Some Extra notes about Gluconeogenesis

As we said that the Glucogenic precursors are Lactate, Glycerol and amino acids (all except Lysine and Leucine)

Amino acids: Dr Mahmoud mention Glutamate as an example, Glutamate is transaminated to α-Ketoglutarate then α-Ketoglutarate is converted by TCA cycle steps to oxaloacetate, then Oxaloacetate is used for Gluconeogenesis

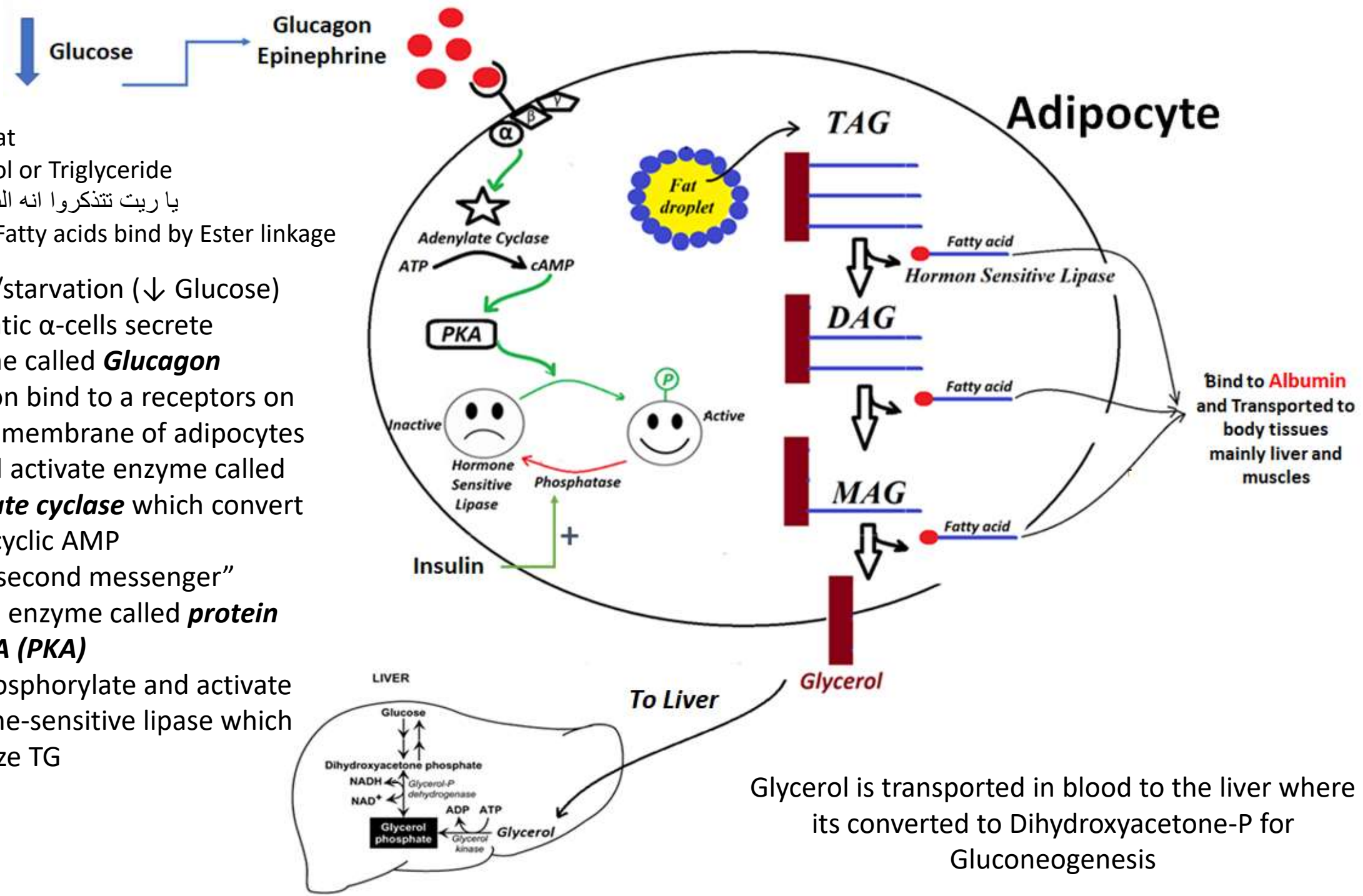
Other example is Alanine where alanine is transaminated to pyruvate, then the pyruvate is used for Gluconeogenesis

You think about Aspartate??

Glycerol: come from hydrolysis of Triglyceride (Fat) in adipose tissues

Triglyceride are synthesized in the liver or adipose tissues or come from Diet but ***stored only*** in adipose tissue

- Liver Triglycerides are transported to the adipose tissue as Lipoprotein called ***VLDL*** "Very low density lipoprotein"
- Dietary Triglyceride are transported from the intestinal mucosal cells to the adipose tissue as Lipoprotein called ***Chylomicron***



TAG = TG = Fat
Triacylglycerol or Triglyceride
يا ريت تتذكروا انه الدهون بتتكون من
Glycerol + 3 Fatty acids bind by Ester linkage

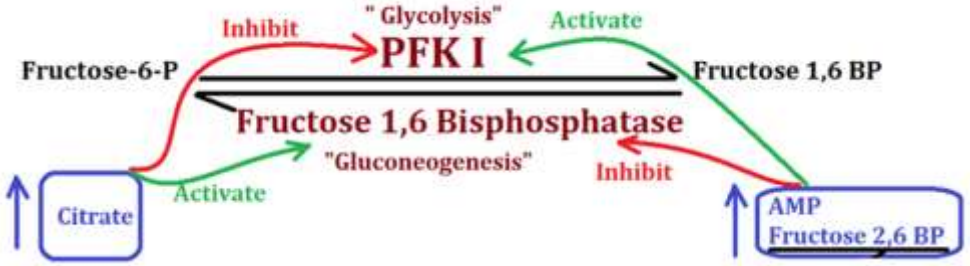
1. Fasting/starvation (↓ Glucose)
2. Pancreatic α-cells secrete hormone called ***Glucagon***
3. Glucagon bind to a receptors on the cell membrane of adipocytes
4. This will activate enzyme called ***adenylate cyclase*** which convert ATP to cyclic AMP
5. cAMP "second messenger" activate enzyme called ***protein kinase A (PKA)***
6. PKA phosphorylate and activate Hormone-sensitive lipase which hydrolyze TG

Glycerol is transported in blood to the liver where its converted to Dihydroxyacetone-P for Gluconeogenesis

Reciprocal control:

A substance that activate one direction of a reaction while inhibit the other direction

Example AMP and Fructose 2,6 BP activate PFK-1 (Glycolysis) and at the same time they inhibit Fructose 1,6 Bisphosphatase (Gluconeogenesis)



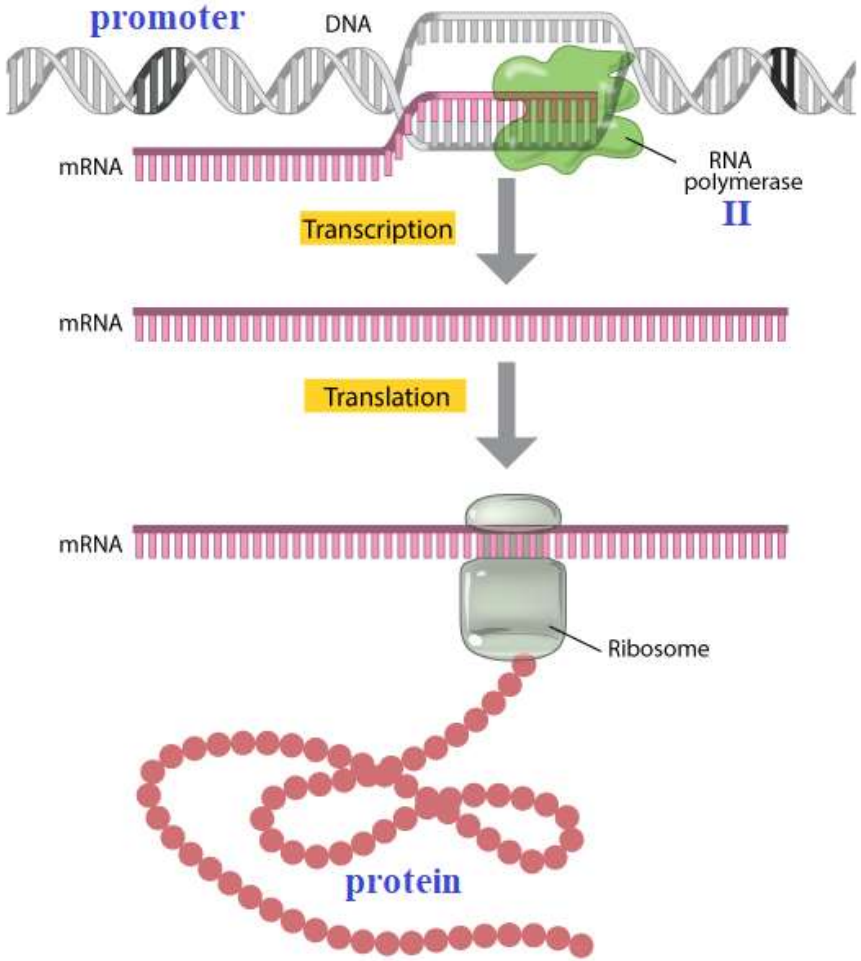
Note: We said that Glucagon induce the gene of PEPCK, how?

Basics

the genes is transcribed to mRNA in eukaryotic cells by enzyme called ***RNA-polymerase II***

At the beginning of each gene there is a small segment called ***promoter*** where the RNA-polymerase II bind to the gene to start transcription

Some proteins facilitate binding of RNA-polymerase II to specific genes these proteins called ***specific transcription factors***



The promoter of PEPCK contain segment called ***cAMP-response element (CRE)*** which bind to a transcription factor called ***cAMP-response element Binding protein (CREB)***

When CREB bind to the promoter of PEPCK gene it will facilitate binding of RNA-polymerase II → increase transcription of this gene → more PEPCK mRNA → more PEPCK

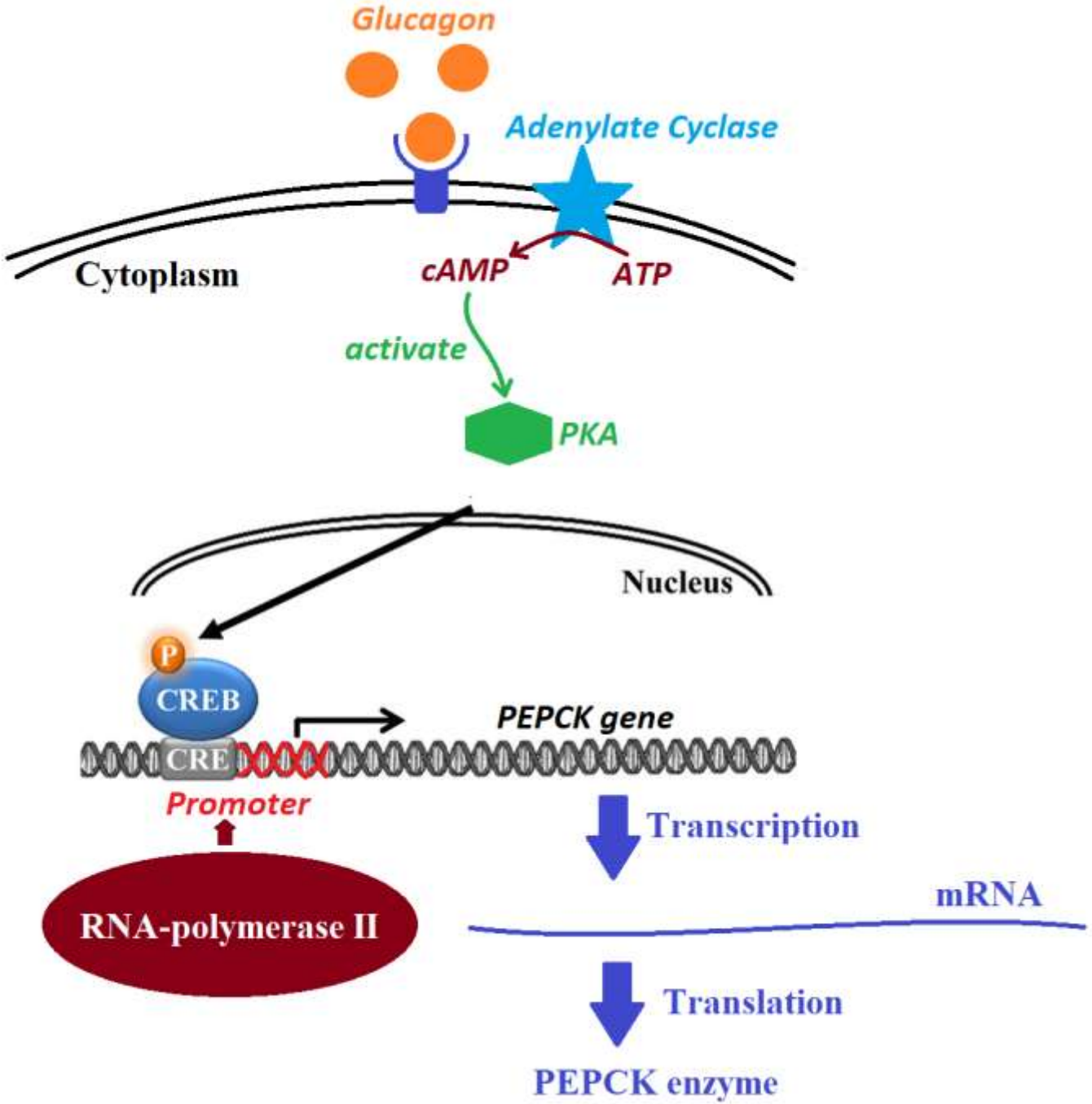
Now

Glucagon activate adenylate cyclase which convert ATP to cAMP

cAMP activate PKA

PKA enter the nucleus → phosphorylate and activate CREB → phosphorylated CREB activate the transcription of PEPCK gene

Genetic control is a long-term control, while other types of control such as phosphorylation of enzymes and allosteric controls are short term and rapid



Metabolism of sugars other than glucose (Fructose and Galactose)

General information about glucose:

What is the fate of Glucose:

- Glycolysis if energy is needed
- Glycogen synthesis if energy level of the cell is high
- Pentose phosphate pathway

what decide if glucose go through glycolysis or stored as Glycogen?

Answer: the energy charged of the cell

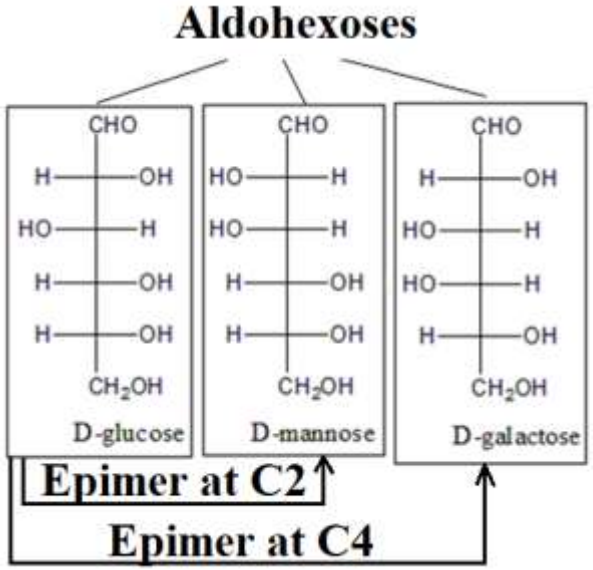
The energy charge is ATP/AMP ratio

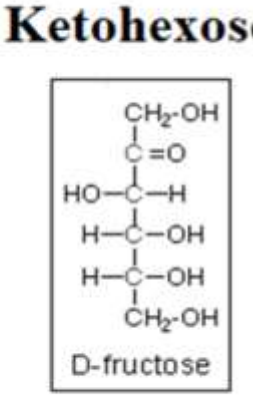
If ATP/AMP ratio is high → ATP is high → no need for glycolysis → Glucose is used for Glycogen synthesis

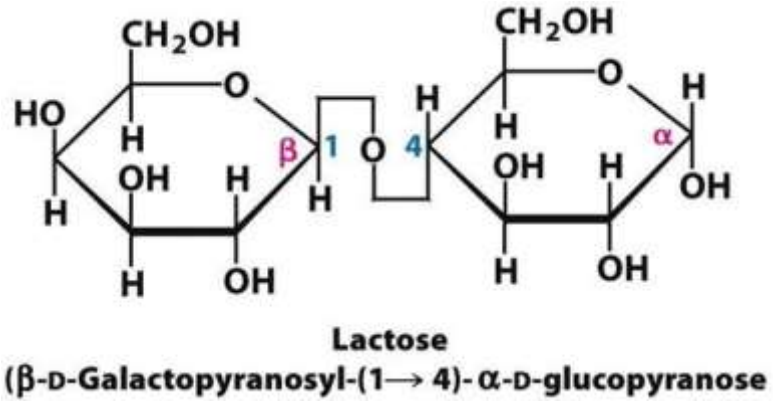
If ATP/AMP ratio is low → ATP is low → activate glycolysis inhibit Glycogen synthesis

Metabolism of Monosaccharides and Disaccharides

- Fructose
- Galactose
- Mannose
- Lactose (Milk Sugar)



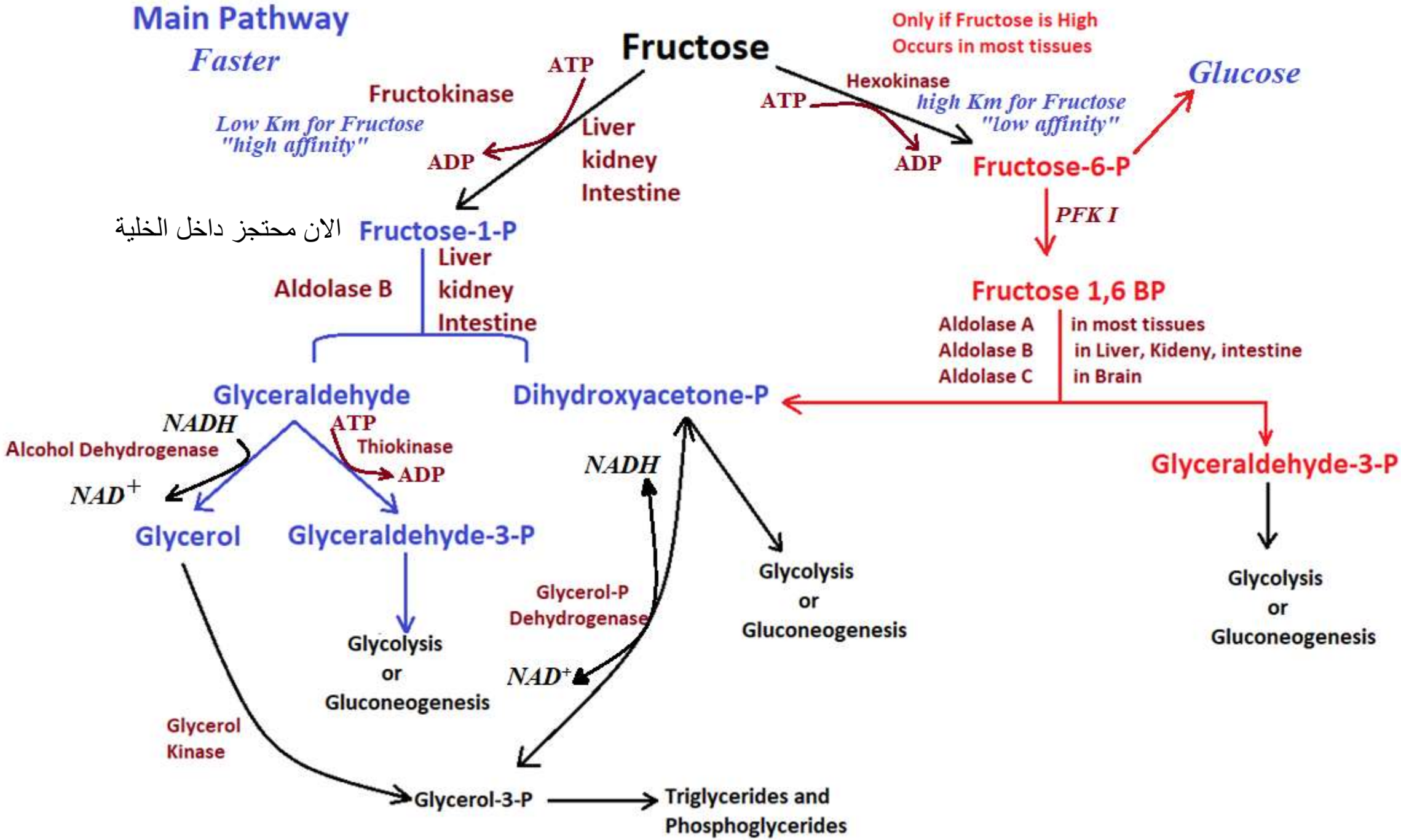




Lactose is a disaccharide consist of Galactose attached to Glucose by β 1-4 glycosidic linkage
Lactose is not a mixture of galactose and Galactose
Lactose is digested in the intestine by enzyme called Lactase releasing Galactose and Glucose that can be absorbed to blood

1. Fructose

- 10% of daily calories
- Sources: Sucrose (سكر المائدة), Fruit, honey and corn Syrup which is used as sugar substituent (بديل)
- Sucrose is digested by ***Sucrase*** producing Glucose and Fructose
- Fructose Does NOT require Insulin to Enter the cells, and it does NOT stimulate Insulin Secretion


Main Pathway
Faster
Fructose
ATP
Fructokinase
Low Km for Fructose
"high affinity"
ADP
Liver
kidney
Intestine
Only if Fructose is High
Occurs in most tissues
Hexokinase
ATP
high Km for Fructose
"low affinity"
ADP
Glucose
Fructose-6-P
PFK I
الان محتجز داخل الخلية
Fructose-1-P
Aldolase B
Liver
kidney
Intestine
Fructose 1,6 BP
Aldolase A
Aldolase B
Aldolase C
in most tissues
in Liver, Kideny, intestine
in Brain
Glyceraldehyde
Dihydroxyacetone-P
NADH
Alcohol Dehydrogenase
NAD+
ATP
Thiokinase
ADP
Glyceraldehyde-3-P
Glycerol
Glyceraldehyde-3-P
NADH
Glycerol-P
Dehydrogenase
NAD+
Glycolysis
or
Gluconeogenesis
Glycolysis
or
Gluconeogenesis
Glycolysis
or
Gluconeogenesis
Glycerol
Kinase
Glycerol-3-P
Triglycerides and
Phosphoglycerides

In Words

- Most Fructose converted in the Liver, Kidney and Intestine to Fructose-1-P by ***Fructokinase***

→ then Fructose-1-P cleaved (يكسر) by ***Aldolase B*** in these tissues producing Dihydroxyacetone-P and Glyceraldehyde

- **Glyceraldehyde** either

a. reduced to Glycerol by alcohol Dehydrogenase (use NADH) then glycerol is phosphorylated by Glycerol Kinase (use ATP) forming Glycerol-3-P which is used in the synthesis of Fat and phospholipids

b. Converted to glyceraldehyde-3-P for glycolysis or Gluconeogenesis by Thiokinase (use ATP)

- **Dihydroxyacetone-P**

a. Used in Glycolysis or Gluconeogenesis

b. Converted to Glycerol-3-P by Glycerol-P Dehydrogenase (use NADH)

If Fructose is High

Hexokinase in most tissues (mainly muscles) convert Fructose to Fructose-6-P then to Fructose1,6-BP

Fructose 1,6 BP cleaved by Aldolase A (most tissues), Aldolase B (Liver, Kidney, Intestine) Aldolase C (Brain) to Glyceraldehyde-3-P and Dihydroxyacetone-P

Note: Aldolase B can Cleave Fructose-1-P and Fructose 1,6 Bisphosphate

Conversion of Glucose to Fructose

- Normally Sorbitol produced in Lens, retina, Kidney, Nerves and RBCs is transported to liver to be converted to Fructose with ***Slow Clearance*** خروجه من الخلايا بطيء

- In Uncontrolled Diabetes مرضى السكري, Glucose level is High in Lens, retina, Kidney, Nerves and RBCs
  (these Tissues Do NOT need Insulin)

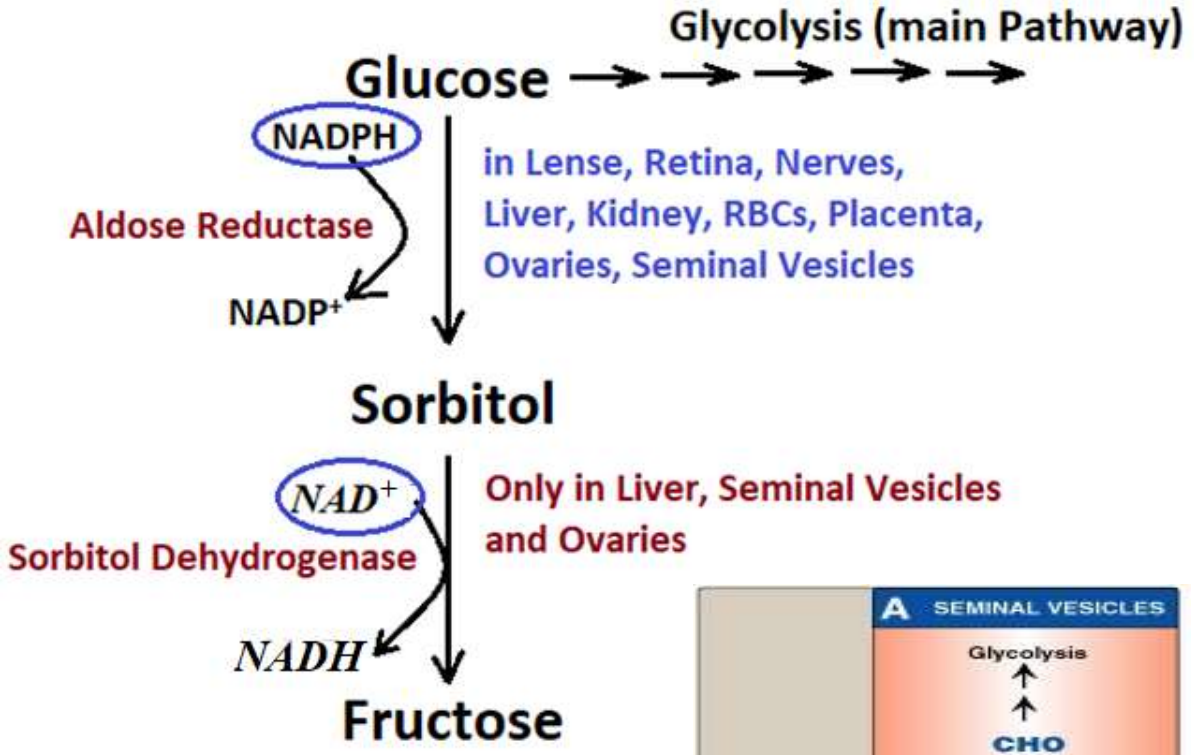
Consequently بالتالي Sorbitol will accumulate in these Tissues increasing the Osmotic pressure leading to cell death

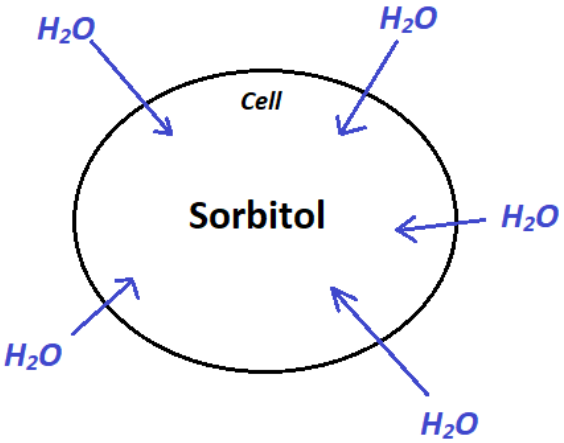
→ Cataract سوائل في عدسة العين, Peripheral Neuropathy مشاكل في الاعصاب الطرفية, Nephropathy مشاكل في الكلية, Retinopathy مشاكل في الشبكية

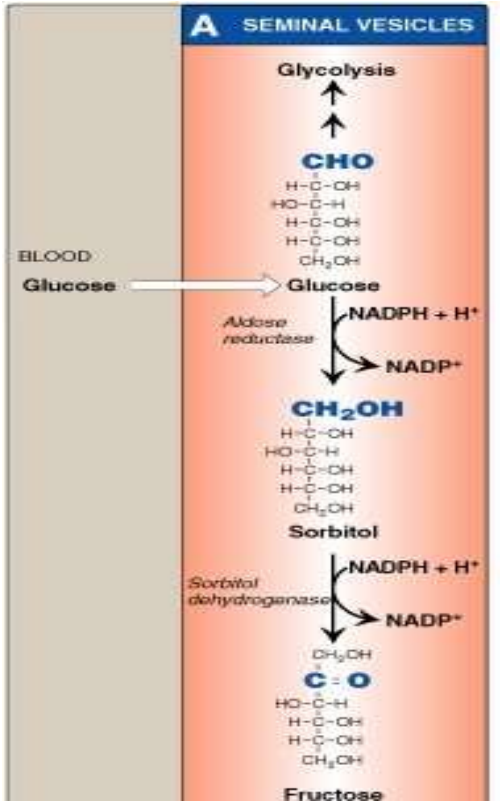
- Also increase production of Sorbitol consume يستهلك NADPH

Seminal vesicles convert glucose to fructose because sperm prefer fructose as energy source

Deficiency of fructose correlate to male infertility عقم







Genetic Diseases of Fructose Metabolism

1. Essential Fructoseuria

- Deficiency of ***Fructokinase***, rare Autosomal Recessive (متنجي) disease
- Leads to increase Fructose in Blood → Eliminated in urine
- Its Benign (حميد) Disease with NO symptoms

2. Fructose-1,6-Bisphosphatase Deficiency

- A very rare autosomal recessive disease.
- The disease results from inherited defects in the F1,6 BPase gene (gene symbol: FBP1) that encodes the hepatic form of this enzyme.
- It leads to accumulation of fructose 1,6 biphosphate which inhibits glycogen phosphorylase enzyme (glycogenolysis) and severely (بشكل حاد) impaired (يؤثر) hepatic gluconeogenesis and leads to episodes (نوبات) of hypoglycemia, ketosis and lactic acidosis.
- Hypoglycemia leads to high fatty acids degradation to acetyl-CoA→ acetyl-CoA is converted to ketone bodies which are acids and cause Ketoacidosis, also impaired gluconeogenesis leads to accumulation of Lactate causing Lactic acidosis

الاهم والاخطر

3. Hereditary Fructose Intolerance (HFI)

- Also called “Fructose Poisoning”, Autosomal Recessive disease
- Lack of ***Aldolase B***

الفوسفات محتجزة مع ال Fructose

- ➢ So Fructose-1-P trapped inside the cell, Trapping phosphate binding to it
- ➢ This will leads to ↓Pi ↓ATP ↑AMP (low energy charge) this will inhibit Glycogen degradation (Glycogen phosphorylase require Pi), inhibition of Gluconeogenesis and Protein synthesis (require ATP)
- ➢ Also accumulation Fructose-1-P will activate Glucokinase in the liver by releasing it from GKRP “Glucokinase regulatory protein” so the liver will trap glucose causing lethal hypoglycaemia
- ➢ Also there are enzyme called ***AMP-dependant kinase (AMPK),*** this enzyme also can release Glucokinase from GKRP in this disease there will be high AMP level → high activity of AMPK → activation of Glucokinase
- ➢ High Fructose-1-P will inhibit Fructokinase → prevent fructose uptake → high blood fructose → Fructoseuria

- Symptoms:

- Sever Hypoglycemia
- Hepatomegaly and liver damage (تضخم الكبد)
- Low Pi leads to activation of enzyme called ***AMP deaminase*** which degrade AMP to Uric acid leading to Hyperurecemia (High Uric acid)
- hyperlactic academia (high lactic acid) due to inhibition of gluconeogenesis

- Therapy: Rapid Detection and prevention of Fructose in Diet

الاعراض تظهر after weaning

بعد الفطام غندما يبدء الطفل ياكل اشياء غير الحليب

Galactose Metabolism obtained mainly from Lactose “Dairy products”

Minor Pathway ⟵ ⟶ Major Pathway

aldose Reductase

Galactose

Galactokinase

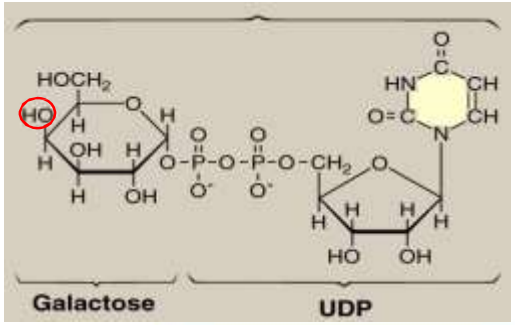
Galactitol

NADP+ ⟵ NADPH

in Liver, Kidney, Lens
Retina.....

In most Tissues
Mainly in Liver

Galactose-1-P



Galactose is mainly metabolized in ***liver***

UDP-Glucose → Glucogen

Galactose 1-P
Uridyl-transferase
(GALT)

??

UDP-Galactose

Glucose-1-P + UTP

Glucose-6-P

Glycolysis
or
Gluconeogenesis

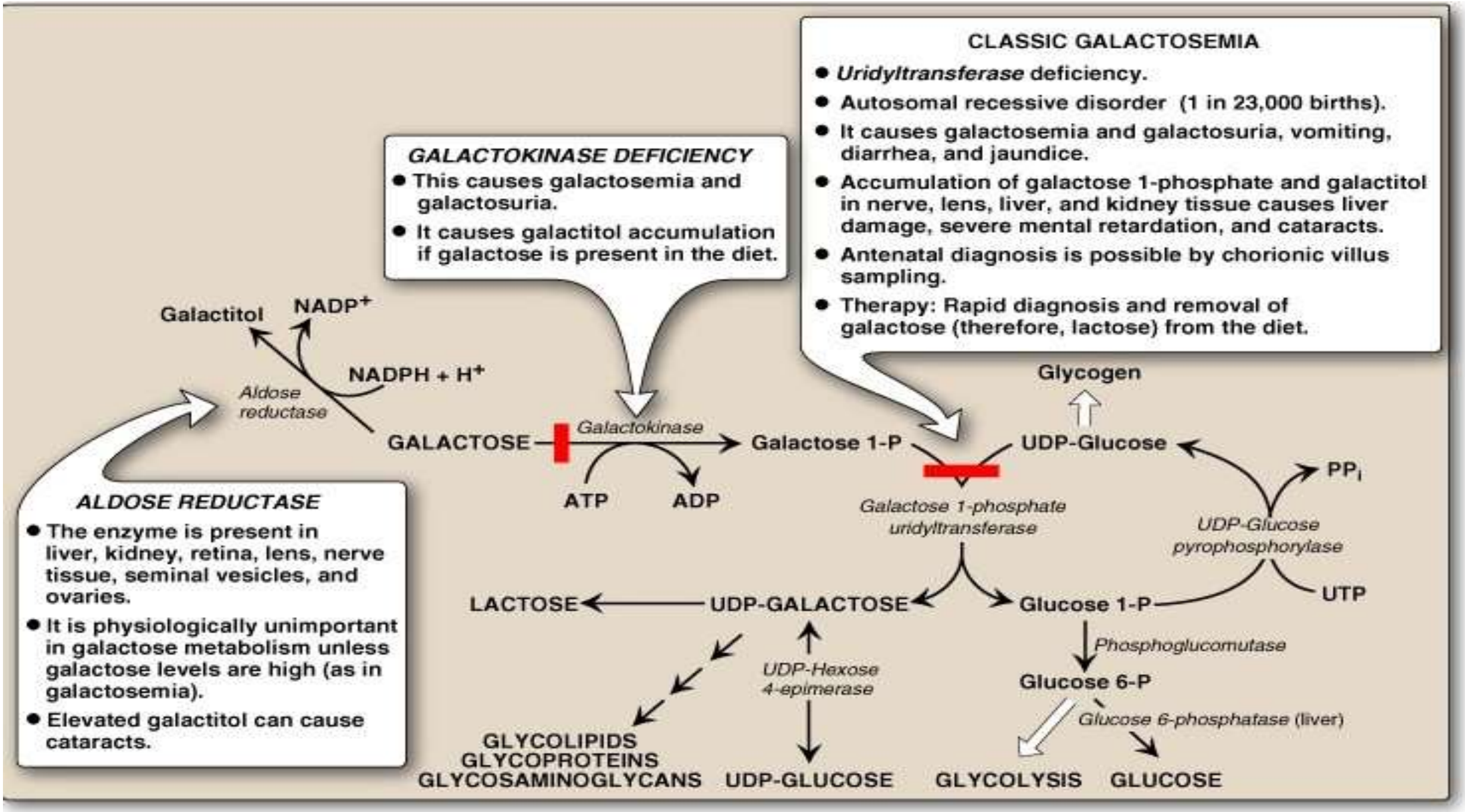
Lactose
in the Mumary glands
during Lactation
في غدد الحليب اثناء الرضاعة

used to synthesize
Glycolipids
Glycoproteins
Glycosaminoglycans

Reversible

UDP-Hexose
4-Epimerase

UDP-Glucose


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.
GALACTOKINASE DEFICIENCY
This causes galactosemia and galactosuria.
It causes galactitol accumulation if galactose is present in the diet.
Galactitol
NADP+
NADPH + H+
Aldose reductase
GALACTOSE
Galactokinase
ATP
ADP
Galactose 1-P
Glycogen
UDP-Glucose
PPi
Galactose 1-phosphate uridyltransferase
UDP-Glucose pyrophosphorylase
UTP
LACTOSE
UDP-GALACTOSE
Glucose 1-P
Phosphoglucomutase
Glucose 6-P
UDP-Hexose 4-epimerase
Glucose 6-phosphatase (liver)
GLYCOLIPIDS
GLYCOPROTEINS
GLYCOSAMINOGLYCANS
UDP-GLUCOSE
GLYCOLYSIS
GLUCOSE
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 words

- The main source of Galactose is the disaccharide ***Lactose*** (from dairy products), which is digested in the intestine by Lactase releasing glucose and galactose which are absorbed to blood
- The major pathway of galactose metabolism is catalyzed by ***galactokinase (GALK-1)*** which found in all tissues but mainly in liver

1. Galactose is phosphorylated at C1 forming Galactose-1-P (ATP is the source of phosphate) by ***galactokinase (GALK-1)***
2. Galactose-1-P react with UDP-glucose forming UDP-galactose + Glucose-1-P, this step is catalyzed by ***Galactose-1-P Uridyl-transferase (GALT)***

Glucose1-P is either:

- React with UTP forming UDP-glucose by ***UDP-glucose pyrophosphorylase***
- Converted to Glucose-6-P by ***phosphoglucomutase*** then Glucose-6-P is either converted to Glucose by ***Glucose-6-phosphatase*** or enter Glycolysis if energy is needed

UDP-galactose is:

- Converted to UDP-glucose by ***UDP-Hexose 4-epimerase (GALE)*** is a reversible reaction
- Used for the synthesis of Glycolipids, Glycoproteins or GAGs
- Added to Glucose forming Lactose in the mammary glands during breast-feeding

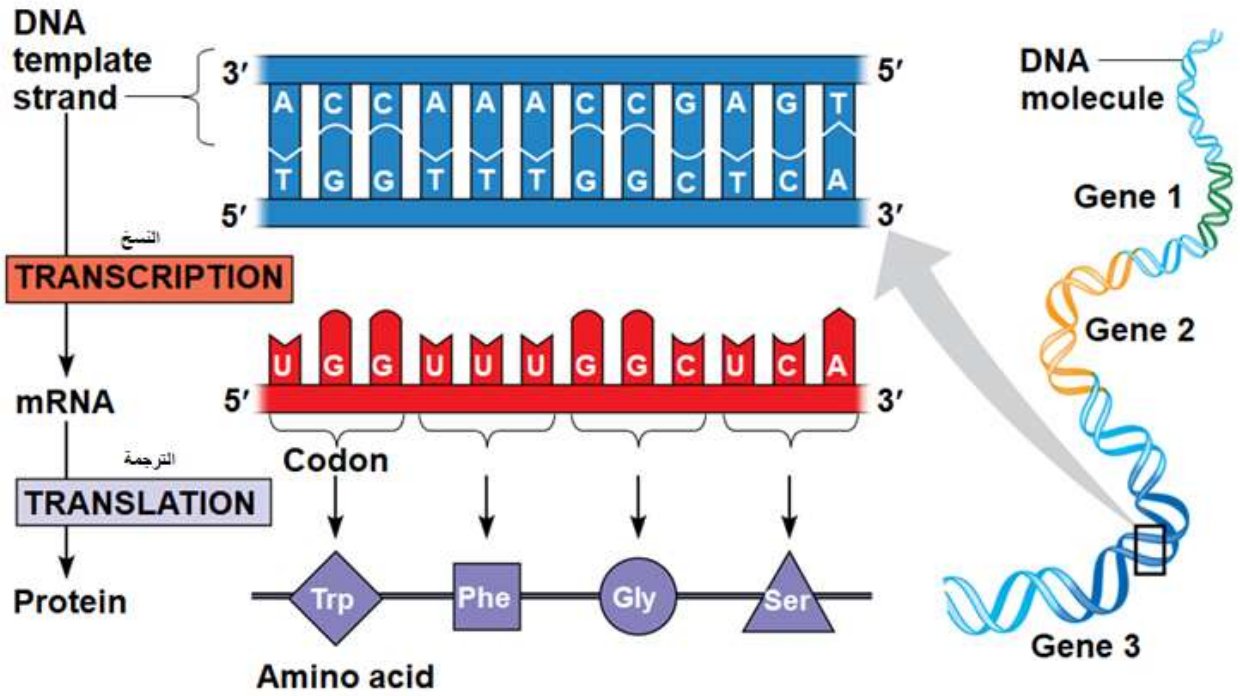
Minor pathway for Galactose metabolism:

Galactose is reduced to galactitol by ***Aldose reductase*** in the Liver, ovaries, seminal vesicles,Lens, retina, Kidney, Nerves and RBCs

Accumulation of Galactitol will cause Cataract, Liver failure and mental retardation

Some basic genetics

Mutation: change in the nucleotide sequence of the gene such as substitution of one nucleotide for another



- Each 3 nucleotide in the mRNA called ***Codon***
- Each codon represent a specific amino acid
- **3 stop codons** that stop the translation process UAA, UAG, UGA

If one nucleotide is change in the gene (point Mutation), the result will be a change in one codon in the mRNA

- If the new codon translated to an amino acid of the same class of the normal amino acid (i.e nonpolar/nonpolar) → ***Sense mutation***
- If the new codon translated to an amino acid of different class of the normal amino acid (i.e nonpolar/Basic) → ***Missense mutation***
- If the new codon become a stop codon (AAA for proline become UAA) → ***Nonsense mutation*** that cause premature termination of the translation process

Genetic deficiency In Galactokinase, Galactose-1-P Uridyl transferase, or UDP-hexose 4-Epimerase will leads to accumulation of Galactose in blood a disease called ***Galactosemias***

Symptoms:

1. Galactose will be converted to Galactitol by Aldose reductase
2. Accumulation of galactitol will leads to:

- Cataract
- Liver failure
- Mental retardation
- Galactosuria (excretion of galactose in the urine)

Management: avoid milk and dairy products (avoid Lactose)

Symptoms appears early after birth when the baby on breastfeeding

3 Types of Galactosemias:

Galactosemia Type I: **Galactose-1-P Uridylyl transferase (GALT)** deficiency (most common galactosemia and also called **Classic Galactosemia**)

Galactosemia Type II: **Galactokinase (GALK-1)** deficiency

Galactosemia Type III: **UDP-hexose 4-Epimerase (GALE)** deficiency

Classic Galactosemia Type 1: Galactose-1-P Uridyltransferase (GALT)

- Over 230 different mutations have been described in the gene encoding human GALT.
- Most common mutation is Missense mutation leads to **substitution of arginine (R) for glutamine (Q)** at amino acid 188 which lies close to the active site of the enzyme (Q188R).
- K285N, S135L, and N314D.

غير طبيعي — الطبيعي

Q188R: the amino acid at position 188 is substituted from Glutamine to Arginine

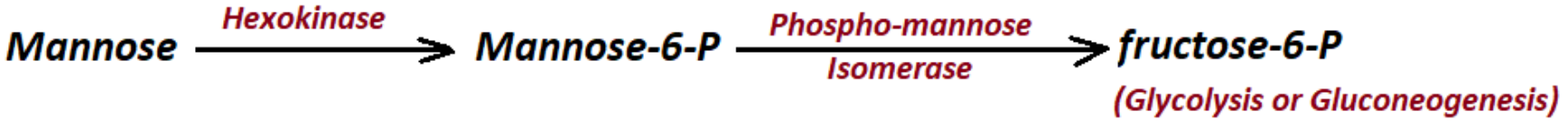
Type 2 Galactosemia: deficiency of galactokinase (GALK1).

- More than 30 different mutations have been found in the GALK1 gene in patients with type 2 galactosemia.
- The most common mutations in the GALK1 gene are **missense** mutations.
- Particular mutation in codon 28 that changes the normal Pro codon to a Thr codon (P28T) is quite high.

Type 3 Galactosemia: UDP-galactose-4-epimerase (GALE).

- Over 20 different mutations have been identified in the GALE gene in type 3 galactosemia patients.
- The most common mutation in the severe form of type 3 galactosemia is a **missense** mutation that changes codon 94 from a Val to a Met (V94M) codon.

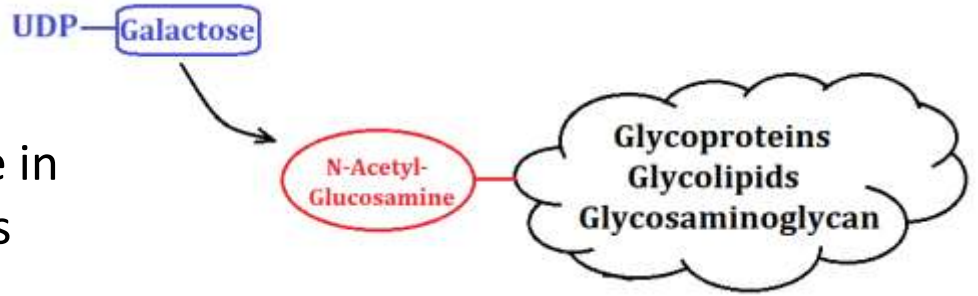
Mannose Metabolism



Lactose Synthesis in Lactating mothers

- There is an enzyme found in our cells called ***Galactosyl-transferase (Protein A)***

Normally This Enzyme transfer Galactose to N-acetyl-glucoseamine in Glycoproteins, Glycolipids and GAGs



This Enzyme has very high Km to Glucose → cannot transfer Galactose to glucose for Lactose synthesis

غدد انتاج الحليب

After Birth; Lactating mammary glands **ONLY** Synthesize protein called **α-Lactalbumin (Protein B) "effect of prolactin"**

This protein bind to Galactosyl-transferase and lowers the Km for Glucose

So; it start transferring Galactose to Glucose producing Lactose
Protein A + Protein B = UDP-galactose:glucose galactosyltransferase or Lactose Synthase