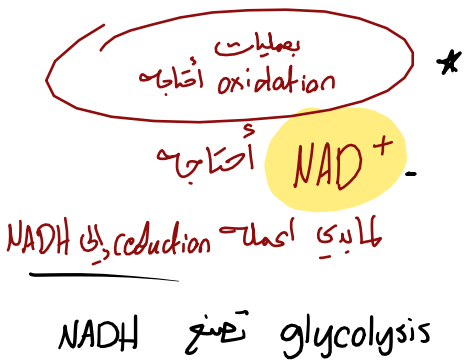
Pentose phosphate pathway and NADPH

goal to produce NADPH

https://chatgpt.com/share/6a105569-4630-83eb-8a03-d804a1bb0dbf

overview might help



The pentose phosphate pathway

HMP - shunt

- also called the hexose monophosphate shunt or 6-phosphogluconate pathway
- It occurs in the **cytosol** of the cell.
- It consists of two, irreversible oxidative reactions, followed by a series of reversible sugar-phosphate interconversions
- **No ATP** is directly consumed or produced in the cycle.
- Carbon one of glucose 6-phosphate is released as CO_2, and two NADPH are produced for each glucose 6-phosphate molecule entering the oxidative part of the pathway.

decaroxylation

(irreversible)

G6P → 2 NADPH

1 Ribulose - 5 -P

- The pathway provides a major portion of the body's NADPH, which functions as a biochemical reductant. (reducing agent)

steriodal اي اشي -
NADPH احتاجه

The pentose phosphate pathway

لازم تكون ماكلين
Fed state
(insulin)

- Ribose 5-phosphate is required for the biosynthesis of nucleotides and provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or the degradation of structural carbohydrates in the body.

- The oxidative portion of the pentose phosphate pathway occurs in:

  - **Liver** and **lactating mammary glands**, which are active in the biosynthesis of fatty acids
  - **Adrenal cortex**, which is active in the NADPH-dependent synthesis of steroids
  - **Erythrocytes**, which require NADPH to keep glutathione reduced.

oxidized NADPH → $NADP^+ + H^+$

during metabolism radicls are produced
highly reactive

radicals يحول
لأشي آمن لما
oxidatio تعمله

RBCs

كل عملية
reduction
لازم
يقابلها
oxidation

NADPH is required in large quantities in all of the following except:

1. ○ Liver
2. ○ Brain
3. ○ Erythrocytes
4. ☒ Adrenal cortex
5. ○ Lactating mammary glands

2

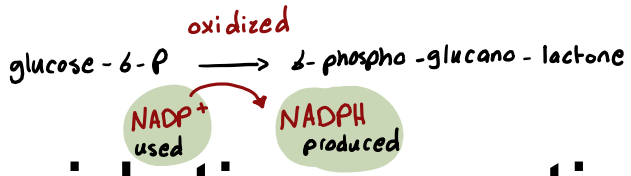
Next

cyclic ester

lactone

cyclic amide

lactane



Irreversible oxidative reactions

https://youtu.be/eXXpUxg9vn4?si=SwNUNgg2hfrdiqM1 (easy explanation)

"irreversible"

Dehydrogenation of glucose 6-phosphate (the rate limiting step)

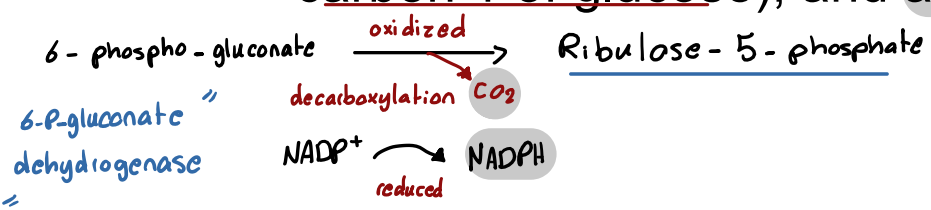
- **Glucose 6-phosphate dehydrogenase** (G6PD) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone in a reaction that is specific for NADP as its coenzyme which produce one molecule of NADPH
- The enzyme is competitively inhibited by NADPH (product) so its regulated by the NADP/NADPH ratio in the cell
- Insulin enhances G6PD gene expression (well-fed state)

- stimulate it -

Formation of ribulose 5-phosphate

H_2O → H^+

- Phosphogluconolactone is hydrolyzed by **6-phosphogluconolactone hydrolase** (irreversible and not rate-limiting). to give 6-phospho-gluconate
- The subsequent oxidative decarboxylation of 6-phosphogluconate is catalyzed by **6-phosphogluconate dehydrogenase** (irreversible) to produce a pentose sugar-phosphate (ribulose 5-phosphate), CO_2 (from carbon 1 of glucose), and a second molecule of NADPH



hich enzyme does not use NAD+ as cofactor during its reaction:

1. ○ Glyceraldehyde 3-P dehydrogenase ✗
2. ○ Pyruvate dehydrogenase ✗
3. ○ Lactate dehydrogenase ✗
4. ○ Glucose 6-P dehydrogenase
5. ○ Malate dehydrogenase ✗

4

Next

it uses $NADP^+$ → NADPH

Which of the following limits step in oxidative reaction of pentose phosphate pathway

الاجابة: dehydrogenation of glucose 6-phosphate

Reversible nonoxidative reactions

- The nonoxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids. These reactions catalyze the interconversion of three-, four-, five-, six-, and seven- carbon sugars.

- These reversible reactions permit ribulose 5-phosphate to be converted either to ribose 5-phosphate or to intermediates of glycolysis-fructose 6- phosphate and glyceraldehyde 3-phosphate.

- In reductive biosynthetic reactions, there is a great need for NADPH, so transketolase (which transfers two-carbon units) and transaldolase (which transfers three-carbon units) convert the ribulose 5-phosphate to glyceraldehyde 3-P and fructose 6-P, which are intermediates of glycolysis

- At increased demands for ribose to synthesize nucleic acids, the non-oxidative reactions can provide the biosynthesis of ribose 5-P from G-3-P and F-6-P in the absence of the oxidative steps

Which of the following may result from the nonoxidative reactions of the pentose phosphate pathway?

A. Glyceraldehyde 3-phosphate

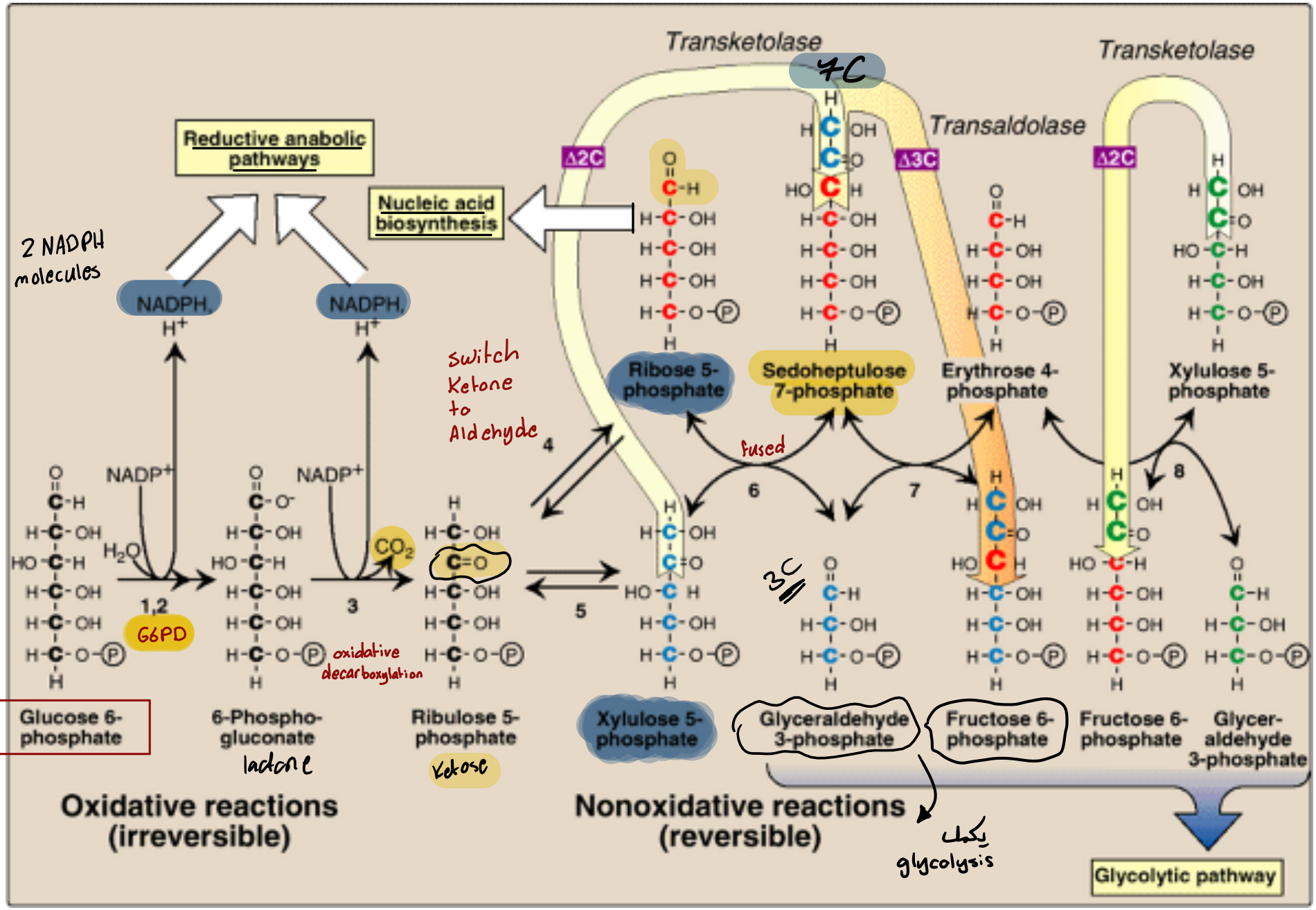
B. Fructose 6-phosphate

C. Ribose 5-phosphate

D. All of the above

Correct answer: D. All of the above

جابت ايش الانزيم بال ppp يلي بكون reversible
الجواب transketolase اتوقع


Transketolase
Transketolase
Transaldolase
Reductive anabolic pathways
Nucleic acid biosynthesis
2 NADPH molecules
NADPH, H+
NADPH, H+
NADP+
NADP+
H2O
CO2
1,2
G6PD
3
oxidative decarboxylation
4
5
6
7
8
fused
switch Ketone to Aldehyde
Δ2C
Δ3C
Δ2C
4C
3C
Ribose 5-phosphate
Sedoheptulose 7-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate
Glucose 6-phosphate
6-Phospho-gluconate
lactone
Ribulose 5-phosphate
Ketose
Xylulose 5-phosphate
Glyceraldehyde 3-phosphate
Fructose 6-phosphate
Fructose 6-phosphate
Glycer-aldehyde 3-phosphate
Oxidative reactions (irreversible)
Nonoxidative reactions (reversible)
يكمل glycolysis
Glycolytic pathway

NADPH

Extra Ⓟ group

- The coenzyme NADP differs from NAD only by the presence of a phosphate group (PO4-) on one of the ribose units

- The steady-state ratio of NADP/NADPH in the cytosol of hepatocytes is approximately 0.1, which favors the use of NADPH in reductive biosynthetic reactions

low

$\frac{NADP^+}{NADPH} = \frac{1}{10}$

reduced form

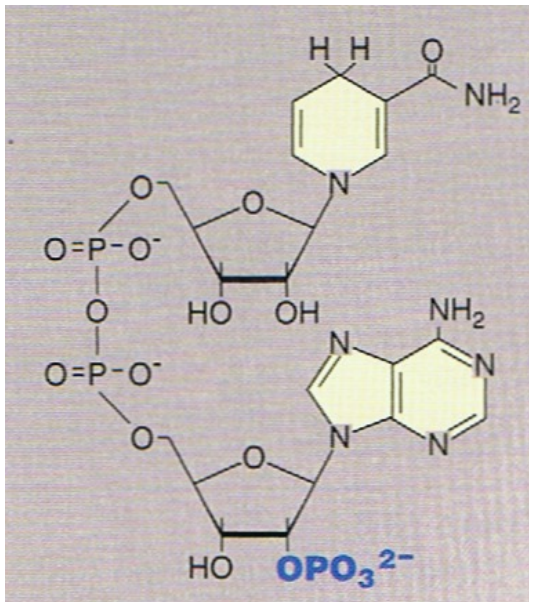
- This contrasts with the high ratio of NAD/NADH approximately 1000 in the cytosol of hepatocytes, which favors an oxidative role for NAD

$\frac{NAD^+}{NADH} = \frac{1000}{1}$ oxidized form

Coenzyme system	Major form present	Main role
$NADP^+$/NADPH	NADPH abundant	Reductive biosynthesis
NAD^+/NADH	NAD^+ abundant	Oxidative energy production

A simple memory trick:

- **NADPH helps build**
- **NAD^+ helps break down**



- p&p -

Uses of NADPH

H_2O_2

A. Reduction of hydrogen peroxide

protection against reactive oxygen species (radicals)

- Hydrogen peroxide is formed from the partial reduction of molecular oxygen (produce radicals)
- It is formed continuously as by-products of aerobic metabolism, through reactions with drugs and environmental toxins, or when the level of antioxidants is diminished, all creating the condition of oxidative stress.
- These highly reactive oxygen intermediates (radicals) can cause serious chemical damage to DNA, proteins, and unsaturated lipids, and can lead to cell death.
- The cell has several protective mechanisms that minimize the toxic potential of these compounds.

Uses of NADPH

Keeps glutathione reduced

A. Reduction of hydrogen peroxide

no protective properties

H_2O_2
Hydrogen peroxide → detoxified by glutathione peroxidase

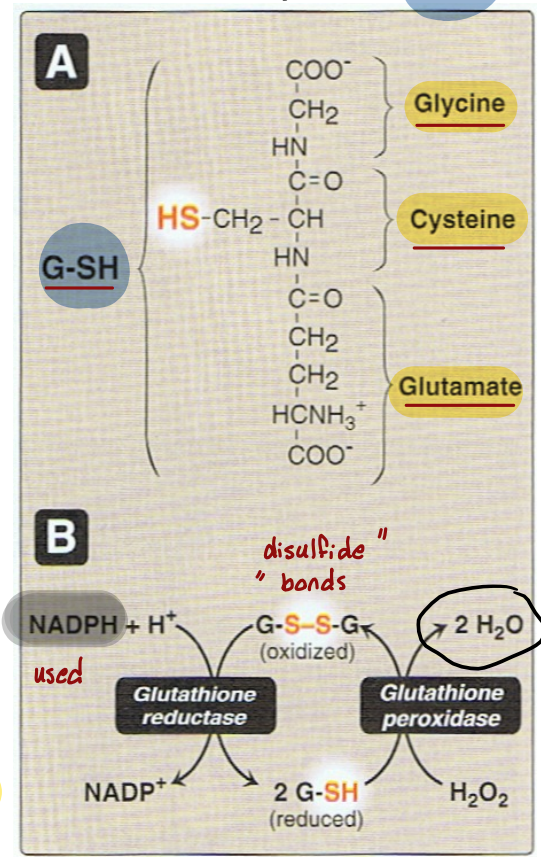
Reduced glutathione (GSH) → oxidized glutathione (GSSG)

glutathione reductase + NADPH regenerate GSH

- Enzymes that catalyze antioxidant reactions:

water > H_2O_2 ↓

- Reduced glutathione, a tripeptide-thiol present in most cells, can chemically detoxify hydrogen peroxide that is catalyzed by the selenium-requiring glutathione peroxidase, forms oxidized glutathione, which no longer has protective properties



- The cell regenerates reduced glutathione in a reaction catalyzed by glutathione reductase, using NADPH as a source of reducing electrons. NADPH indirectly provides electrons for the reduction of hydrogen peroxide

donates electrons

RBCs

- Erythrocytes are totally dependent on this pathway for their supply of NADPH so any defect, hydrogen peroxide will accumulate, threatening membrane stability and causing red cell lysis

RBCs have no other source of NADPH

- H_2O_2 accumulation
- hemolysis

Uses of NADPH
A. Reduction of hydrogen peroxide

superoxide dismutase → H_2O_2 H_2O_2 → H_2O (water)

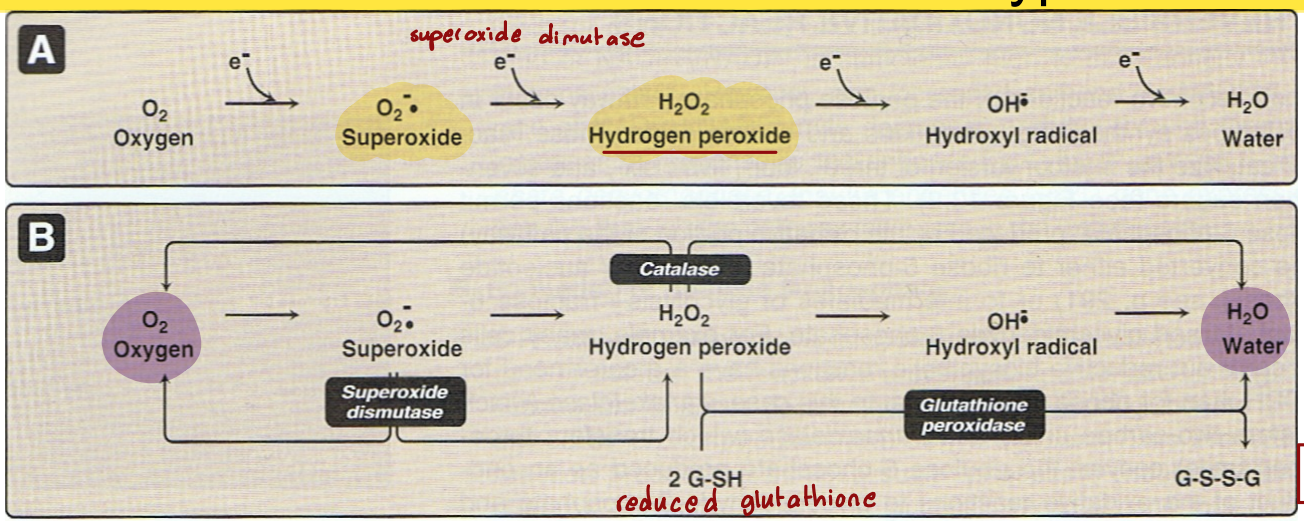
- Superoxide dismutase and catalase, catalyze the conversion of other toxic oxygen intermediates to harmless products so guard the cell against the toxic effects of reactive oxygen species. radicals

Food

- Antioxidant chemicals: A number of intracellular reducing agents such as ascorbate, vitamin E, and β-carotene, are able to reduce and detoxify oxygen intermediates in the laboratory.

(reducing agents)

- Consumption of foods rich in these antioxidant compounds has been correlated with a reduced risk for certain types of cancers



glutathione peroxidase

- drug detoxification
- steroid hydroxylation
- vitamin D activation

Uses of NADPH

B. Cytochrome P450 monooxygenase system

- Monooxygenases incorporate one atom from molecular oxygen into a substrate (creating a hydroxyl group), with the other atom being reduced to water. OH
- In the cytochrome P450 monooxygenase system, NADPH provides the reducing equivalents required by this series of reactions
  power (electrons)
- The overall reaction catalyzed by a cytochrome P450 enzyme is:

steroid

$$R\text{-}H + O_2 + NADPH + H^+ \rightarrow R\text{-}OH + H_2O + NADP^+$$

provides electron

- where R may be a steroid, drug, or other chemical

+ NADPH

- Mitochondrial system: involved in the hydroxylation of steroids that makes them more water soluble.
  - in the steroid hormone-producing tissues, such as the placenta, ovaries, testes, and adrenal cortex, it is used to hydroxylate intermediates in the conversion of cholesterol to steroid hormones
  - The liver uses this system in bile acid synthesis
  - the kidney uses it to hydroxylate vitamin 25-hydroxycholecalciferol (vitamin D) to its biologically active 1 ,25-hydroxylated form.

vitamin D activation

Mitochondrial system
-hydroxylation of steroid
-in liver ueses system in bile
- kidney to activation vitamin D
-all answers (الجواب)

may activate a drug
OR
Inactivate a drug

Uses of NADPH

B.Cytochrome P450 monooxygenase system

drug metabolism (detoxification of xenobiotics)

- Microsomal system: found associated with the membranes of the smooth endoplasmic reticulum (particularly in the liver) is the detoxification of foreign compounds (xenobiotics). These include numerous drugs and such varied pollutants as petroleum products, carcinogens, and pesticides مبيدات حشرية

- It can be used to hydroxylate these toxins, using NADPH as the source of reducing equivalents in order to:
  - activate or inactivate a drug
  - make a toxic compound more soluble, thus facilitating its excretion in the urine or feces
  - Frequently the new hydroxyl group will serve as a site for conjugation with a polar compound, such as glucuronic acid, which will significantly increase the compound's solubility. glucose مؤكسد

the goal is to increase polarity + excretion.

- which help in excretion -

Drug/toxin
→ hydroxylation by Cytochrome P450
→ more polar
→ conjugation with glucuronic acid phase 2
→ excretion

Concept	Must Remember
Cytochrome P450 needs	NADPH
Main reaction	Hydroxylation
Location for detoxification	Smooth ER
Main organ	Liver
Purpose	Make compounds water soluble
Detoxifies	Drugs + xenobiotics
Important in	Steroid synthesis

CNS أدوية
hydroxylation increase polarity but still active

NADPH oxidase forms superoxide radicals to kill bacteria

Uses of NADPH

C. Phagocytosis by white blood cells

(Respiratory burst in phagocytes)

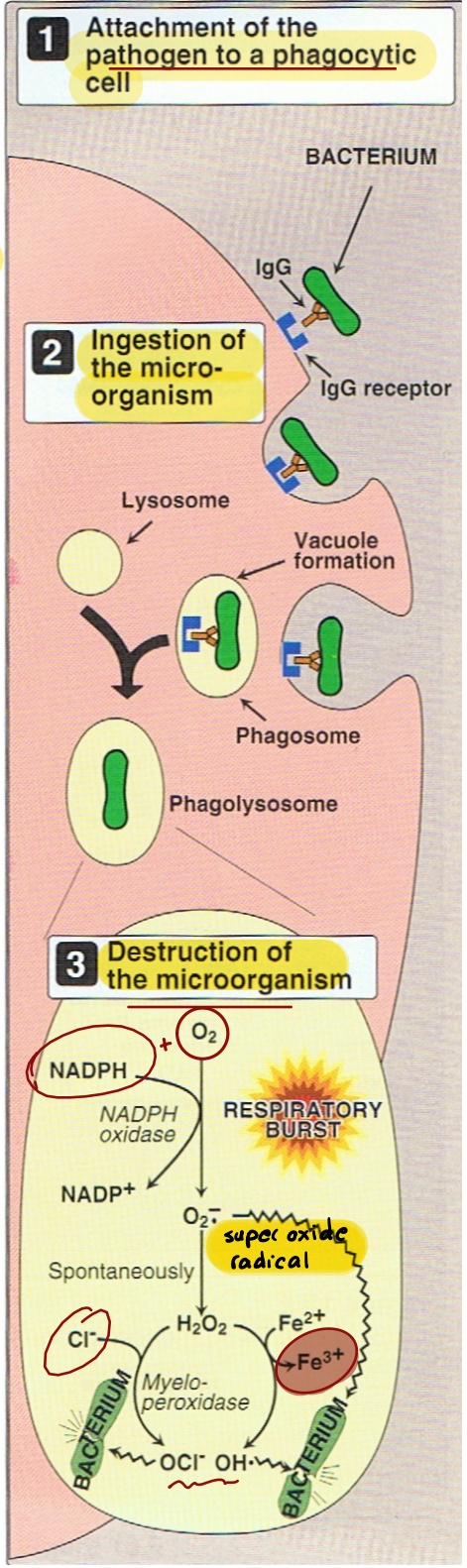
- NADPH provides the reducing equivalents for phagocytes in the process of eliminating invading microorganisms

- **NADPH oxidase** uses molecular oxygen and NADPH electrons to produce superoxide radicals, which can be converted to peroxide, hypochlorous acid, and hydroxyl radicals using Myeloperoxidase enzyme.

- A genetic defect in NADPH oxidase causes chronic granulomatosis, a disease characterized by severe, persistent, chronic infections.

- Any superoxide that escapes the phagolysosome is converted to hydrogen peroxide by superoxide dismutase (SOD). H_2O_2

- Excess peroxide (oxidizing agent) is either neutralized by catalase (turn it into water) or



N + O_2 = NO

Arginine ت L-

Uses of NADPH

NO

D. Synthesis of nitric oxide

- Nitric oxide (NO) is recognized as a mediator in a broad array of biologic systems.

ex. phagocytes

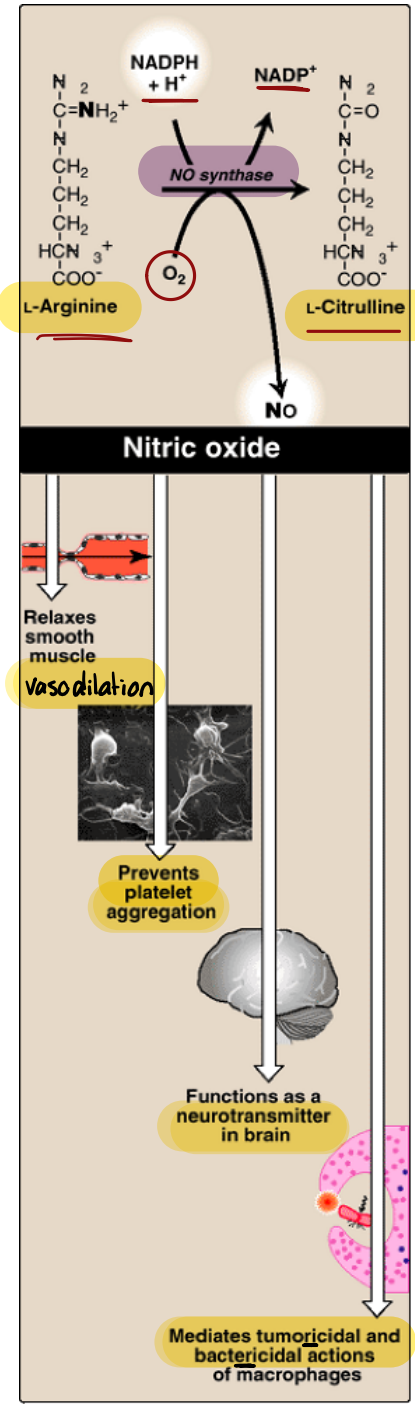
- NO is the endothelium-derived relaxing factor, which causes **vasodilation** by relaxing vascular smooth muscle. NO also acts as a **neurotransmitter**, prevents **platelet aggregation**, and plays an essential role in **macrophage function**

- NO is a free radical gas that has a very short half-life in tissues (three to ten seconds) because it reacts with oxygen and superoxide, and then is converted into nitrates and nitrites.

O_2 radical

- Synthesis of NO:
  - It is synthesized by the cytosolic NO synthase.
  - Flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), heme, and tetrahydrobiopterin are coenzymes for the enzyme

Angina (Buccal nitrates)



Which of the following statements regarding nitric oxide (NO) is correct?

A. Nitric oxide is synthesized by cytosolic nitric oxide synthase.

B. FMN, FAD, heme, and tetrahydrobiopterin act as coenzymes for NO synthesis.

C. NO has an important role in macrophage function and vasodilation.

D. All of the above.

D

Which of the following statements about nitric oxide (NO) is incorrect?

A. Nitric oxide causes vasoconstriction by contracting vascular smooth muscle.

B. Nitric oxide has a long half-life in tissues, lasting several hours.

C. Nitric oxide synthase does not require any coenzymes for NO synthesis.

D. All of the above.

D

وسؤال عن NO
وجوابه all

Glucose 6-Phosphate dehydrogenase deficiency

No NADPH production

- This deficiency is a genetic disease characterized by hemolytic anemia. G6PD deficiency impairs the ability of the cell to form the NADPH that is essential for the maintenance of the reduced glutathione pool.

RBCs

- The cells most affected are the red blood cells because they do not have additional sources of NADPH. Free radicals and peroxides formed within the cells cannot be neutralized, causing denaturation of protein (as hemoglobin) and membrane proteins.

- The cells become rigid, and they are removed by the reticuloendothelial system of the spleen and liver.

- Hemolytic anemia can be caused by the production of free radicals and peroxides following the taking of oxidant drugs, ingestion of fava beans or severe infections.

-isosulfide
-dinitrate

طلبت ال incorrect بال NADPH

-NADPH doesn’t effect with G-6-pD deficiency

Glucose 6-Phosphate dehydrogenase deficiency

- Babies with G6PD deficiency may experience neonatal jaundice appearing one to four days after birth.
  (1-4) days
- The degree of severity of the anemia depends on the location of the mutation in the G6PD gene
- Class I mutations are the most severe (for example, G6PD Mediterranean). They are often associated with chronic nonsphercytic anemia.
- Class III mutations (for example, G6PD A-) cause a more moderate form of the disease

Most Important Enzymes to Memorize

Enzyme	Importance
G6PD	Rate-limiting enzyme
Transketolase	Requires thiamine
Glutathione reductase	Uses NADPH
Glutathione peroxidase	Detoxifies H_2O_2
NADPH oxidase	Respiratory burst
Superoxide dismutase	Converts superoxide → H_2O_2
Catalase	Detoxifies peroxide → water

Which of the following enzymes utilizes NADH rather than NADPH in its reaction:

1. ○ Cytochrome P450
2. ○ NO synthase
3. ○ Glutathione reductase
4. ◉ Glyceraldehyde 3-P dehydrogenase
5. ○ NADPH oxidase

4

Question 3 / 56

The pentose phosphate pathway is used in all of the following except:

1. Synthesis of ribose sugar
2. Synthesis of NADPH
3. Utilization of its product to kill microorganisms in macrophages
4. Utilization of its products to reduce the toxic potential of some compounds
5. Synthesis of Glutathione

5

Next