Biochemistry

Title =Carbohydrate metabolism
Lec no =13
Done By =Baraa Safi

وقل رب زدني علما

Carbohydrate metabolism

Hexose mono Phosphate pathway

HMP, Glucronic acid pathways and non-glucose metabolism

Ahmed Salem, MD, MSc, PhD, FRCR

CHO metabolism	*1. Glycolysis* *a. First phase* *b. Second phase* *2.Pentosephosphate pathway (HMP)* *3.Metabolism of non-glucose sugars* *a.metabolism of fructose.* *b.metabolism of galactose* *c.metabolism of glucuronic acid* *3. Glycogen metabolism* *a. Glycogen synthesis* *b. Glycogen breakdown*

Minor Pathways for Glucose Oxidation

- **A. Hexose Monophosphate pathway (HMP-pathway)**

- **B. Uronic Acid Pathway (Glucuronic Acid Pathway)**

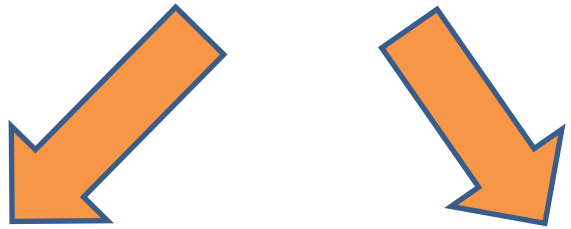
(B + A) are alternative pathway for glucose oxidation.

صدفهم مش أنهم يعطوك طاقة (صدفهم تصنيع (Pentosis) اللي جمعه الـ (metabolic intermediate) أو الـ (NADPH)

FATE OF GLUCOSE

Oxidation احرقه لو محتاج		Storage أو اخزنه في الثلاجات	Conversion أو احوله لحاجات
Major pathway	Minor pathway		
Glycolysis ↓ Pyruvate ↓ Acetyl Co-A ↓ Krebs cycle ↓ R. chain	- pentose phosphate pathway *Or* - Uronic acid pathway	As glycogen by glycogenesis in Liver and Muscles	e.g. - To lipid by lipogenesis or - To ptn

Pentose phosphate pathway
(Hexose Monophosphate pathway or HMP-pathway)



The source of **ribose phosphate** for synthesis of RNA and DNA

NADPH is a major product of the pentose phosphate pathway in all cells

- The pentose phosphate pathway is a cytosolic pathway present in all cells
- This pathway is active in the cytosol of many cells e.g. liver, adipose tissues, adrenal cortex, ovaries, testis, RBCs and retina.

- **The pentose phosphate pathway is divided into:**

أنت بتبلش هون ←
عشان ينتج عندك: (G-6-P)
(CO2 / 2 NADPH / R-5-P)
(irreversible) العملية

Irreversible redox stage (Oxidative phase), which yields both NADPH and pentose phosphates.

one molecule of glucose (G6P) gives:
- **1 molecule of CO2**
- **2 molecules of NADPH**
- **1 molecule of ribulose 5- phosphate**

Keto-Ribo-sugar

Reversible interconversion stage (non-oxidative phase), in which excess pentose phosphates are converted into glycolytic intermediates (عشان يعطيك توازن)

يعني بالخطوة الأولى أنت بتعطي أحد النواتج المطلوبة (NADPH)

Oxidative phase steps

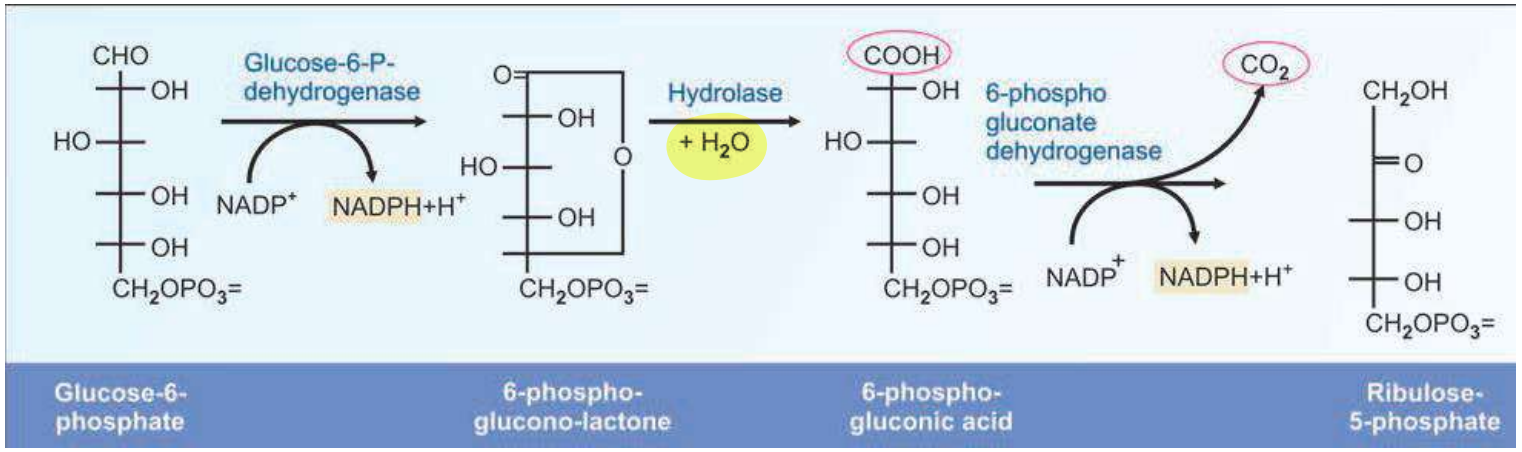
1. Glucose 6-P is oxidized by NADP+ dependent glucose 6-P dehydrogenase → 6-phosphogluconolactone
   - Rate limiting step

6-phosphogluconolactone

2. Lactone is hydrolyzed by gluconolactone hydrolyase → 6-phosphogluconic acid

3. *Decarboxylation of 6-phosphogluconic acid catalyzed by 6-phosphogluconate dehydrogenase →
   - 1 x Ribulose 5-P
   - 2 x NADPH+H
   - 1 x CO2

(بتحليهم بالخطوة 3 إلا واحد منه (NADPH



We start with 3 Glucose 6-P to obtain 3 ribulose 5-P to enter non-oxidative phase

(Glycolytic intermediate) هرفنا هون نعمل

Non-Oxidative phase steps

(3 Ribulose-5-P بـ اصنا بنبلش)

All reactions are reversible

1. Ribulose 5-P is a substrate for 2 enzymes:
   - Epimerase → xylulose 5-P (x2)
   - Isomerase → ribose 5-P → product

2. Transketolase reaction
   - Tansketolase is a thiamine pyrophosphate dependent enzyme
   - It transfers 2 carbon units (with a keto group) from xylulose 5-P to ribose 5-P forming:
     - Sedoheptulose 7-P
     - Glyceraldehyde 3-P
   - In thiamine deficiency, transketolase activity is ↓

$5^{K}C + 5^{A}C \rightleftharpoons 3C + 7C$ (3C: aldose, 7C: Ketose; 2C: Ketogroup)

aldose عشانه انت نقلت (Ketogroup الـ)

3. Transaldolase* enzyme: transfers 3 carbons (with keto group) from sedoheptulose 7-P to glyceraldehyde 3-P forming:
   - fructose 6-P
   - eythrose 4-P

$7^{K}C + 3^{A}C \rightleftharpoons 4C + 6C$ (4C: aldose, 6C: Ketose; 3C: Ketogroup)

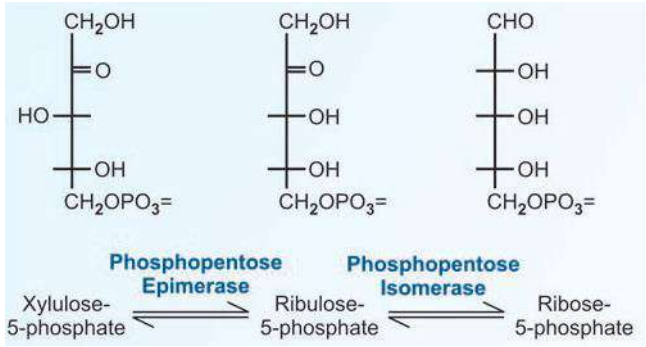
4. Transketolase reaction: transfers 2 carbons from the remaining 3rd xylulose 5-P to eythrose 4-P forming:
   - fructose 6-P
   - glyceraldehyde 3-P

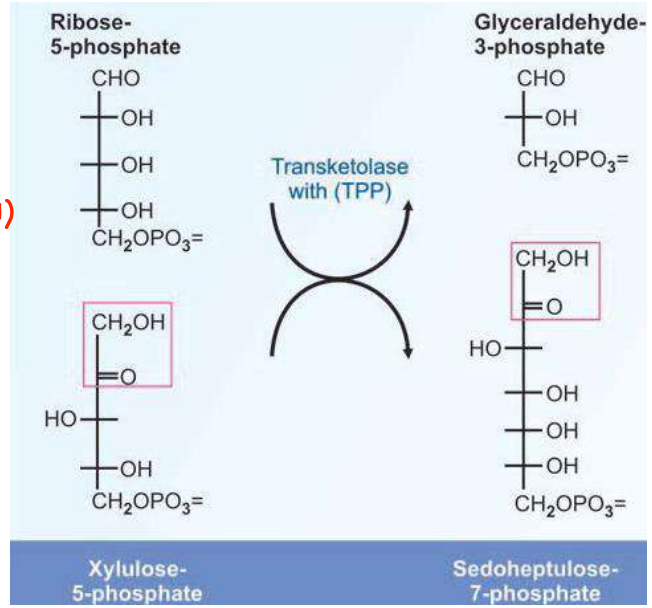
(اللي ضلت بالتفاعل الأول)

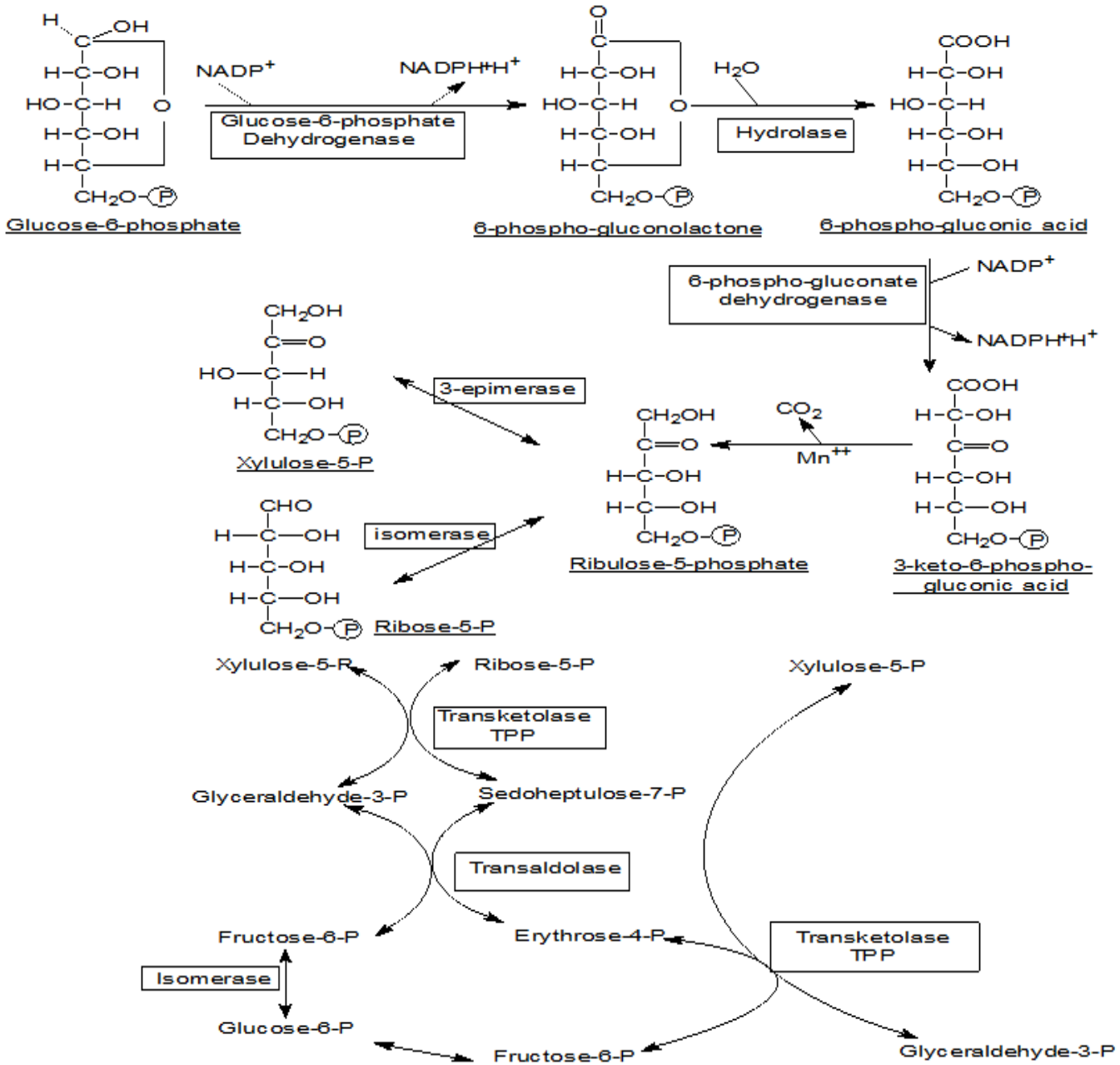
$5^{K}C + 4^{A}C \rightleftharpoons 3C + 6C$ (3C: aldose, 6C: Ketose; 2C: Ketogroup)

5. The produced 2 fructose 6-P are converted to 2 glucose 6-P

+ Glyceraldehyde







We started with 3 x Glucose 6-P and obtained 2 x fructose 6-P + 1 x glyceraldehyde 3-P

Remaining 3 carbons are released as CO2

Glyceraldehyde 3-P is one of the products of 3 important pathways:

- Glycolysis
- Gluconeogenesis
- HMP pathway

Regulation of HMP pathway:

- **Oxidative phase**

- Is controlled by the level of NADP+

- The first reaction (catalyzed by G6PD) is a **rate limiting step** and is **inhibited by ↑ NADPH**

  - **Induction:**

- CHO feeding → ↑ insulin → induction of synthesis of both dehydrogenases leading to **activation** of HMP Shunt

- Fasting → ↓ insulin → repression of synthesis of both dehydrogenases, so HMP is **inhibited**

Non-oxidative phase

- Regulation of this phases allows flexibility as to fulfill needs of various organs for ribose 5-P and NADPH (حسب أنت وين وشو بتحتاج منه الإثنين)
  - If needs for NADPH and ribose 5-P are balanced (e.g. liver)
    - » HMP will proceed through oxidative phase
    - » Formed ribose 5-P will not continue in non-oxidative part

(Ribose-5-P) أنا حققت أهدافي + مابدي أخسر أحد أهدافي

  - If more ribose 5-P is needed (e.g. muscle)
    - » This will be provided only by reversibility of non-oxidative phase

(NADPH) لو أخذ ناطا بالعكس بتعطيك (Ribose-5-P) ومافي داعي لـ (oxidative) دائه مابيخ

  - If more NADPH is needed (e.g. RBCs)
    - » NADPH is produced in oxidative phase → must get rid of excess ribose 5-P (otherwise will feedback inhibit further NADPH production)
    - » The non-oxidative phase gets rid of resultant ribose 6-P

Importance of HMP shunt:

- Important in cells which have a high rate of nucleotide synthesis (bone marrow, skin, gastric mucosa) or need NAPDH:

1. **Formation of pentose phosphates that are used in**
   - Nucleic acid synthesis: DNA, RNA
   - Coenzymes: NAD+, FAD, NADP
   - High energy compounds: ATP, GTP and UTP
   - 2nd messengers: cAMP, cGMP
   - Some vitamins: B2 , B12

2. **Major source of NADPH which is used for**
   - Biosynthesis of FA, cholesterol
   - Lens of eye: **maximum concentration of NADPH, preserves transparency**
   - Bactericidal action
   - **RBC membrane integrity**
   - Coenzyme of cytochrome p450 (v imp in detoxification of harmful substances in liver)

Dietary ribose cannot be utilized by tissues because there is no specific kinase to convert it to ribose-5-phosphate (dietary ribose is excreted in urine)

NADPH for RBC membrane integrity

- NADPH is required to:
  - Keep glutathione in reduced state (via glutathione reductase where NADPH is coenzyme)
    - » Reduced glutathione serves as sulfhydryl buffer → maintains cysteine residue of Hb in reduced state
    - » Plays imp role in detoxification of H_2O_2 (via glutathione perioxidase), which:
      - ↓ RBC lifespan
      - ↑ rate of oxidation of Hb to methemogolbin (cannot carry oxygen)

If H_2O_2 is high →

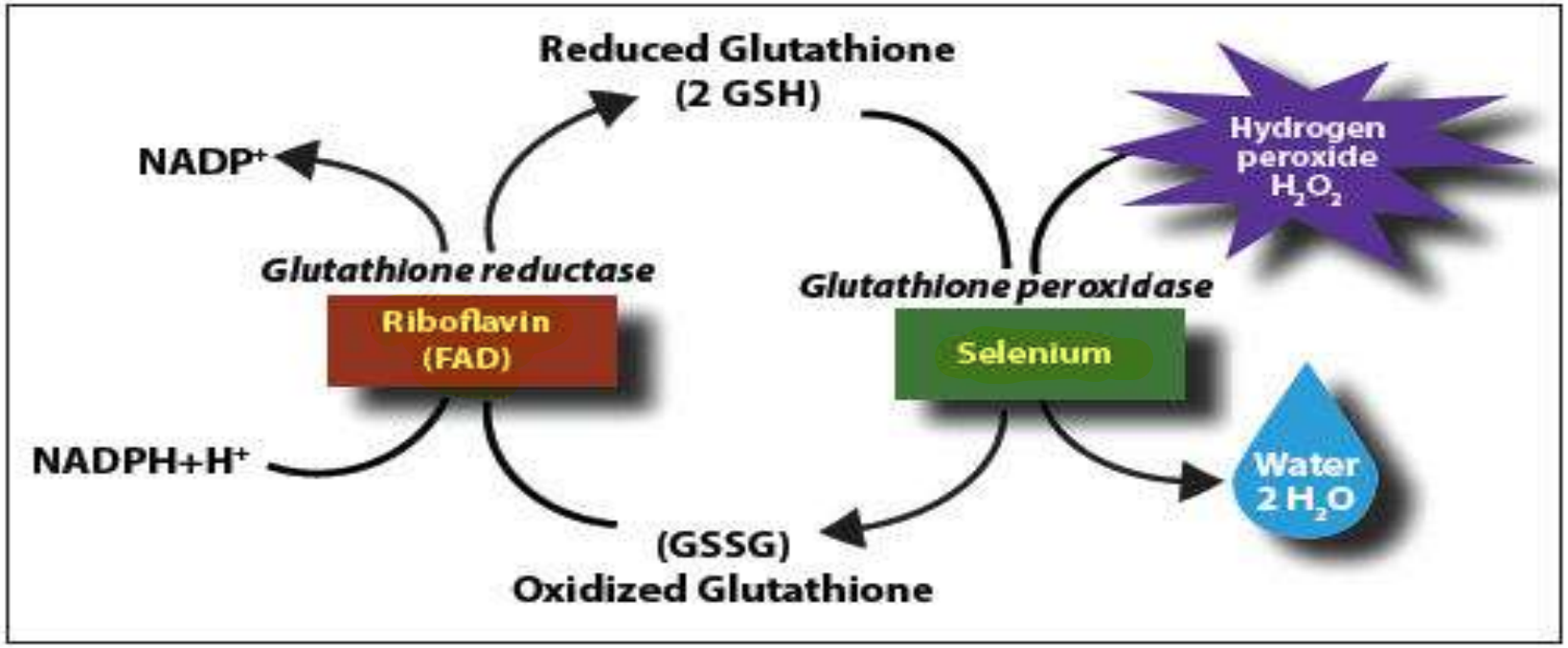
  - Keep ferrous iron of Hb in reduced state:
    - » Prevents accumulation of methemoglobin

→ NADPH, glutathione, glutathione reductase cooperate to preserve integrity of RBC membrane

HMP pathway is the main source of $NADPH+H^+$ required for the reaction of many reductases and hydroxylases.

A- Reductases use of $NADPH +H^+$

- -Glutathione reductase and glutathione peroxidase which are important for removal of H_2O_2. H2 O_2 is powerful oxidant that produce damage of cellular DNA, proteins and phospholipids.

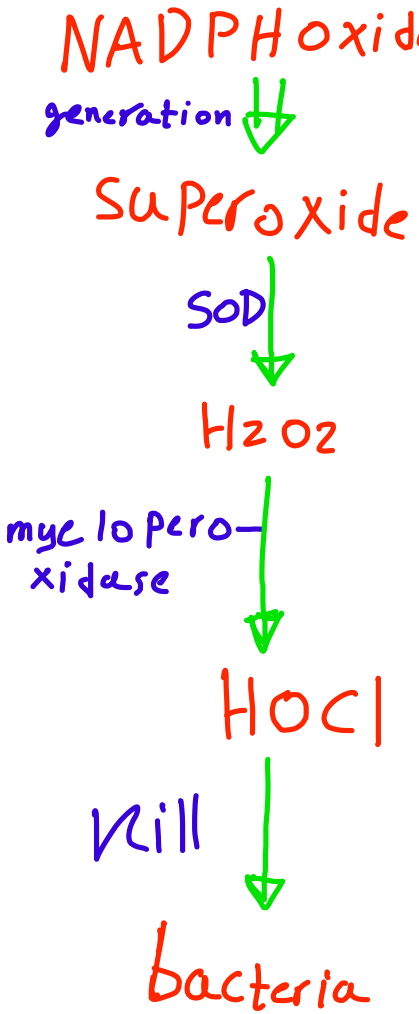


A- Reductases use of NADPH +H^+

- Reductase for fatty acids synthesis
- Retinal reductase (rhodopsin cycle) → vision
- Folate and dihydrofolate reductase
- HMG –CoA reductase for cholesterol synthesis

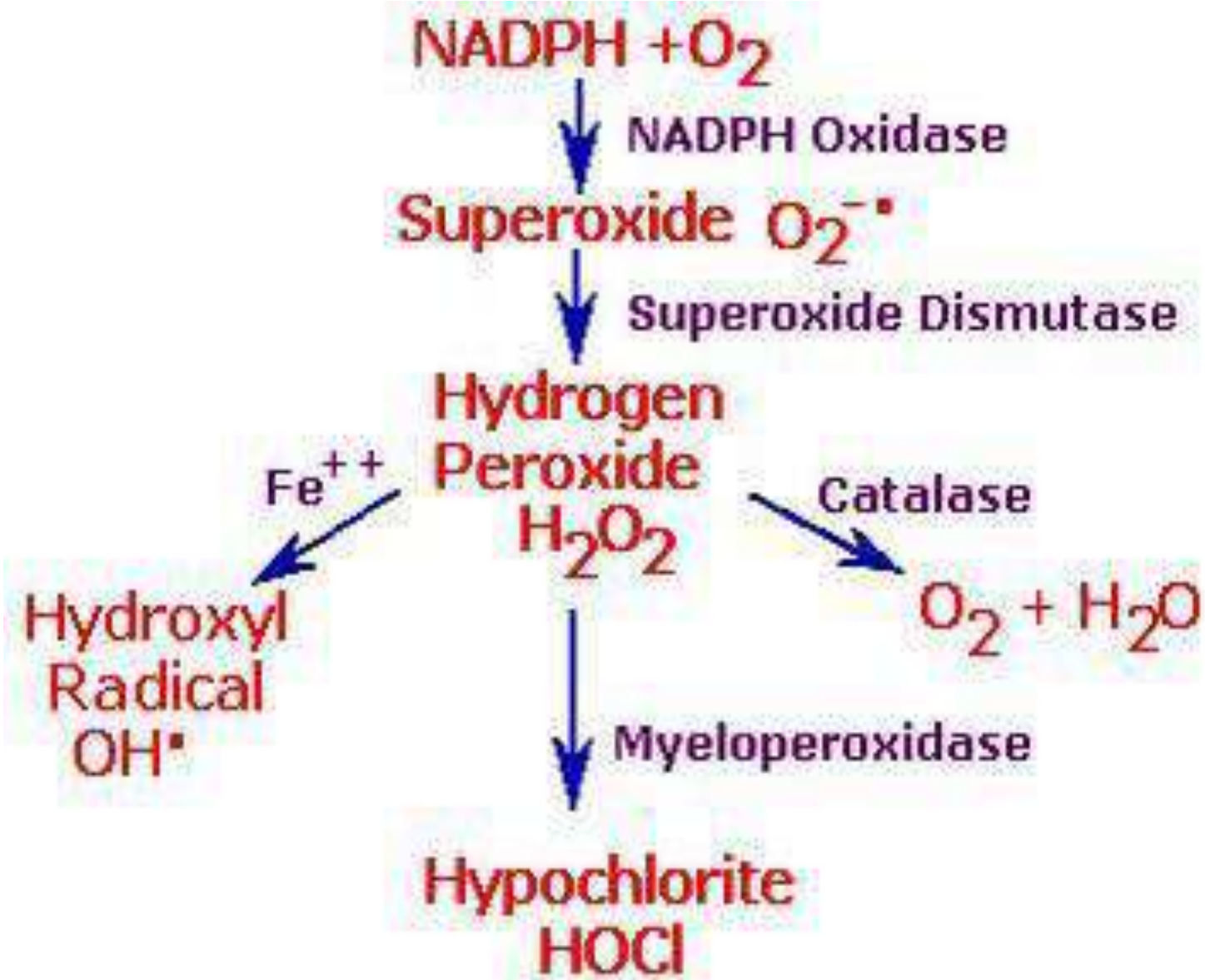
B- Hydroxylases use of NADPH+H^+

- - Hydroxylases of steroid synthesis
- - Phenyl alanine hydroxylase
- - Tryptophan hydroxylase
- - Synthesis of calcitriol



NADPH oxidase:

- It is present in cell membranes of phagocytic cells, and is responsible for generation of superoxide
- Superoxide is converted to H2O2 (by superoxide dismutase "SOD")
- H2O2 is converted to hypochlorus acid (HOCL) by myeloperoxidase that kills the bacteria
- Genetic deficiency of NADPH oxidase produces **chronic granulomatosis**, this disease is characterized by severe and persistent chronic pyogenic infections


NADPH +O2
NADPH Oxidase
Superoxide O2-•
Superoxide Dismutase
Hydrogen Peroxide H2O2
Fe++
Catalase
Hydroxyl Radical OH•
O2 + H2O
Myeloperoxidase
Hypochlorite HOCl

Comparison of HMP pathway and glycolysis

	HMP	Glycolysis
Complexity	Multi-cyclic process	Simple, linear
Oxidation	Early in the pathway	Later in the pathway
CO2	Produced (glucose molecule enter in) لكل	Not produced (Krebs cycle) بصير بال
ATP	Not generated	Generated (6-8 ATP)
Riboses	Are generated	Not generated
Dehydrogenase	NADP-specific	NAD-specific

الأهم

Clinical aspects of HMP pathway

- Congenital hemolytic anemia (favisim)
  - Deficiency of G6PD enzyme, x-linked condition
  - Results in ↓ level of NADPH → ↓ concentration of reduced glutathione
  - → H2O2 ↓ life span of RBCs, and ↑ rate of oxidation Hb into methhemoglobin (cannot carry oxygen)
  - Manifested only after intake of certain oxidant drugs (primaquine, fava beans) → distort RBC membrane resulting in hemolysis
  - Urine turns black, jaundice develops and Hb levels fall (sometimes fatal)
  - **Treatment:** avoid cause, regular RBC transfusions, antioxidants

B. Uronic Acid Pathway (Glucuronic Acid Pathway)

- **Definition:**

  It is an alternative minor oxidative pathway for glucose involving the formation of:

  - glucuronic acid in active form (UDP- glucuronic acid) as intermediate

- **Site:** Cytosol of liver mainly (and kidney) إلى حد أقل

Importance of uronic acid pathway:

(1) Formation of UDP–glucuronic acid (the active donor of glucuronic acid) for:

بهـاء

A-Conjugation with many compounds, to make them more soluble before excretion, for example:

- Glucouronic acid is highly polar so it can be conjugated with less polar compounds
  - Steroid hormones and their metabolites
  - Bilirubin, which is excreted in bile in the form of bilirubin diglucuronide (direct bilirubin)
  - Detoxification reactions e.g. phenols, aspirin, morphine,…

- In humans, development of this conjugation mechanism takes several days to 2 weeks after birth

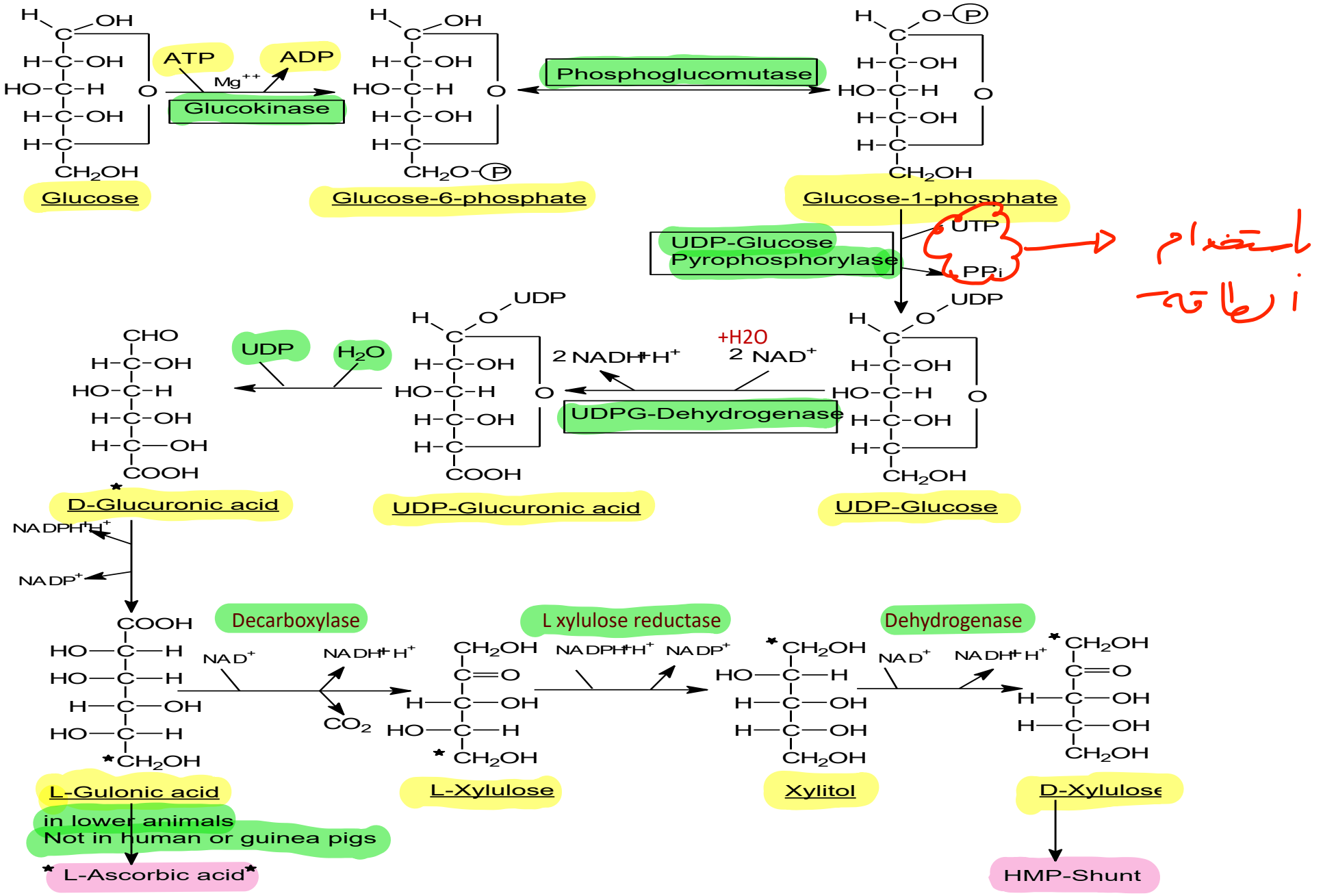
Physiologic jaundice is caused by a combination of:

- increased bilirubin production secondary to accelerated destruction of erythrocytes
- decreased excretory capacity secondary to low levels of ligandin in hepatocytes
- **low bilirubin conjugation with Glucouronic acid**

- B-Synthesis of glycosaminoglycans (GAGs) e.g. heparin and chondroitin sulfate

(2) Formation of vitamin C (L-ascorbic acid): This occurs in some lower animals (not in human or guinea pigs because the enzymes needed to convert L-gulonic acid to L- ascorbic acid are not found in our tissues)

(3) It is converted to L- and then D-xylulose which enters HMP pathway


Glucose
ATP
ADP
Mg++
Glucokinase
Glucose-6-phosphate
Phosphoglucomutase
Glucose-1-phosphate
UDP-Glucose Pyrophosphorylase
UTP
PPi
باستخدام طاقة
UDP-Glucose
+H2O
2 NADH+H+
2 NAD+
UDPG-Dehydrogenase
UDP-Glucuronic acid
UDP
H2O
D-Glucuronic acid
NADPH+H+
NADP+
Decarboxylase
NAD+
NADH+H+
CO2
L-Xylulose
L xylulose reductase
NADPH+H+
NADP+
Xylitol
Dehydrogenase
NAD+
NADH+H+
D-Xylulose
L-Gulonic acid
in lower animals
Not in human or guinea pigs
L-Ascorbic acid
HMP-Shunt

Essential pentosuria:

- It is an inborn error of metabolism caused by **deficiency of L-xylulose reductase** which converts L-xylulose to xylitol

- L-xylulose is not metabolized and is excreted in large amounts in urine (the L-form of sugars are not metabolized) ((بتحوف كتير (Pentose) في الـ (Uria))

- It is a harmless condition needs no treatment

Non glucose metabolism

Metabolism of fructose

- Fructose transport and metabolism are insulin **independent**
  - fructose does not stimulate insulin secretion
  - → less tightly regulated c.f. glucose

- Only few tissues can metabolize fructose (**liver**, kidney, intestinal mucosa, adipose tissue **BUT NOT brain**)

على عكس

- Renal threshold for fructose is low → more radially excreted in urine c.f. glucose

- Most fructose is ultimately converted to glucose (e.g. 50% converted to glucose in intestines) (عشان نه هيك الـ (Glucose) والـ (fructose) كثير مترابطات)

Fructose metabolism steps

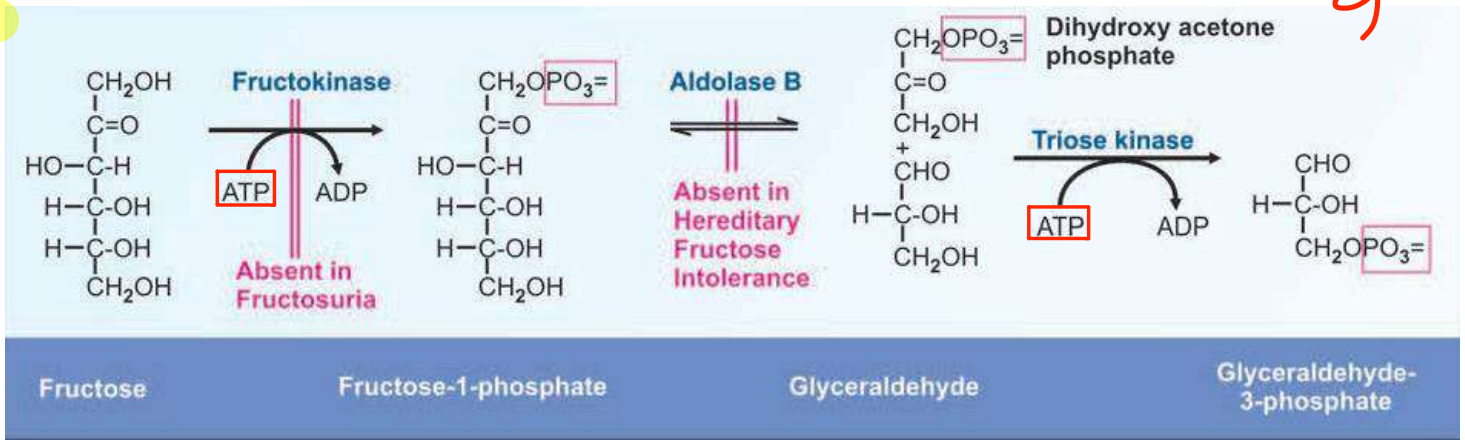
- Step 1: phosphorylation to form fructose 1-P
  - *Rate limiting step*
  - Catalyzed by fructokinase (insulin independent)
  - Rate depends primarily on fructose concentration
- Step 2: cleavage to DHA-P and glyceraldehyde
  - Aldolase B catalyzes this step
- Step 3a: glyceraldehyde is then phosphorylated
  - To glyceraldehyde 3-P
  - Triose kinase catalyzes this **step (ATP is used)**
- Step 3b: DHAP is converted to glyceraldehyde 3-P
  - Triose phosphate isomerase catalyzes this step

The 2 trioses can be:

- metabolized by glycolytic pathway
- Combined to form fructose 1,6 bi-P (by aldolase) reversible

→ **Most dietary fructose is converted to glucose by gluconeogenesis**

2(ATP) نضر



Fructose in organs

- Absorption of fructose is relatively slow:
  - Fructose is used as a sweetener for drinks in diabetics it causes little rise in blood glucose

(يتم استخدامه بكميات قليلة لأنه إذا كان كثير كلّه بيتحول إلى (Glucose

- Free fructose is mainly metabolized by the liver

- Free fructose is present in large quantities in seminal vesicles
  - Energy of sperms derived from fructose
  - Fructose is secreted from seminal vesicles → estimation of fructose in semen is imp

Hereditary وراثي fructose intolerance

- Inborn error of fructose metabolism manifested by vomiting and loss of appetite
- **Defect:** Aldolase B (therefore fructose 1-P cannot be metabolized)
- Accumulation of fructose 1-P in liver →
  - fructose induced hypoglycemia during fasting
    - due to inhibition of **glycogen phosphorylase** leading to accumulation of glycogen

Fructosuria:
- Benign حميد metabolic defect
- Due to deficiency of fructokinase
- Only abnormality is fructose excretion in urine

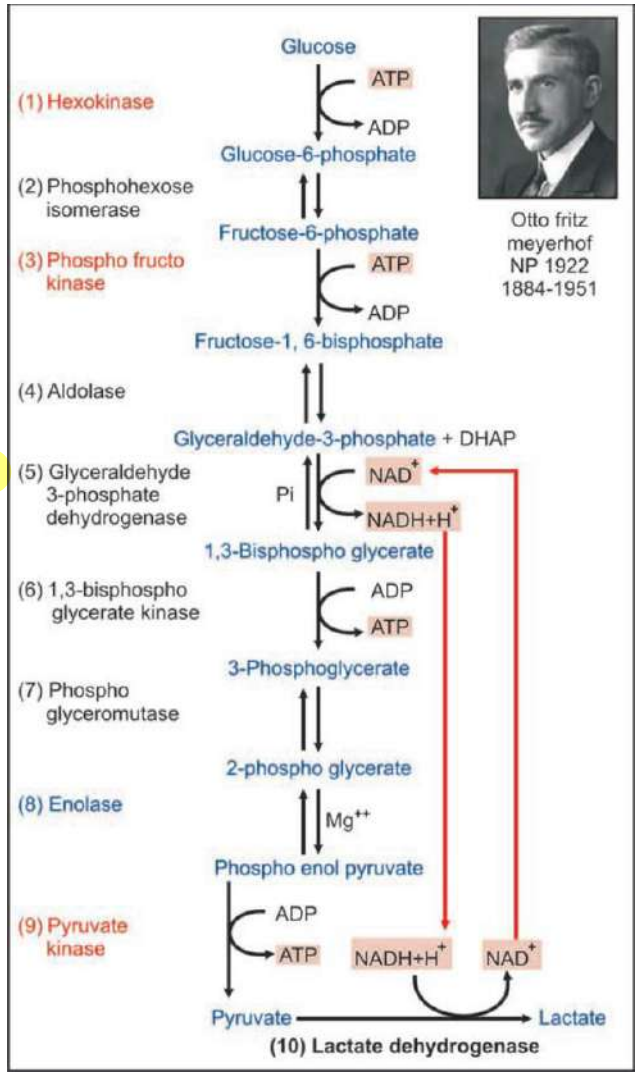
F-1-P is inhibitor for glycogen phosphorylase

Important facts about fructose

- Diabetes
  - Oxidation of fructose is independent on insulin or glucose level
  - → so in diabetic patients, fructose metabolism is not affected
  - In small amounts, fructose could be useful for diabetics
  - Large amounts of fructose can severely damage liver due to depleting ATP stores/ or it is converted to glucose

- Fructose is atherogenic (تصلب الشرايين)
  - Glucokinase and phophofructokinase bottlenecks in glucose metabolism not present (ما بتوقف زي الجلوكوز لو زاد)
  - Fructose rapidly enters tissues →
    - Enhanced FA synthesis
    - ↑ serum triglycerides and LDL cholesterol (سيء)

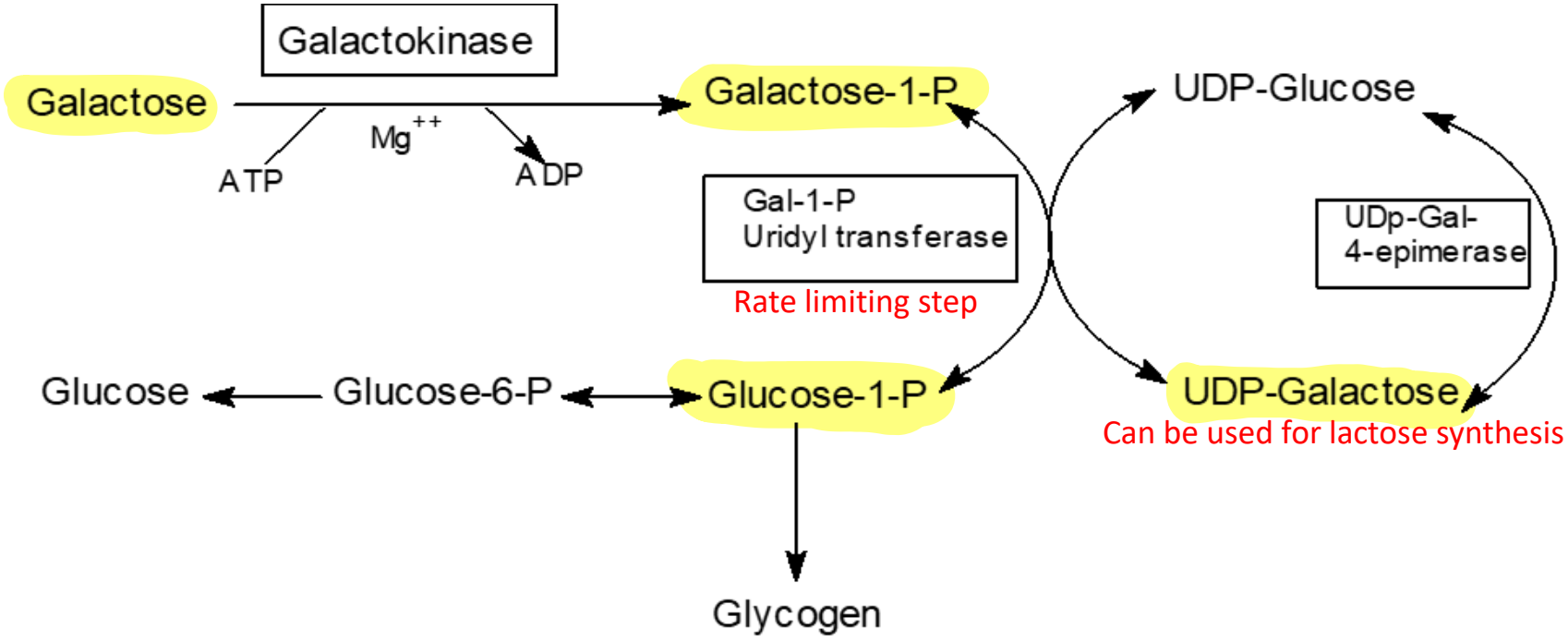
In extrahepatic tissues fructose is converted to fructose 6-P by hexokinase
- Hexokinase has a very low affinity for fructose (higher km) compared to glucose
- So it is not a significant pathway for fructose metabolism, unless it is present in very high concentration in blood



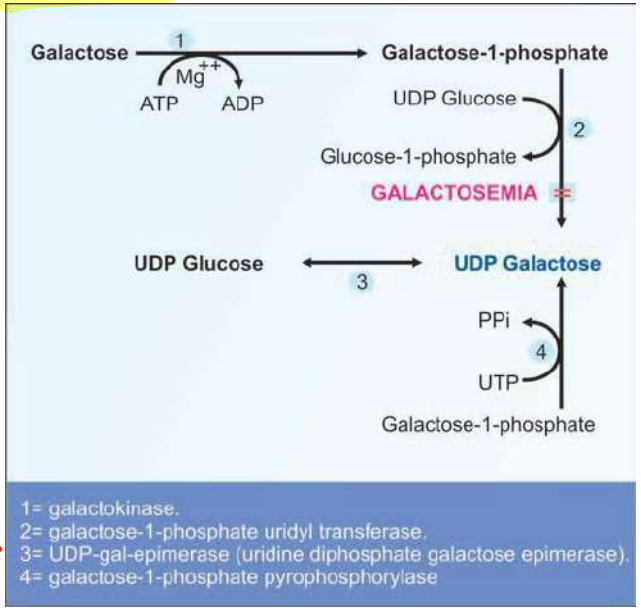
Galactose metabolism

- Most galactose comes from lactose (principle sugar in milk)
- Lactose is hydrolyzed to galactose and glucose by **lactase** in intestines
- Following absorption, galactose is transported to liver and converted to glucose
- Galactose is important in:
  - Glycolipids
  - Glycoproteins
  - Lactose during lactation الرضاعة

Steps to convert galactose to glucose



- Reaction is reversible
- If dietary supply of galactose is deficient, glucose can still be epimerized to galactose



If we need to produce lactose in mammary tissues:

UDP glactose + glucose → lactose (enzyme is lactase synthase)

مهم

* الأم المرضعة مش بالضرورة توخذ كثير (Galactose) لأنها بتقدر تحول منه (Glucose → Galactose)

Galactosemia: (تراكم الـ Galactose في الدم)

- Congenital disease caused by deficiency of:
  - **Galactokinase (mild disease)**
  - **Galactose-1-P uridyl transferase** or **UDP-Gal epimerase (sereve disease)** (most common and sever)

- The deficiency of **galactose-1-P uridyl transferase is more common**

It is characterized by:

1) **Galactosemia** after the intake of galactose or lactose

2) **Galactosuria**

Due to glactokinase is indirectly inhibited or absent

إعتام عدسة العين غباش

3) **Cataract in infancy** (Opacity in eye lens that looks white in color)

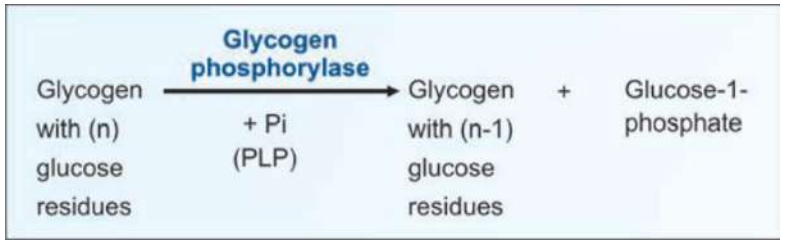
- *Cataract is due to:*

  Accumulation of galactose in the eye lens which is reduced to its alcohol galactitol by the enzyme **aldose reductase** → increase osmotic pressure → Over-hydration of lens → Denaturation of the natural translucent lens proteins → Cataract

لأنه بجذب السحب من وراه شفافة

4) Deficiency of the enzyme galactose 1- phosphate uridyltransferase leads to accumulation of galactose 1-phosphate and **depletion of liver phosphate** needed for glycogenolysis and this leads to attacks of hypoglycemia after galactose or lactose feeding

(liver enlargment) بجعل كبدته

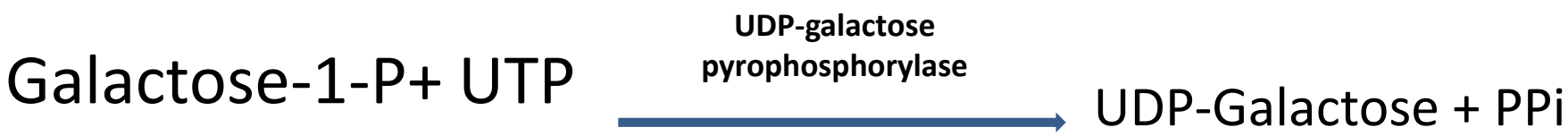


5) **Liver cell failure:** In uridyl transferase deficiency, increases Galactose-1-P which leads to depletion of Pi. So, no ATP formation in liver leading to liver cell failure

- Jaundice
- Mental retardation التخلف

- Galactosemia treatment must be started early in life: the baby is fed lactose free milk formula and galactose free diet after weaning الفطام

- Later on, ”at 15 years” children who have Galactose-1-P uridyl transferase deficiency can utilize galactose normally due to the development of the enzyme **UDP-galactose pyrophosphorylase** which can replace the Galactose-1-P uridyl transferase



- Children are able to form UDP-Gal from UDP-Glucose by the epimerase, which explain their normal growth and development.

Read from book (DM Vasudevan, Textbook of Biochemistry)

- Paragraph on Polyol pathway (chapter 10, page 119)

عليه سؤال بالإمتحانه (هيو بالسلايد القادم ☺)

سوال بالہ متحانہ

POLYOL PATHWAY OF GLUCOSE

Sorbitol is very poorly absorbed from intestine. It involves the reduction of glucose by aldose reductase to sorbitol, which can then be oxidized to fructose. This would amount to the inter-conversion of glucose to fructose (Fig. 10.8).

Glucose when converted to sorbitol, cannot diffuse out of the cell easily and gets trapped there. Sorbitol is normally present in lens of eyes. But in **diabetes mellitus**, when glucose level is high, the sorbitol concentration also increases in the lens. This leads to osmotic damage of the tissue and development of **cataract**. Galactitol also causes cataract (see under galactose metabolism).

Fructose is present in semen in large quantities. It is produced by the polyol pathway. The polyol pathway is active in brain and fructose is seen in CSF. This pathway is inactive in liver.

الجلوكوز يتحول إلى فركتوز عن طريق (Polyol pathway)

(POLYOL PATHWAY)

Integration of metabolism 23/8/2023

- Topics (from Textbook of Biochemistry for Medical Students, 6th edition, chapter 8, page 84-89):
  - **Types of metabolic pathways (10 min) → 1 student**
  - **Metabolic profile of organs (20 min) → 2 students**
    - Intro/ Brain, skeletal muscles (10 min)
    - Adipose tissue, liver, cardiac muscle (10 min)
  - **Effect of exercise on metabolic profile (10 min) → 1 student**
  - **Metabolic adaptations during starvation (10 min) → 1 student**
  - **Key enzymes under well fed, fasting and starvation conditions (table 8.4; 10 min) → 1 student**