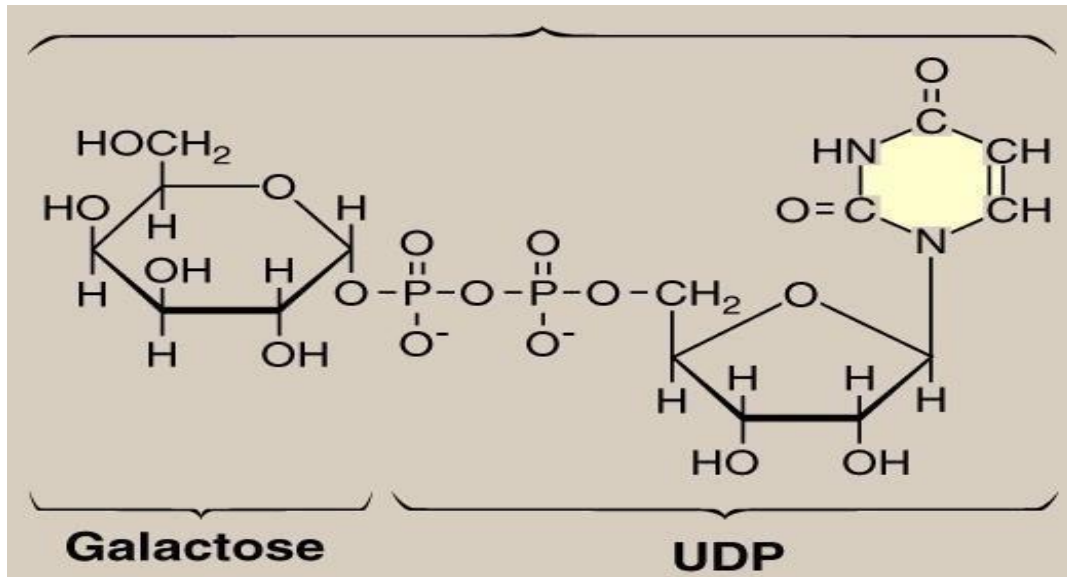
Just like glucose-UDP in glycogen synthesis.

It's a very important intermediate that is used in synthetic pathways, such as glycoproteins, glycolipids, GAGs, etc.

- Galactose is rarely found as a galactose monomer. Normally, you'll find it a part of lactose, or another disaccharide. The purpose of galactose metabolism is not energy production (unlike fructose), but rather a precursor for the synthesis of other molecules, such as GAGs. Sugar components of glycoproteins, glycolipids, GAGs are mainly glucose and galactose, as well as modified forms of these sugars. Fructose and galactose don't induce insulin secretions; therefore, they enter the cells in an insulin-independent manner.

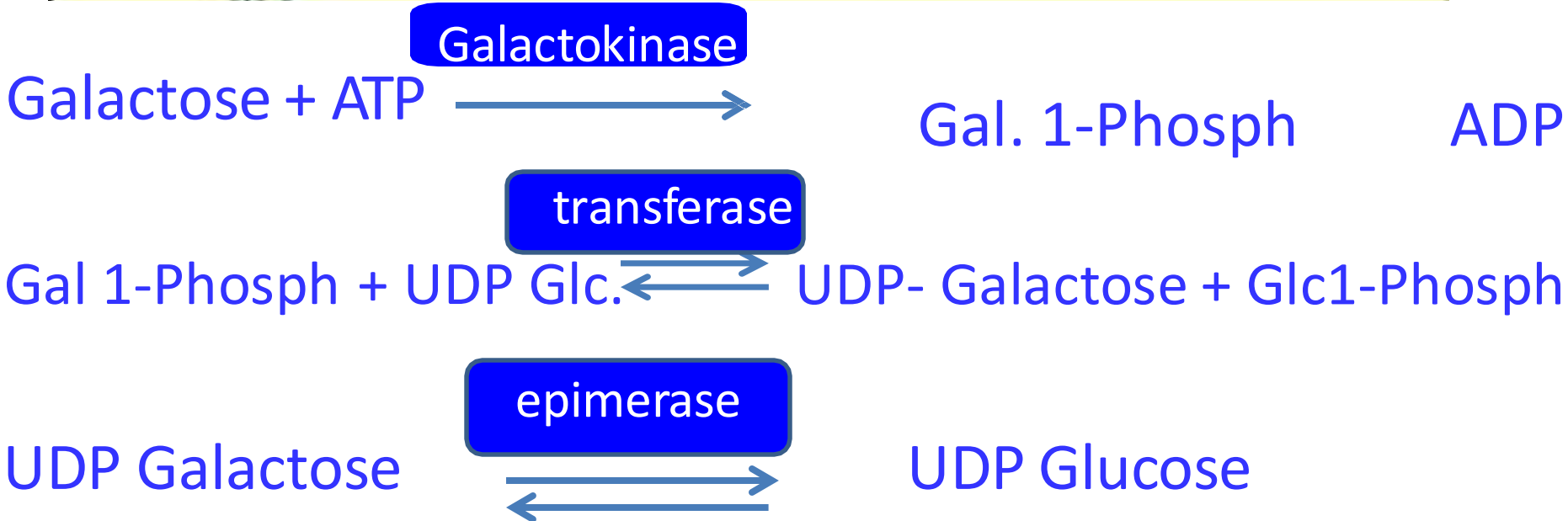
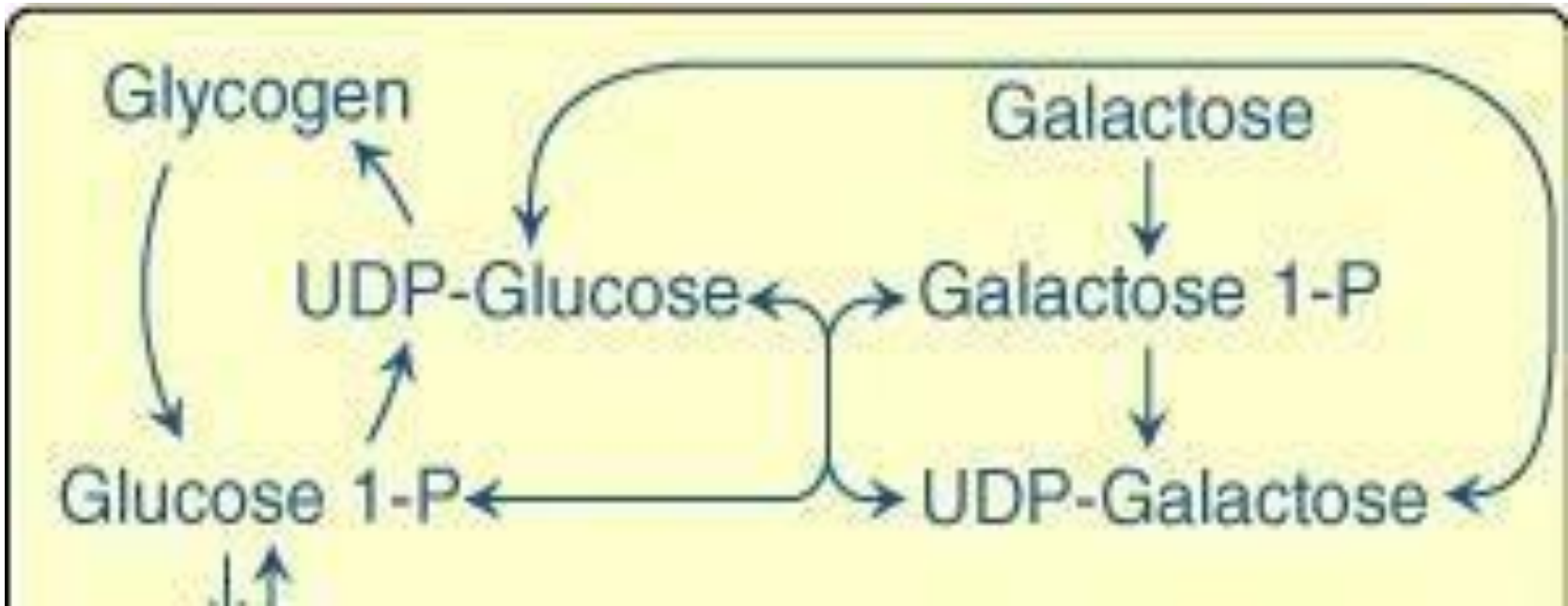
Recall: Hexokinase can phosphorylate galactose to produce galactose 6-phosphate. However, galactose 1-phosphate is needed → galactose must depend on its own specific pathway.

# Galactose Metabolism



- C4 OH group is on the **left** in galactose, faces **upward** in the ring structure
- C4 OH group is on the **right** in glucose, faces **downward** in the ring structure

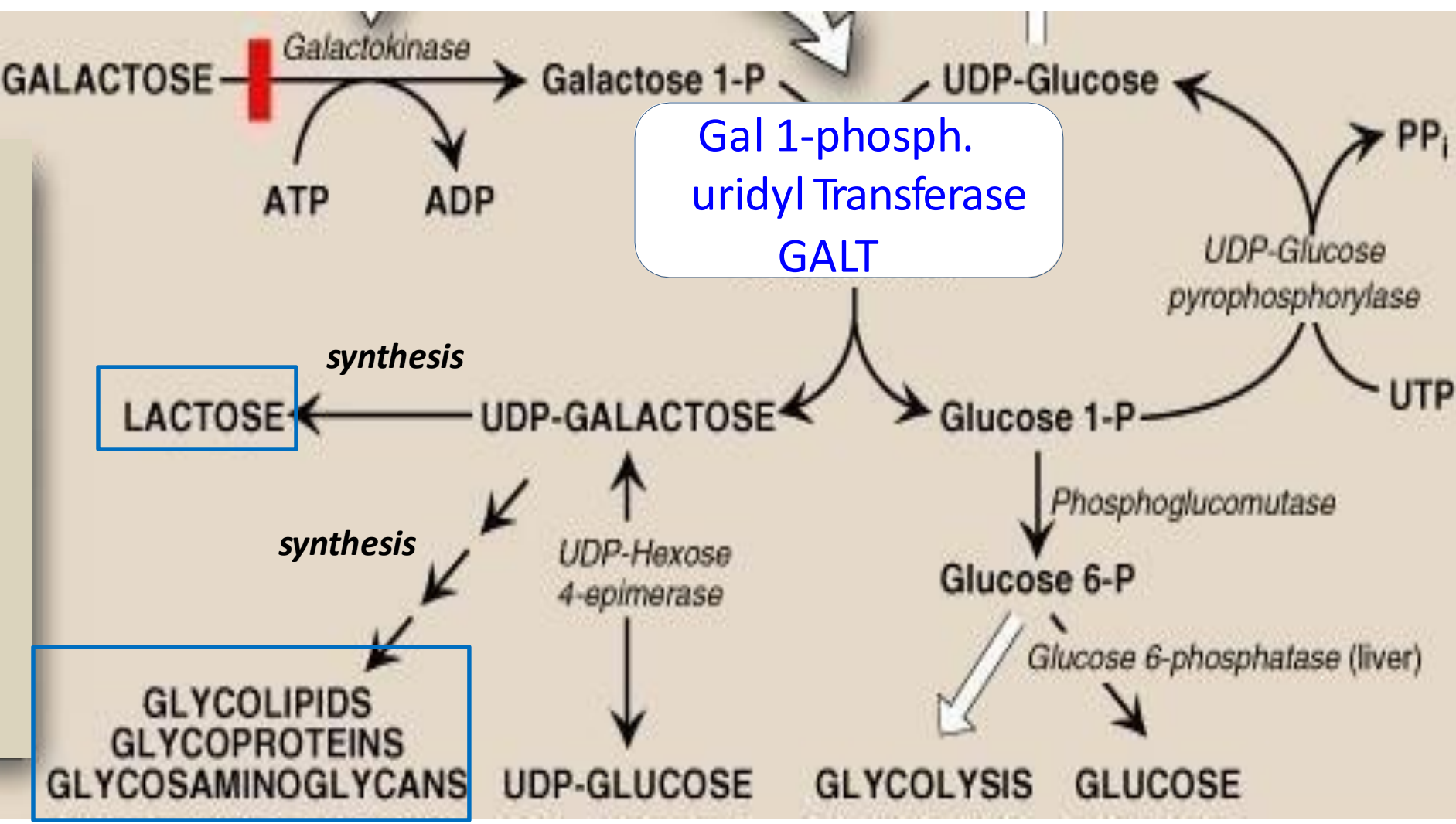
# Galactose Metabolism



## Galactose Metabolism:

- Galactose first gets phosphorylated by galactokinase which produces galactose 1-p (ATP used)
- Then UDP-Glucose (like the one in glycogen synthesis) is used by transferase (GALT), which takes the UDP from glucose & adds it to galactose as well as take the phosphate from galactose & adds it to glucose → producing both UDP-galactose and glucose 1-p
- UDP-galactose is then used in various ways & also could be epimerized (by epimerase) back to UDP-glucose to be used in glycogen synthesis if there was excess available.

# Galactose metabolism and fates



## Further explanation of Galactose metabolism and fates:

UDP-galactose can be used in (main uses):

- lactose synthesis in nursing women (non-nursing women and even men also produce modified lactose with glucose & galactose).
- Synthesize sugar components (glycolipids, glycoproteins & glycosaminoglycans).
- If there is excess, it will be epimerized to UDP-glucose used in glycogen synthesis.

Glucose 1-p (by phosphoglucomutase) becomes glucose 6-p & used in:

- In cells like muscle, process stops here and glucose 6-p is used in glycolysis.
- Other cells like liver, phosphate is removed to produce glucose by phosphatase (so basically, we produced glucose from galactose in the end).
- Or glucose 1-p can react with UTP to produce UDP-glucose directed to glycogen synthesis or reacts again with a new galactose.

# Disorders of Galactose Metabolism

Hereditary disease

- Deficiency of GALT → classic Galactosemia
- Accumulation of Galactose 1-Phosphate and galactose → Completes first step & gets halted at second step

- Similar consequences to those in fructose intolerance

Uses ATP for nothing → drop in ATP → increase in AMP → Uric acid or hyperuricemia, accumulation of both galactose 1-p and galactose, conduction of galactitol & burst of the cell → causes cataracts, mental retardation due to neurons getting damaged & dying

- Galactose ..... → Galactitol production

- Deficiency of Galactokinase

→ Activates aldose reductase to produce galactitol (a polyalcohol)

→ Worse than fructokinase deficiency (has no solution)

Galactitol (similar to sorbitol) gets trapped in the cell which drags H<sub>2</sub>O molecules, causes water retention & swelling & burst.

- Accumulation of Galactose ..... → Galactitol



# Disorders of Galactose Metabolism

Sugar alcohol

## GALACTOKINASE DEFICIENCY

- This causes galactosemia and galactosuria.
- It causes galactitol accumulation if galactose is present in the diet.

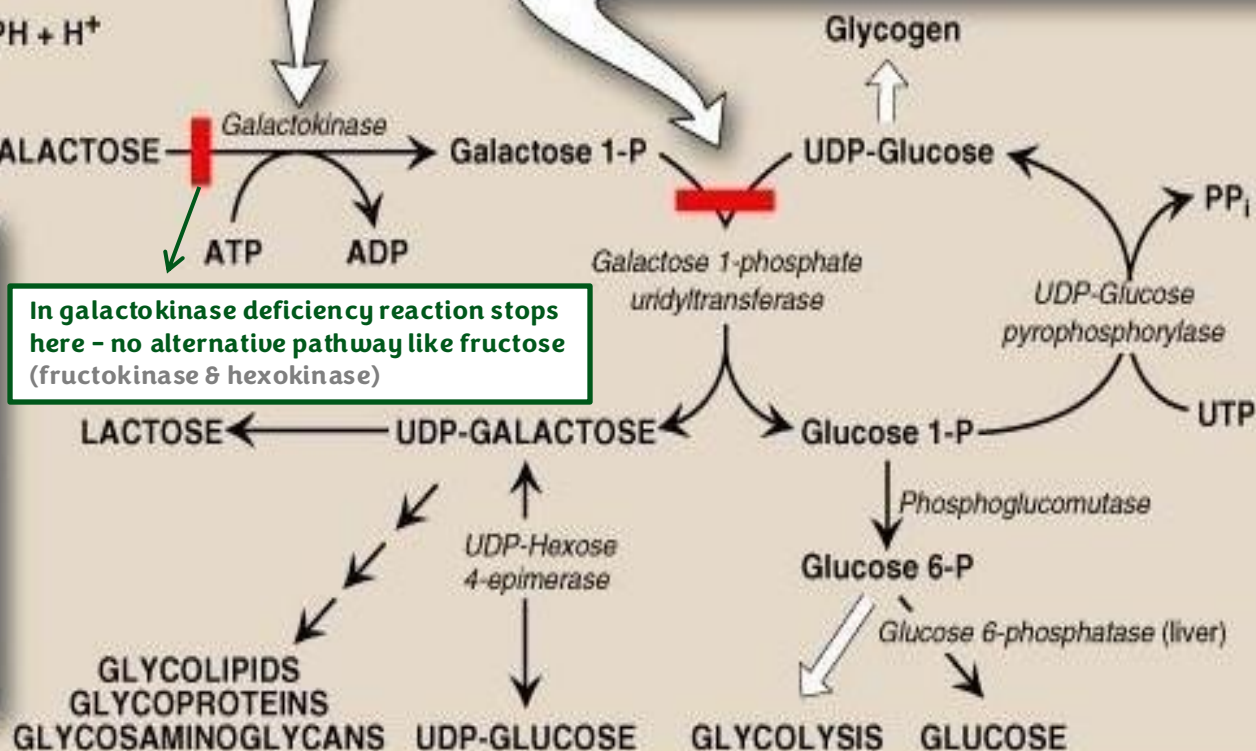
## CLASSIC GALACTOSEMIA

- *Uridyltransferase* deficiency.
- Autosomal recessive disorder (1 in 23,000 births).
- It causes galactosemia and galactosuria, vomiting, diarrhea, and jaundice.
- Accumulation of galactose 1-phosphate and galactitol in nerve, lens, liver, and kidney tissue causes liver damage, severe mental retardation, and cataracts.
- Antenatal diagnosis is possible by chorionic villus sampling.
- Therapy: Rapid diagnosis and removal of galactose (therefore, lactose) from the diet.

## ALDOSE REDUCTASE

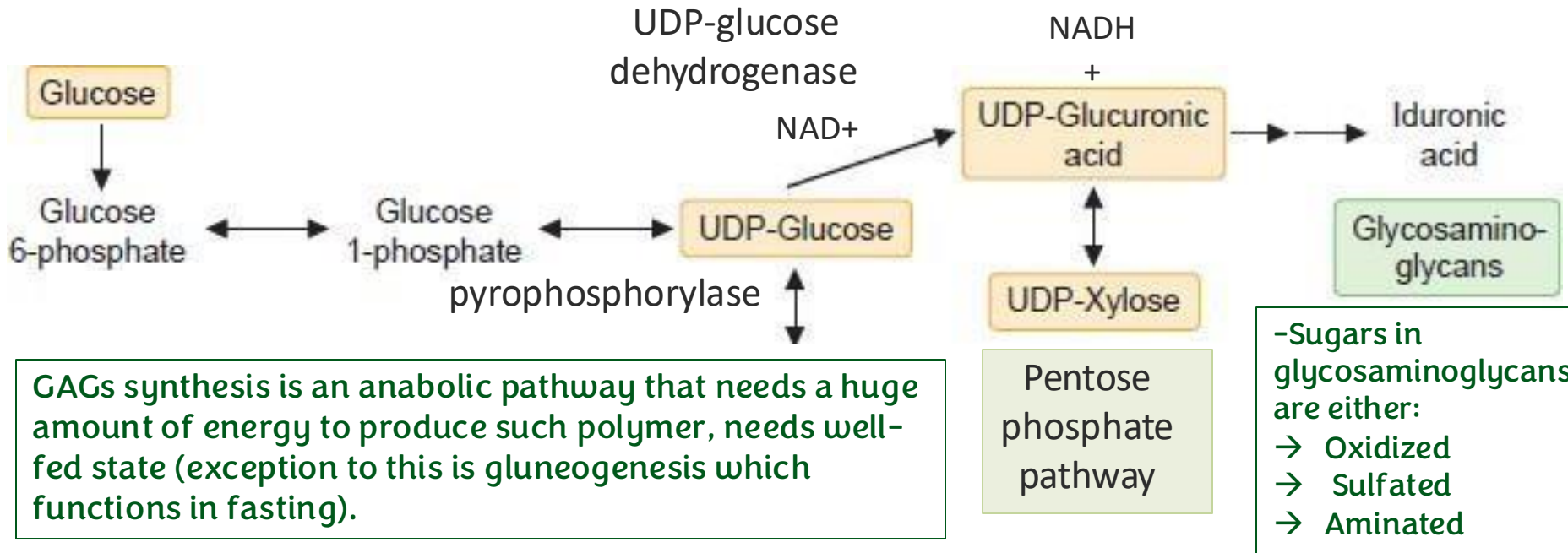
- The enzyme is present in liver, kidney, retina, lens, nerve tissue, seminal vesicles, and ovaries.
- It is physiologically unimportant in galactose metabolism unless galactose levels are high (as in galactosemia).
- Elevated galactitol can cause cataracts.

In galactokinase deficiency reaction stops here - no alternative pathway like fructose (fructokinase & hexokinase)



# Metabolism of Oxidised Glucose

Used mainly in glycosaminoglycans synthesis



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

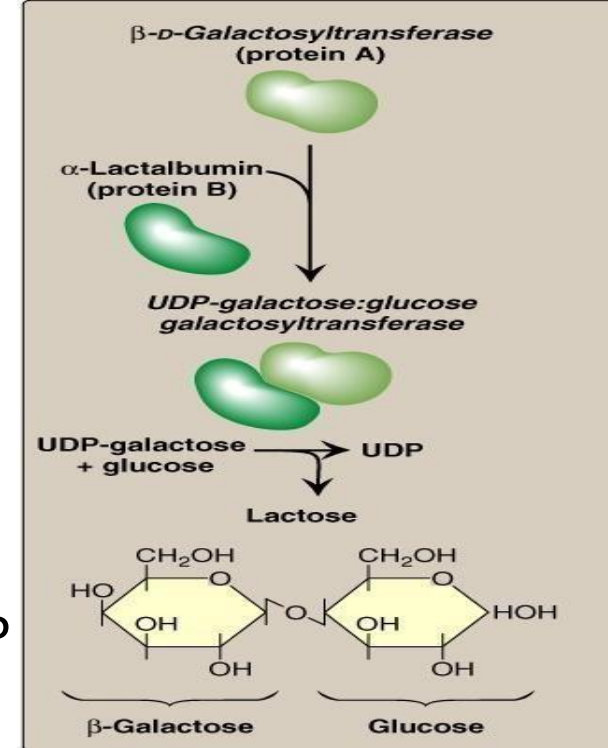
## Diagram explanation:

- High glucose concentration, glucose gets phosphorylated to glucose 6-p (like first step of glycolysis).
- Isomerization to glucose 1-p (like glycogen synthesis).
- Reaction with UTP to make UDP-glucose (also like glycogen synthesis). ~well this is getting old quickly 🙄
- Then gets oxidized by UDP-glucose dehydrogenase which reduces  $\text{NAD}^+$  to  $\text{NADH}$  producing UDP- glucuronic acid which is used to produce glycosaminoglycans or to supply pentose phosphate pathway.

# Lactose (Galactosyl $\beta$ (1 $\rightarrow$ 4) glucose) Synthesis

$\rightarrow$  Lactose is made of glucose & galactose connected via beta (1-4) linkage

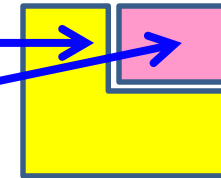
- Produced by mammary glands  $\longrightarrow$  To be part of milk (milk sugar)
- Galactosyl  $\beta$  (1 $\rightarrow$ 4) glucose is found in glycolipids and glycoproteins



Lactose synthase



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

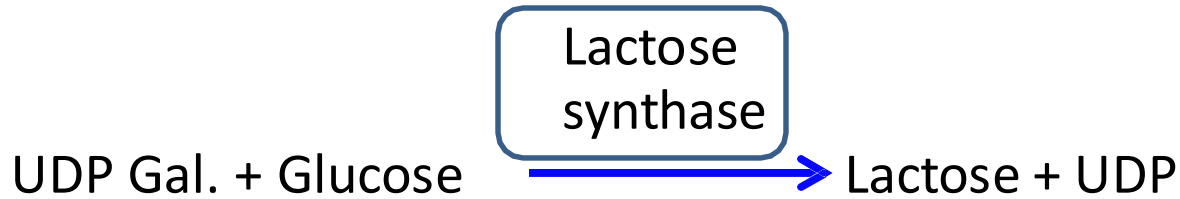


Lactose synthesis in mammary glands

In glycolipids and N-linked glycoprotein synthesis + Can be used for GAGs too, etc.



## Lactose synthesis in mammary glands:



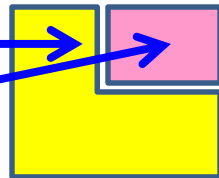
- Lactase synthase forms a reaction between UDP-galactose (has to be this form) & a glucose residue and connects them via beta(1-4) linkage and releases UDP, producing lactose
- The process happens in mammary glands (with A & B protein complex)

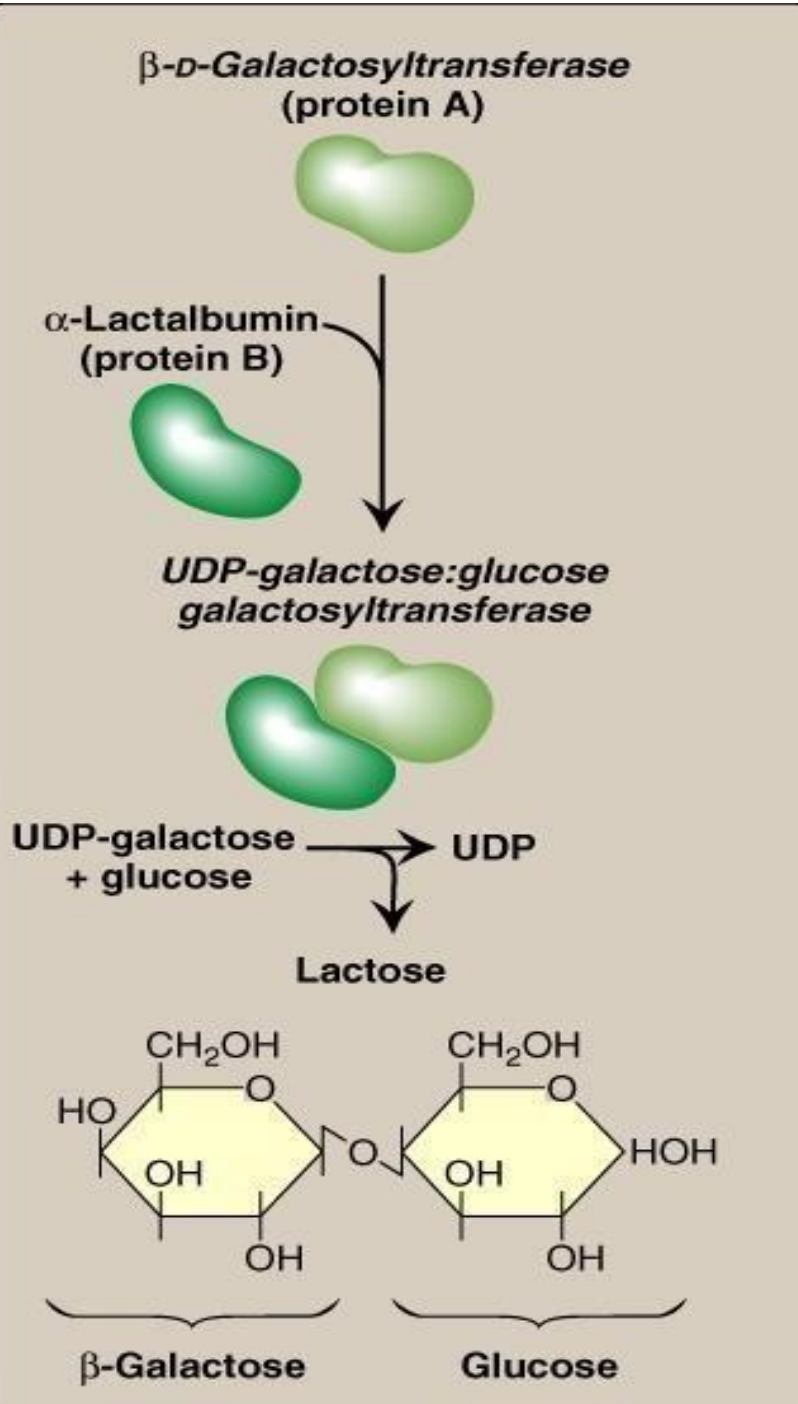
## Lactose synthase structure:

**Galactosyl transferase** (yellow part)  
→ Enzyme part (protein A)  
→ Connects both UDP-galactose & glucose

**α-lactalbumin** (pink part)  
→ Protein, not enzyme (protein B)  
→ Its role is ensuring enzyme part of lactose synthase (part A) takes only glucose in mammary glands to guarantee formation of lactose (selective)

Other cells have **no protein B**, only protein A.  
So modified glucose like N-acetyl glucosamine can enter, this allows modified lactose to form.





# Lactose Synthesis in Mammary Glands

## Extra Information mentioned in regard to some students' questions:

→GAGs are a part of the extra cellular matrix, the connective tissue is mostly made of ECM, which is very dynamic & reacts with the environment and gets affected by it.

~Dr. Dialah gave an example to emphasize the importance of GAGS & ECM:

-There is a tissue in the eye which regulates intraocular pressure (pressure in the eye), this tissue has channels between cells -like roads- that allows passage of eye fluids & drainage to control eye pressure.

-when you change the position of your head, your eye pressure changes which makes this tissue adapt to preserve the ocular pressure at a normal range (more pressure could push on optic nerve & cause other problems)

-one way to do this is through GAGs in proteoglycans, once pressure increases, branches are reduced to allow free passage of fluids which decreases pressure.

-So GAGs are very important & dynamic, they are susceptible to complications & other problems which can be caused by low UDP-galactose

-Hexokinase cannot function instead of galactokinase because it gives galactose 6-p not galactose 1-p, cannot continue in the same path.

### More context:

- GAGs, particularly in the **trabecular meshwork** and the **aqueous humor**, are involved in the regulation of the drainage of fluid from the eye. Any alteration in the structure or function of these GAGs can affect the drainage system and, as a result, IOP.
- Changes in the properties of GAGs in the **trabecular meshwork** could contribute to the development of **glaucoma**, as they may influence the resistance to aqueous humor outflow and lead to elevated IOP.

For any feedback, scan the code or click on



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	4 10	“Aldolase B catalyzes the cleavage of <b>fructose-1,6-bisphosphate...</b> ” “Just like glucose-UDP in <b>glucose</b> synthesis.”	“Aldolase B catalyzes the cleavage of <b>fructose-1-phosphate...</b> ” “Just like glucose-UDP in <b>glycogen</b> synthesis.”
V1 → V2			



## : Additional Resources

## رسالة من الفريق العلمي:

### Reference Used:

(numbered in order as cited in the text)

1. Lippincott's Biochemistry 8<sup>th</sup> Edition  
p. 406-417
2. Hereditary Fructose Intolerance
3. ...

### Extra References for the Reader to Use:

1. Video
2. Webpage
3. ...

سَلِّمْ أُمُورَكَ لِلإِلهِ فَرِمَا جَعَلَ الشَّدَائِدَ لِلرَّخَاءِ سَبِيلًا  
وَأَرْخِ فُؤَادَكَ مِنْ شِكْوِكَ إِنَّهُ رَبٌّ كَرِيمٌ لَا يُزِدُ نَزِيلًا  
وَأَرْخِ العَطَاءَ مَعَ البَلَاءِ فَكَمْ تَلَا يُسْرٌ عَسِيرًا لَا يَدُومُ طَوِيلًا (:)

اللهم إني استودعتك ما قرأت وما حفظت، وما تعلمت، فرده عند  
حاجتي إليه، إنك على كل شيء قدير، حسبنا الله ونعم الوكيل

اللهم سخر لعبادك الضعفاء ملائكة السماء وجنود الأرض اللهم مئة  
ألف من الملائكة مُرَدِّفِينَ لعبادك الضعفاء في غزة وبلاد الشام  
والسودان. اللهم بحق عزتك أرينا عجائب قدرتك انصرهم على  
الأعداء. اللهم لا تمر هذه الايام إلا وقد فرجت عنهم بقدرتك يا  
قادر يا رحيم.