Pentose phosphate pathway and NADPH

Five carbons

موازي لل glycolysis
بصنعها و بتحرقو

The pentose phosphate pathway

- 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 CO2, and two NADPH are produced for each glucose 6-phosphate molecule entering the oxidative part of the pathway.
- The pathway provides a major portion of the body's NADPH, which functions as a biochemical reductant.

The pentose phosphate pathway

- Ribose 5-phosphate is required for ② biosynthesis of nucleotides ② provides a mechanism for the metabolic use of five-carbon sugars obtained from the diet or ③ degradation of structural carbohydrates in the body.

metabolism of ribos sugers through this pathway

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

NADPH باقي الي تحتاج

A. **Liver** and **lactating mammary glands**, which are active in the biosynthesis of fatty acids

بعتبع long chain fatty acids

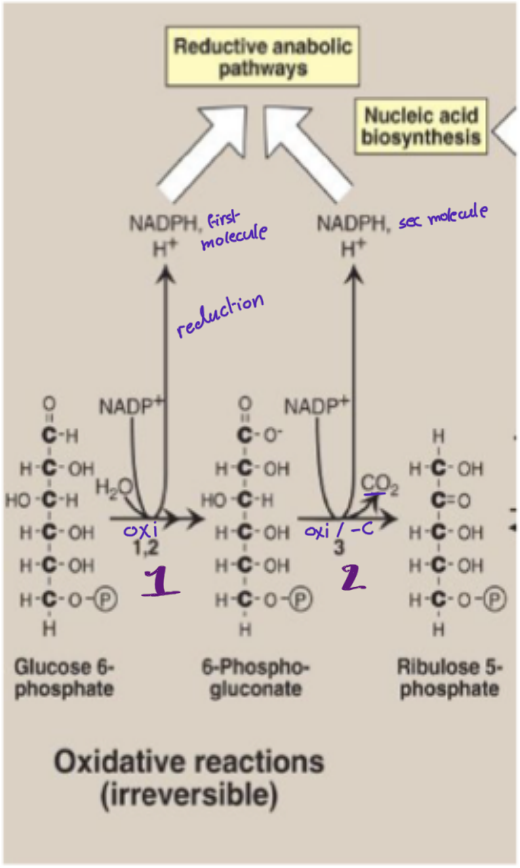
milk

needs NADPH

B. **Adrenal cortex**, which is active in the NADPH-dependent synthesis of steroids

C. **Erythrocytes**, which require NADPH to keep glutathione reduced.

Irreversible oxidative reactions (two reactions)



1 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

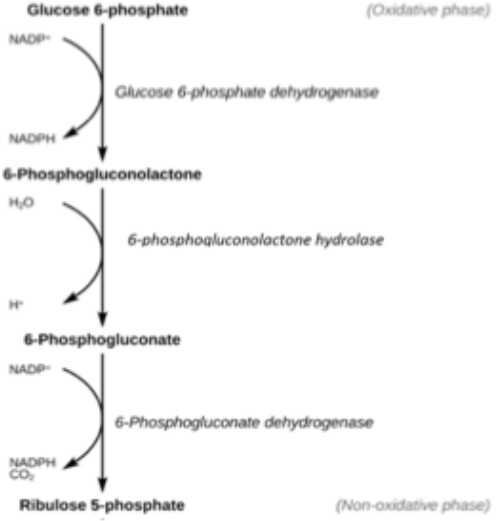
The enzyme is competitively inhibited by NADPH so its regulated by the NADP/NADPH ratio in the cell

Insulin enhances G6PD gene expression (well-fed state)

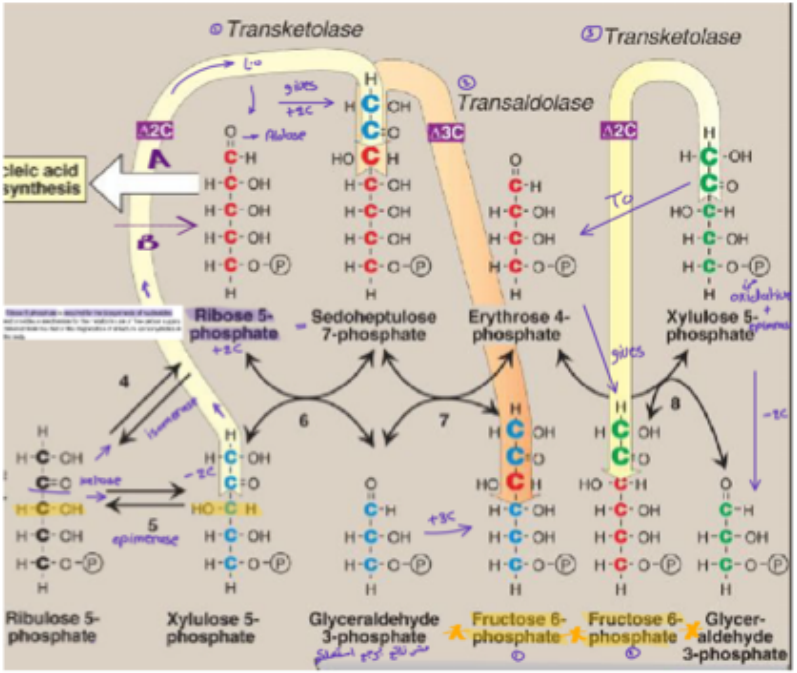
2. Formation of ribulose 5-phosphate

- Phosphogluconolactone is hydrolyzed by **6-phosphogluconolactone hydrolase** (irreversible and not rate-limiting).

- 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



Reversible nonoxidative reactions

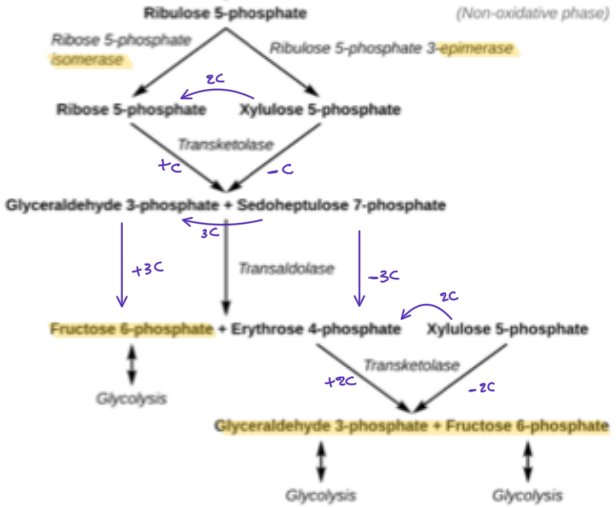


The nonoxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids. These reactions catalyze the interconversion of three-, four-, five-, six-, and seven- carbon sugars.

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



Glucose 6-Phosphate dehydrogenase deficiency

- 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.

- 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.

no NADPH → free radicals accumulation
+
① - ③
= Hemolytic anemia

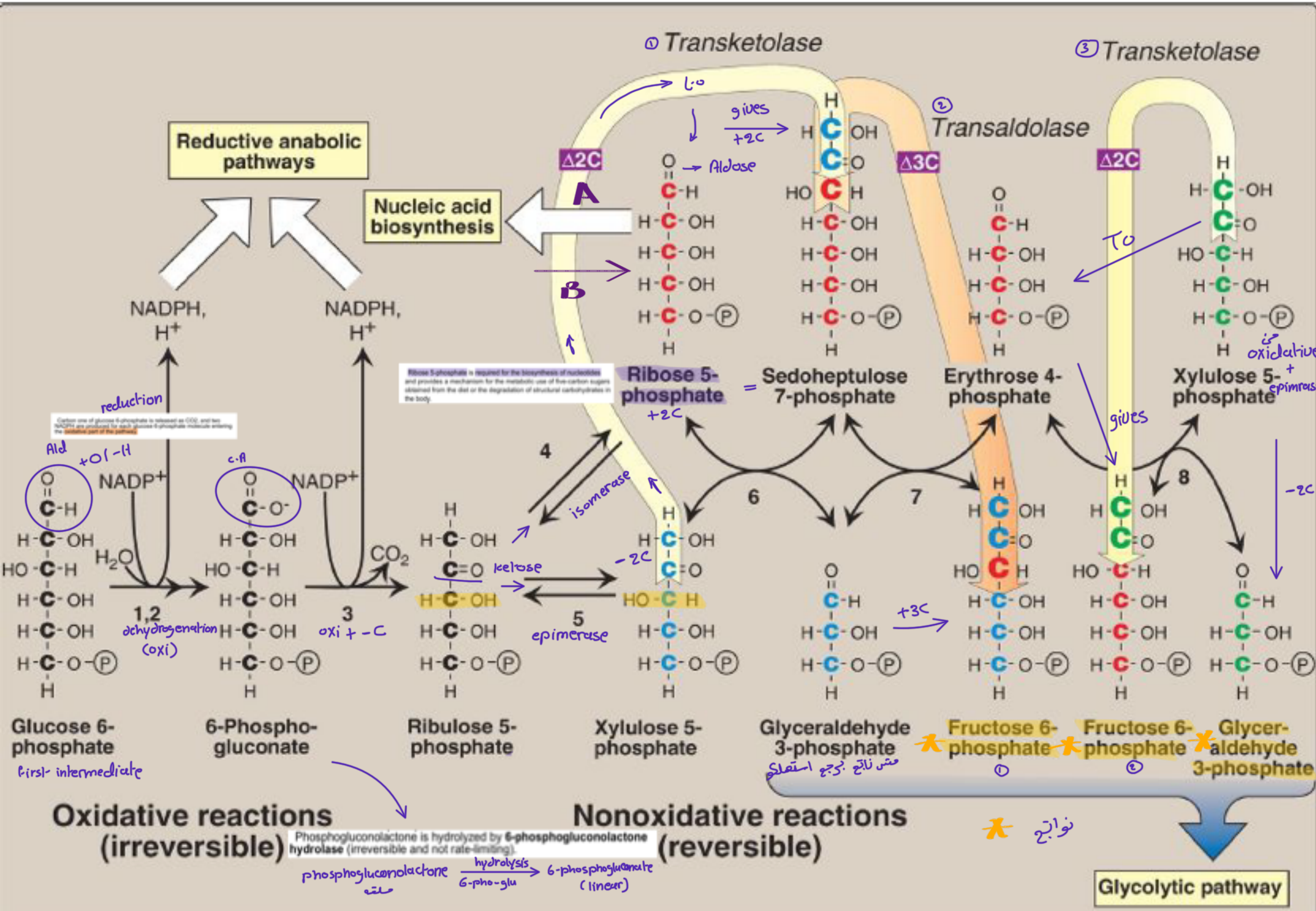
Glucose 6-Phosphate dehydrogenase deficiency

- Babies with G6PD deficiency may experience neonatal jaundice appearing one to four days after birth.

- 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.

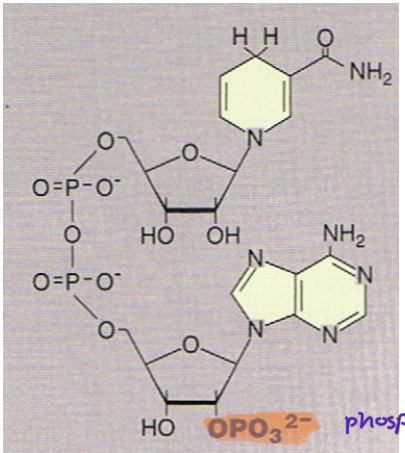
- Class III mutations (for example, G6PD A-) cause a more moderate form of the disease



① Transketolase
③ Transketolase
② Transaldolase
Δ2C
Δ3C
Δ2C
Reductive anabolic pathways
Nucleic acid biosynthesis
NADPH, H+
NADPH, H+
NADP+
NADP+
H2O
CO2
1,2
3
4
5
6
7
8
Glucose 6-phosphate
6-Phosphogluconate
Ribulose 5-phosphate
Xylulose 5-phosphate
Ribose 5-phosphate
Sedoheptulose 7-phosphate
Erythrose 4-phosphate
Xylulose 5-phosphate
Glyceraldehyde 3-phosphate
Fructose 6-phosphate
Fructose 6-phosphate
Glyceraldehyde 3-phosphate
Oxidative reactions (irreversible)
Phosphogluconolactone is hydrolyzed by 6-phosphogluconolactone hydrolase (irreversible and not rate-limiting).
Nonoxidative reactions (reversible)
Glycolytic pathway

NADPH

- 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 $\frac{1}{10} = \frac{NADP}{NADPH}$
- This contrasts with the high ratio of NAD/NADH approximately 1000 in the cytosol of hepatocytes, which favors an oxidative role for NAD



Uses of NADPH

A. Reduction of hydrogen peroxide

Hydrogen peroxide is formed from the partial reduction of molecular oxygen

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.

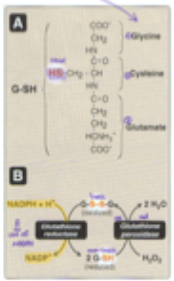
These highly reactive oxygen intermediates can cause serious chemical damage to DNA, proteins, and unsaturated lipids, and can lead to cell death.

The cell has several protective mechanisms that minimize the toxic potential of these compounds.

Enzymes that catalyze antioxidant reactions:

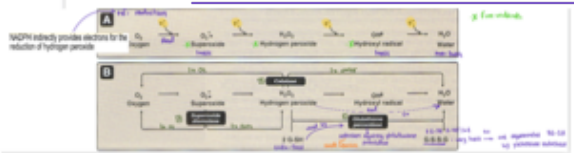
Reduced glutathione, a tripeptide-thiol present in most cells, can chemically detoxify hydrogen peroxide that is catalyzed by the selenium-requiring glutathione peroxidase, forms oxidized glutathione, which no longer has protective properties

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



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

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



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.
- In the cytochrome P450 monooxygenase system, NADPH provides the reducing equivalents required by this series of reactions
- The overall reaction catalyzed by a cytochrome P450 enzyme is:

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

- where R may be a steroid, drug, or other chemical
- 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.
- 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
- It can be used to hydroxylate these toxins, using NADPH as the source of reducing equivalents in order to:
  1. activate or inactivate a drug
  2. make a toxic compound more soluble, thus facilitating its excretion in the urine or feces
  3. 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.

C.Phagocytosis by white blood cells

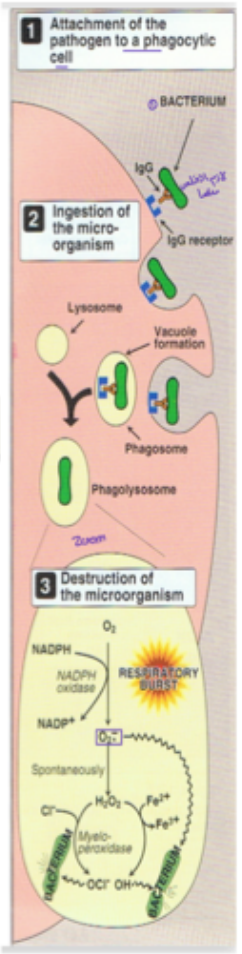
NADPH provides the reducing equivalents for phagocytes in the process of eliminating invading microorganisms

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).

Excess peroxide is either neutralized by catalase or by glutathione peroxidase



D. Synthesis of nitric oxide

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

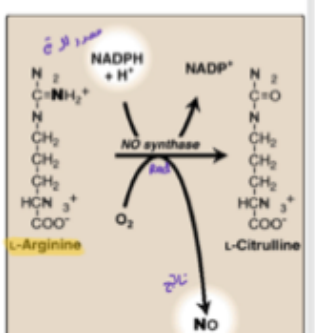
NO is the endothelium-derived relaxing factor, which causes **vasodilation** by relaxing vascular smooth muscle. NO also acts as a **neurotransmitter**, prevents **platelet aggregation**, and plays an essential role in **macrophage function**

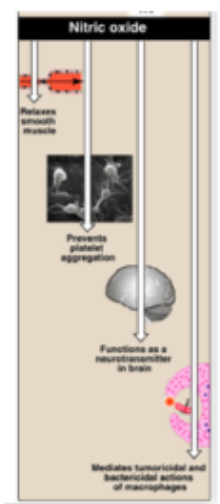
NO is a free radical gas that has a very short half-life in tissues (three to ten seconds) because it reacts with oxygen and superoxide, and then is converted into nitrates and nitrites.

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





Protein metabolism

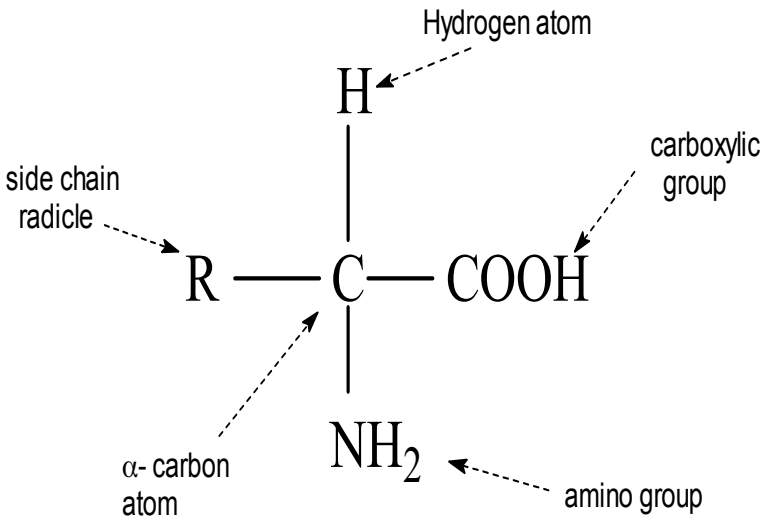
Proteins

- **Nitrogen** is a characteristic component of proteins forming about ***16%*** of their weight i.e. 100 g of protein contains 16 g of nitrogen.
- Proteins are not stored in body as such
- Amino acids are degraded by deamination to ammonia and α-ketoacid
- Ammonia is used to produce urea and excreted in urine
- α-ketoacid can be metabolized to CO2 and water, glucose, fatty acid or ketone bodies

not- D-a-Amino acids

- L-a-Amino acids are the structural or the building units of proteins

- The common amino acids have the general structure depicted in the following figure:



Representation of α Amino Acid

Abbreviations for the 20 Amino Acids

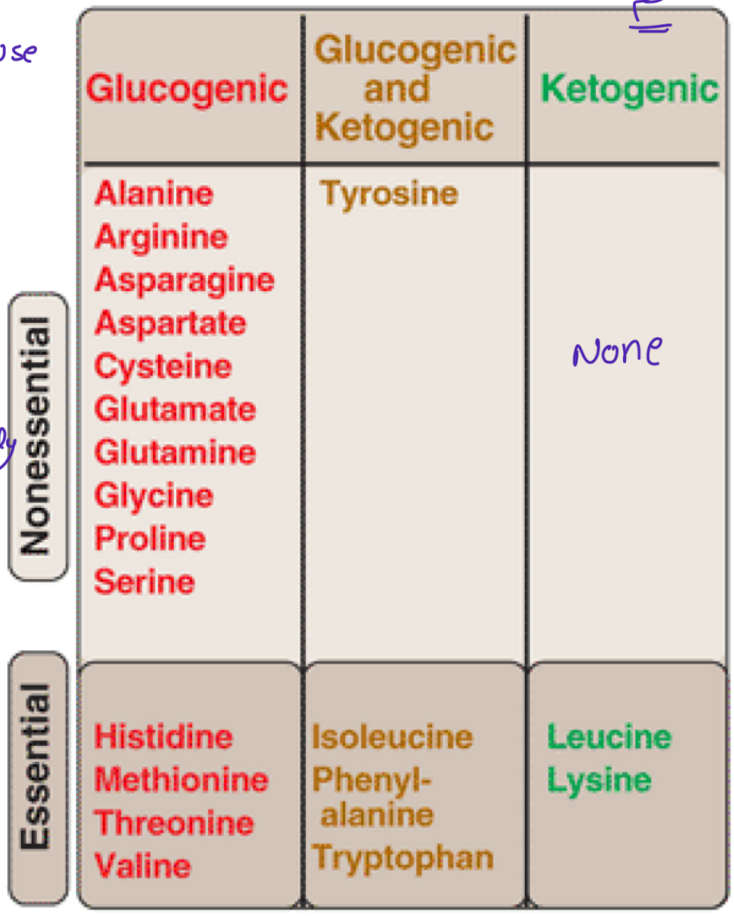
Amino Acid	Abbreviation		**Amino Acid**	Abbreviation	
	Three letter	One letter		Three letter	One letter
Alanine	***Ala***	**A**	Leucine	***Leu***	**L**
Arginine	***Arg***	**R**	Lysine	***Lys***	**K**
Asparagine	***Asn***	**N**	Methionine	***Met***	**M**
Aspartic acid	***Asp***	**D**	Phenylalanine	***Phe***	**F**
Cysteine	***Cys***	**C**	Proline	***Pro***	**P**
Glycine	***Gly***	**G**	Serine	***Ser***	**S**
Glutamine	***Gln***	**Q**	Threonine	***Thr***	**T**
Glutamic acid	***Glu***	**E**	Tryptophan	***Trp***	**W**
Histidine	***His***	**H**	Tyrosine	***Tyr***	**Y**
Isoleucine	***Ile***	**I**	Valine	***Val***	**V**

Metabolic Classification of Amino Acids

① **Glucogenic amino acids:** it's α-ketoacid use to make glucose
AA that can yield pyruvate, oxaloacetate, α-ketoglutarate Succinyl-CoA, fumarate

② **Ketogenic amino acids:** it's α-ketoacid use to make fatty acid / ketones body
AA that can form acetyl-coA, acetoacetyl CoA or β-hydroxybutyrate.

③ **Or both**

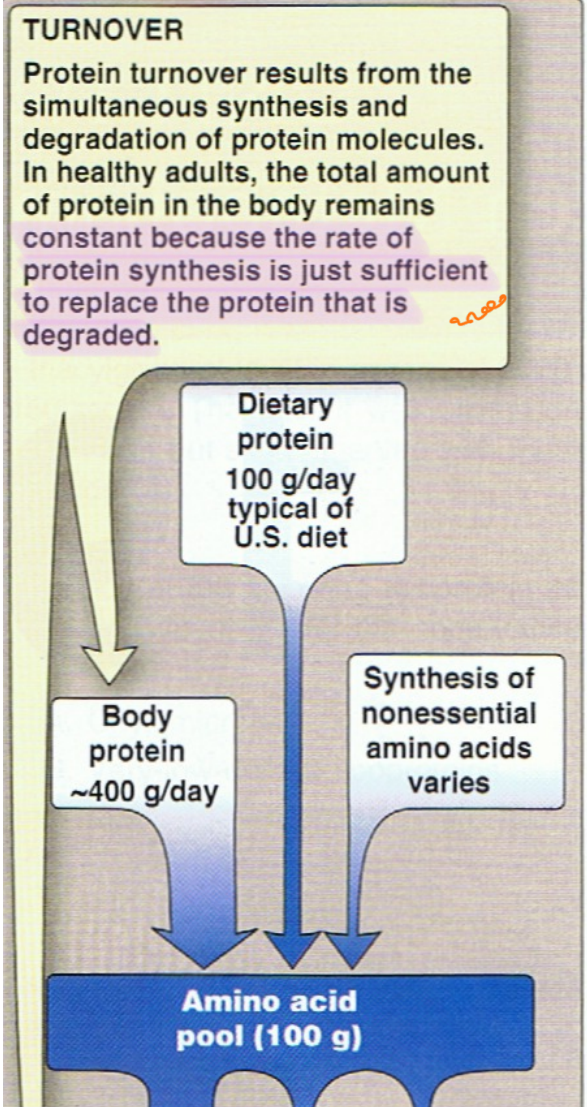


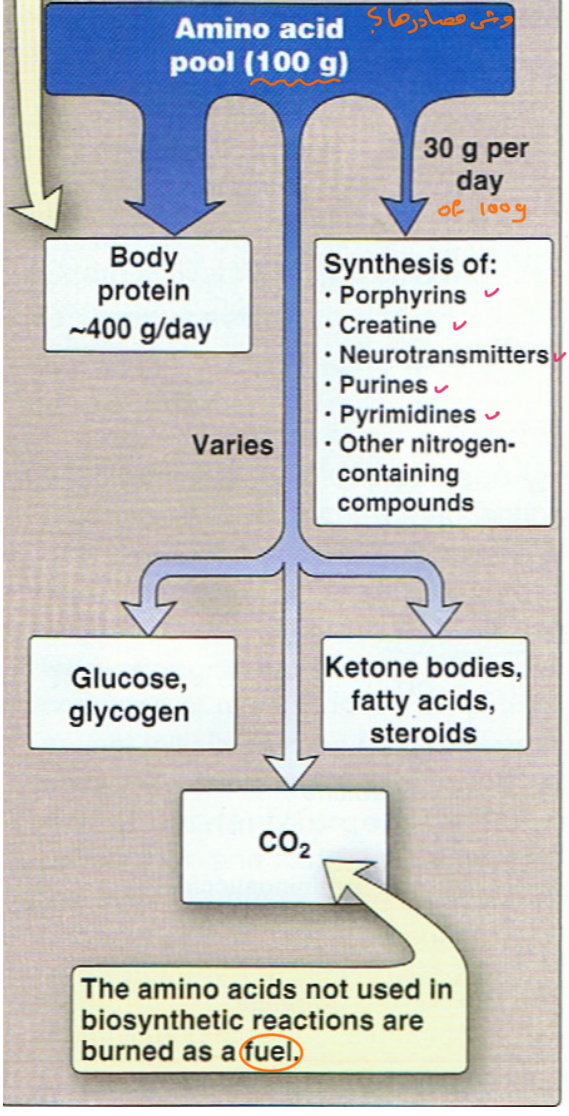
Amino acid metabolism

- Amino acid pool: مخزون
  - There is about 12 kg of protein in 70 kg man
  - 75% of aa are used in synthesis of new tissue proteins only 25% for
  - The remainder is used as precursor for synthesis of many other things substances

نمو و جسم تجدها

- Protein turnover:
  - Proteins are constantly degraded and synthesized which is regulated by the concentration of protein in the cell
  - 300-400 g of proteins are hydrolyzed and resynthesized/day daily
  - Protein turnover varies: [a] short lived (regulatory and misfolded proteins), [b] long-lived (most of tissue proteins) and structurally stable (collagen)


TURNOVER
Protein turnover results from the simultaneous synthesis and degradation of protein molecules. In healthy adults, the total amount of protein in the body remains constant because the rate of protein synthesis is just sufficient to replace the protein that is degraded.
Dietary protein
100 g/day typical of U.S. diet
Body protein
~400 g/day
Synthesis of nonessential amino acids varies
Amino acid pool (100 g)


Amino acid pool (100 g)
30 g per day
Body protein
~400 g/day
Synthesis of:
• Porphyrins
• Creatine
• Neurotransmitters
• Purines
• Pyrimidines
• Other nitrogen-containing compounds
Varies
Glucose, glycogen
Ketone bodies, fatty acids, steroids
CO_2
The amino acids not used in biosynthetic reactions are burned as a fuel.

Nitrogen Balance

- **Positive Nitrogen Balance means N2 intake is more than N2 output:** intake > output

- This exists when intake of N2 exceeds the output. It occurs whenever new tissues are being built up for example:

1- During growth (growing children). نمو
2- Pregnancy. حمل
3- Muscular training. بناء عضل
4- Convulsions from different diseases.
تشنجات

Nitrogen Balance

B. Negative Nitrogen Balance: N2 Output is more than N2 intake:

- It occurs in cases of :

1- Decreased protein intake: e.g. starvation, malnutrition and G.I.T. diseases.

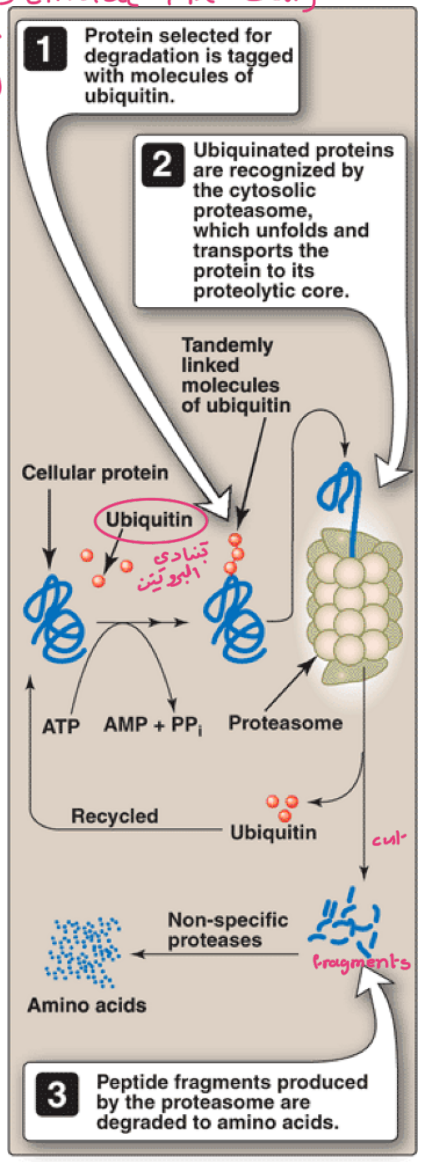
2- Increased Loss of proteins: e.g. in chronic hemorrhage, albuminuria and Lactation on an inadequate protein diet.

3- Increased of protein catabolism: e.g. fever, hyperthyroidism, diabetes mellitus, Cushing syndrome, advanced cancer and post-surgical.

- Prolonged periods of negative nitrogen balance are dangerous and may lead to death.

Protein metabolism

- Protein degradation occurs by:
  - [1] energy dependent ubiquitin-protesome mechanism (endogenous proteins)
  - [2] non-energy dependent lysosomes (extracellular protein)
- Oxidized or ubiquitin tagged proteins are preferentially degraded
- Certain aa sequences:
  - Serine (S)at N-terminal: long t1/2 (>20 hr)
  - Aspartate (D) at N-terminal: short t1/2 (3 min)
  - Proteins rich in the sequence (PEST) are rapidly degraded ← cause: Proline, Glutamic acid, Serine, Threonine



Zymogen: inactive form of a protien
بروتين أولي
يحتاج تنشيط

Digestion of proteins

الي باكلها

- protein is antigenic i.e. able to stimulate an immunologic response. The digestion of protein destroys its antigenicity. So, proteins must be digested into amino acids: so it won't cause immune respond

موقد جسم (مستفيد)

يبدأ بالمعده

1) In the stomach :

بخرب

A- gastric acid: denature the protein

تحليل

B- Pepsin: is the major proteolytic enzyme in the stomach :

- Pepsin is produced and secreted by the chief cells of the stomach as the inactive zymogen, pepsinogen, which activated by HCl produced by parietal cells of stomach. chief → release → zymogen (pepsinogen) + HCl → pepsin
- Pepsin catalyzes the cleavage of proteins into smaller polypeptides. # function

2) in small intestine: large polypeptides are further cleaved to 3-10 oligopeptides and amino acids by a group of pancreatic proteases.

Each of these enzymes has a different specificity (trypsin cleaves only at C-terminal of arginine or lysine). معمم

مثال →

Activation of zymogens: Enteropeptidase converts the pancreatic trypsinogen to trypsin which starts a cascade of proteolytic activity, because trypsin is the activator of all the pancreatic zymogens

كتالية

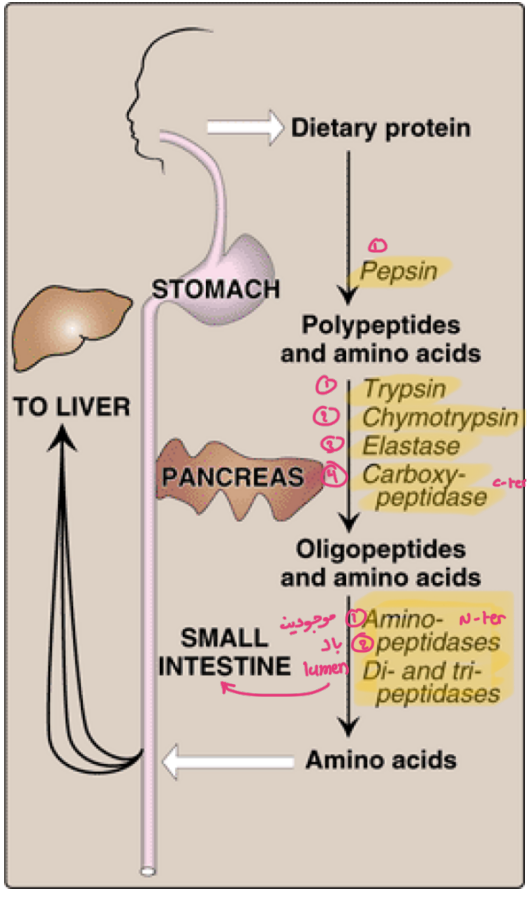
معمم

trypsinogen —Enteropeptidase→ trypsin

Digestion of proteins

Abnormalities in protein digestion:

- In individuals with a deficiency in pancreatic secretion (chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas), the digestion and absorption of fat and protein is incomplete.
- This results in the abnormal appearance of lipids (Steatorrhea) and undigested protein in the feces.



Digestion of oligopeptides by enzymes of the small intestine

- The luminal surface of the intestine contains **aminopeptidase** (an exopeptidase that repeatedly cleaves the N-terminal residue of oligopeptides to produce free amino acids and smaller peptides.

Absorption of amino acids and dipeptides

a.a can be absorbed as di unlike mono glucose

- Free amino acids and dipeptides are taken up by the intestinal epithelial cells.
- the dipeptides are hydrolyzed in the cytosol to amino acids before being released into the portal system (only free amino acids are found in the portal vein)
- The absorption of amino acid is active process that needs energy (ATP).

Transport of aa to the cells

- Amino acids are transported to the cells by active transport systems, driven by the hydrolysis of ATP
- At least seven different transport systems are known that have overlapping specificities for different amino acids.
- For example, one transport system is responsible for reabsorption of the amino acids cystine, ornithine, arginine, and lysine in kidney tubules.

عن طريق ناقل

S-S
not SH
SH
non-polar
can't be execred to urin

Basic = polar → could reabsorped
could execret to urin

Not: Cysteine

إذاً أولاً: دخلت aa على دمي

حصوه

Cystinuria

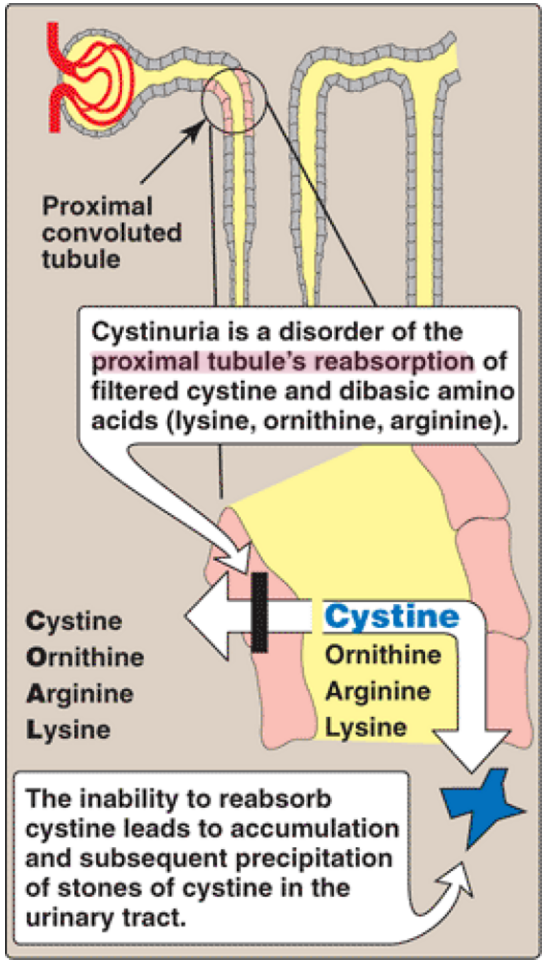
- In the inherited disorder **cystinuria**, this carrier system is defective, resulting in the appearance of all four amino acids in the urine. → but we said cystine can't be excreted bc it's non-polar. → so: بتراكم بالكلية بعمل حصوه

الي بعمل reabsorbe

- Cystinuria is the most common genetic error of amino acid transport.

- The disease expresses itself clinically by the precipitation of cystine to form kidney stones (calculi) that may block the urinary tract.

- Oral hydration is important in treatment for this disorder

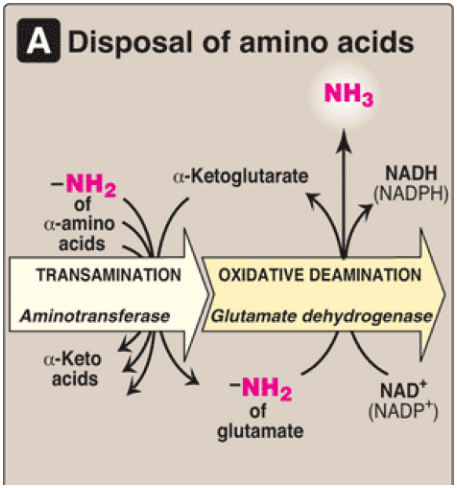


ثانياً : بدي أكسرهم (aa)

Metabolism of amino acids

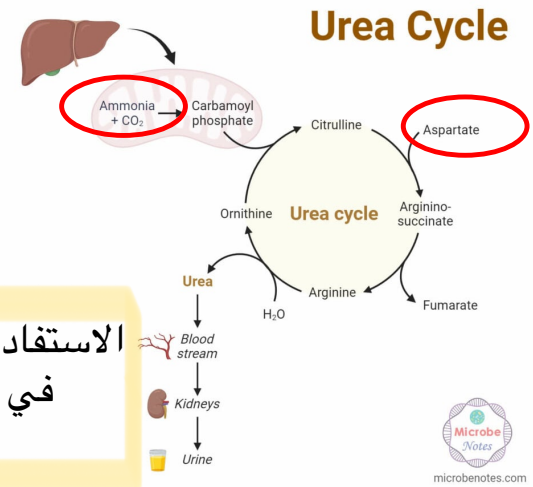
A Transamination (by aminotransferases)

→ α-ketoacid / Glutamate



B Oxidative deamination of amino acids ⬜ removal of nitrogen from aa (NH3)

C Transport of ammonia from tissues to the liver and hyperammonimeia



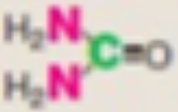
D Urea cycle.

الاستفادة من تكسير الأحماض الأمنية تكمن في تحويلها إلى Alpha ketoacide للاستفادة منه كطاقه

Transamination and oxidative deamination: removal of nitrogen from aa

Removing the α-amino group is essential for producing energy from any amino acid

Urea

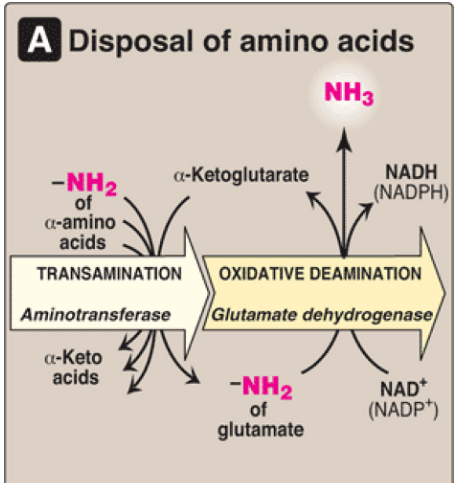


نقل أمين — amine ازالة + تأكسد

Transamination and oxidative deamination reactions which provide ammonia and aspartate, the two sources of urea nitrogen

a.c

The first step is transfer their α-amino group to α-ketoglutarate to produce an α-ketoacid and glutamate.



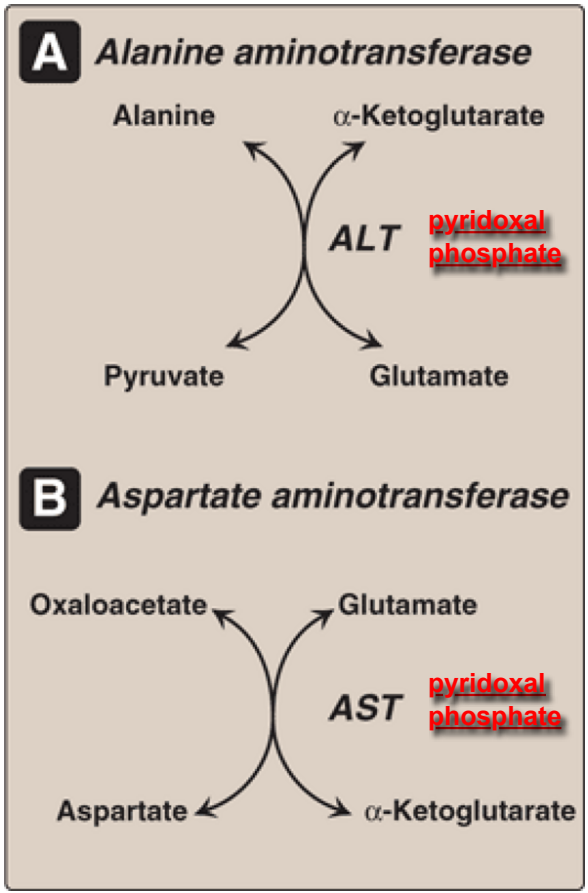
Glutamate produced by transamination can be oxidatively deaminated or used as an amino group donor in the synthesis of nonessential amino acids.

A) Transamination

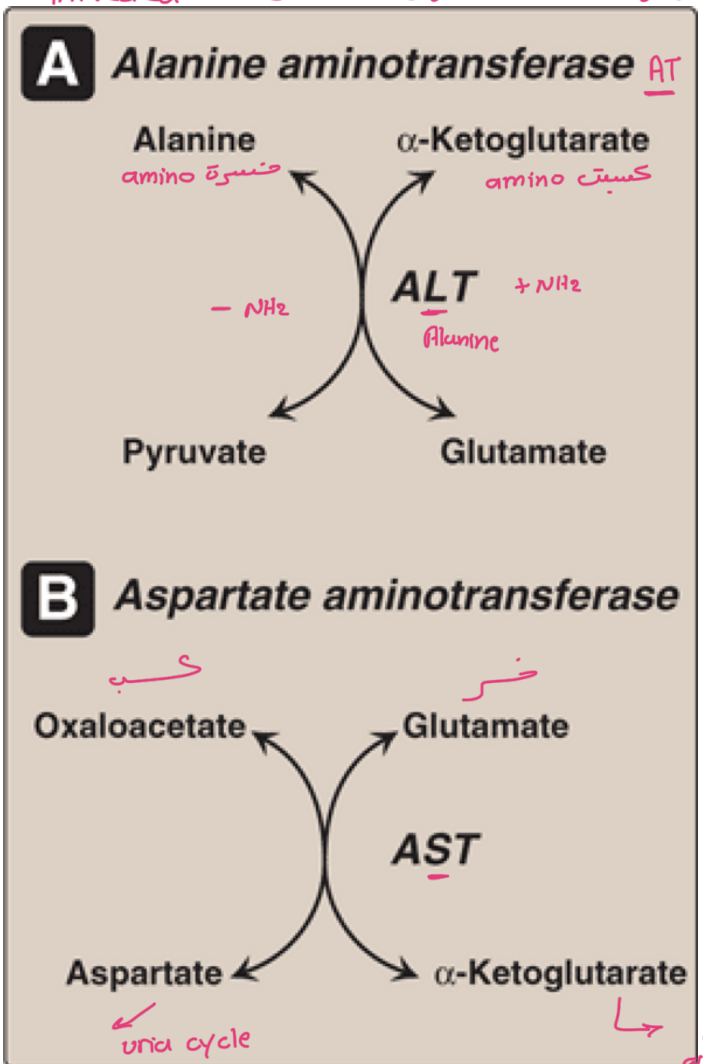
- The transfer of amino groups from one carbon skeleton to another is catalyzed by a family of enzymes called **aminotransferases**.
- These enzymes are found in the cytosol of cells throughout the body (especially the liver, kidney, intestine, and muscle).
- All amino acids (except lysine and threonine) participate in transamination at some point in their catabolism.
- Lysine and threonine lose their α-amino groups by deamination

Aminotransferases

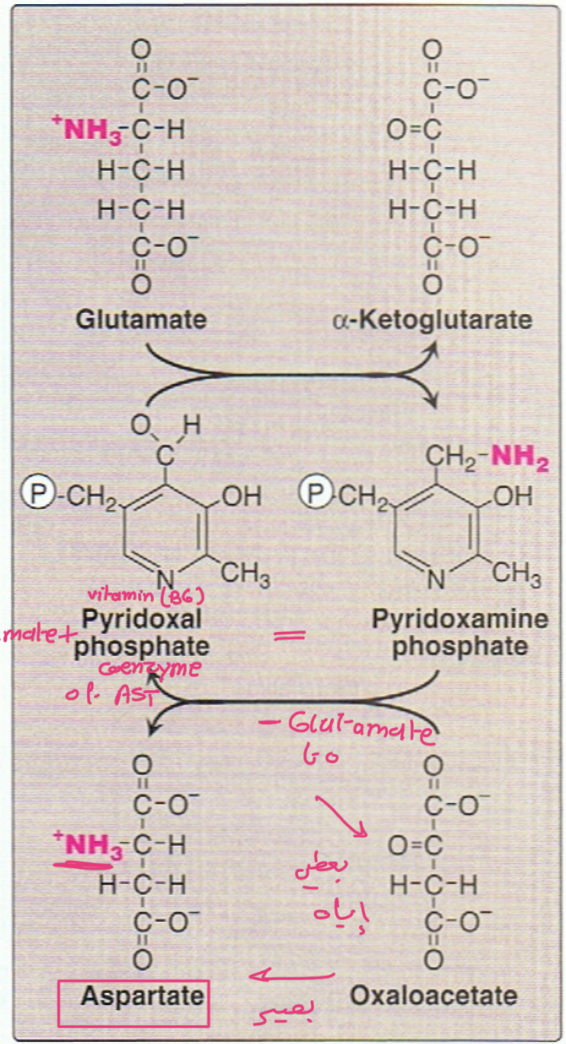
- Each aminotransferase is specific for one or, at most, a few amino group donors and named after that enzyme
- Alanine aminotransferase (ALT): enzyme catalyzes (reversibly) the transfer of the amino group of alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate.
- Aspartate aminotransferase (AST) is During amino acid catabolism, AST transfers amino groups from glutamate to oxaloacetate, forming aspartate, which is used as a source of nitrogen in the urea cycle
- All aminotransferases require the coenzyme **pyridoxal phosphate (vitamin B6)**



All aa go through this process but we are interested more in these two → bc they gives intermeelicats :



- glutamate
- Aspartate



Diagnostic value of plasma aminotransferases

- Aminotransferases are normally intracellular enzymes,)low levels in the plasma)

- The presence of elevated plasma levels of aminotransferases indicates damage to cells rich in these enzymes. Two aminotransferases (AST and ALT) are of particular diagnostic value when they are found in the plasma.

- a. hepatic disease: Plasma AST and ALT are elevated in nearly all liver diseases, specially in extensive cell necrosis (severe viral hepatitis, toxic injury, and prolonged circulatory collapse).

  Elevated serum bilirubin results from hepatocellular damage that decreases the hepatic conjugation and excretion of bilirubin

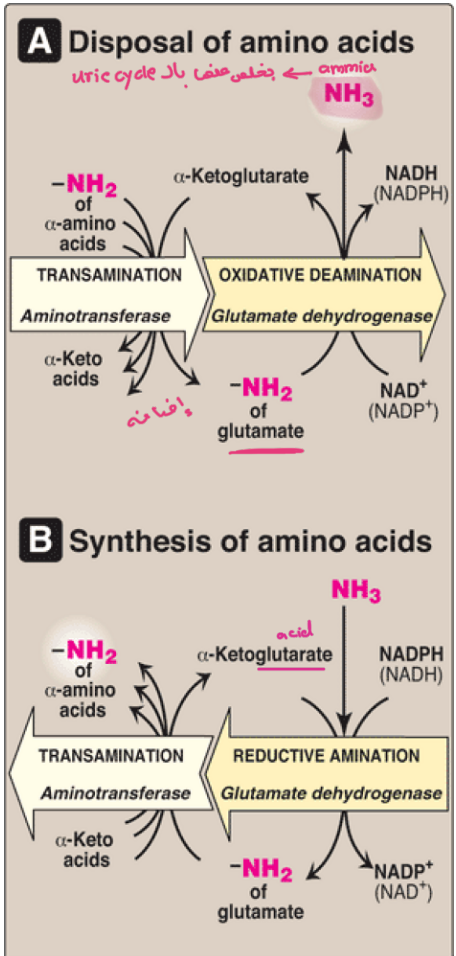
  b. Nonhepatic disease: Aminotransferases may be elevated in nonhepatic disease (myocardial infarction and muscle disorders) but those can be clinically distinguished.

B) Oxidative deamination of amino acids
Glutamate Dehydrogenase

- It is the transfer amino groups from glutamate, oxidative deamination, by glutamate dehydrogenase results in the liberation of the amino group as free ammonia.
- occur primarily in the liver and kidney.
- Glutamate is unique in that it is the only amino acid that undergoes rapid oxidative deamination
- Glutamate dehydrogenase can use either NAD or NADP as a coenzyme. NAD is used primarily in oxidative deamination and NADPH is used in reductive amination

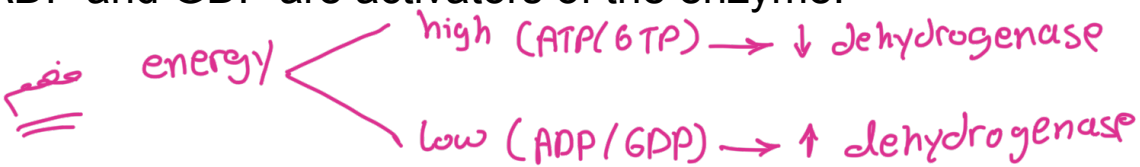
oxi → NAD

red → NADPH



Glutamate dehydrogenase

- The direction of the reaction depends on the relative concentrations of glutamate, α-ketoglutarate. and ammonia, and the ratio of oxidized to reduced coenzymes.
- After ingestion of a meal containing protein, glutamate levels in the liver are elevated and enhance amino acid degradation and the formation of ammonia
- The reaction can also be used to synthesize amino acids from the corresponding α-ketoacids
- ATP and GTP are allosteric inhibitors of glutamate dehydrogenase, whereas ADP and GDP are activators of the enzyme.



D-Amino acid oxidase

Coenzyme: FAD

- D-Amino acids are present in the diet, and are efficiently metabolized by the liver using D-Amino acid oxidase (FAD-dependent enzyme) that catalyzes the oxidative deamination of these amino acid isomers.

- The resulting α-ketoacids can enter the general pathways of amino acid metabolism, and be reaminated to L-isomers, or catabalized for energy.

C) Transport of ammonia from tissues to the liver

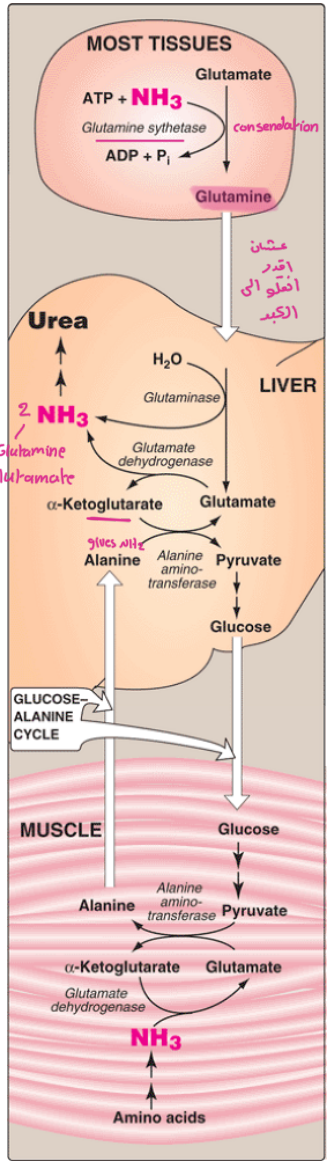
There are two mechanisms:

- one → found in most tissues, uses glutamine synthetase to combine ammonia with glutamate to form glutamine (a nontoxic transport form of ammonia)

  The glutamine is transported in the blood to the liver where is cleaved by glutaminase to produce glutamate and free ammonia

- two → used primarily by muscle (only), involves transamination of pyruvate (the end-product of aerobic glycolysis) to form alanine

  Alanine is transported by the blood to the liver, where it is converted to pyruvate, again by transamination (pyruvate is used in gluconeogenesis). This pathway called the **glucose-alanine cycle**.



D) UREA CYCLE

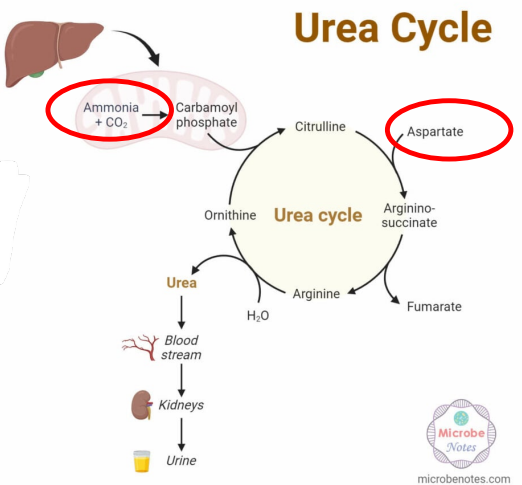
تخلص

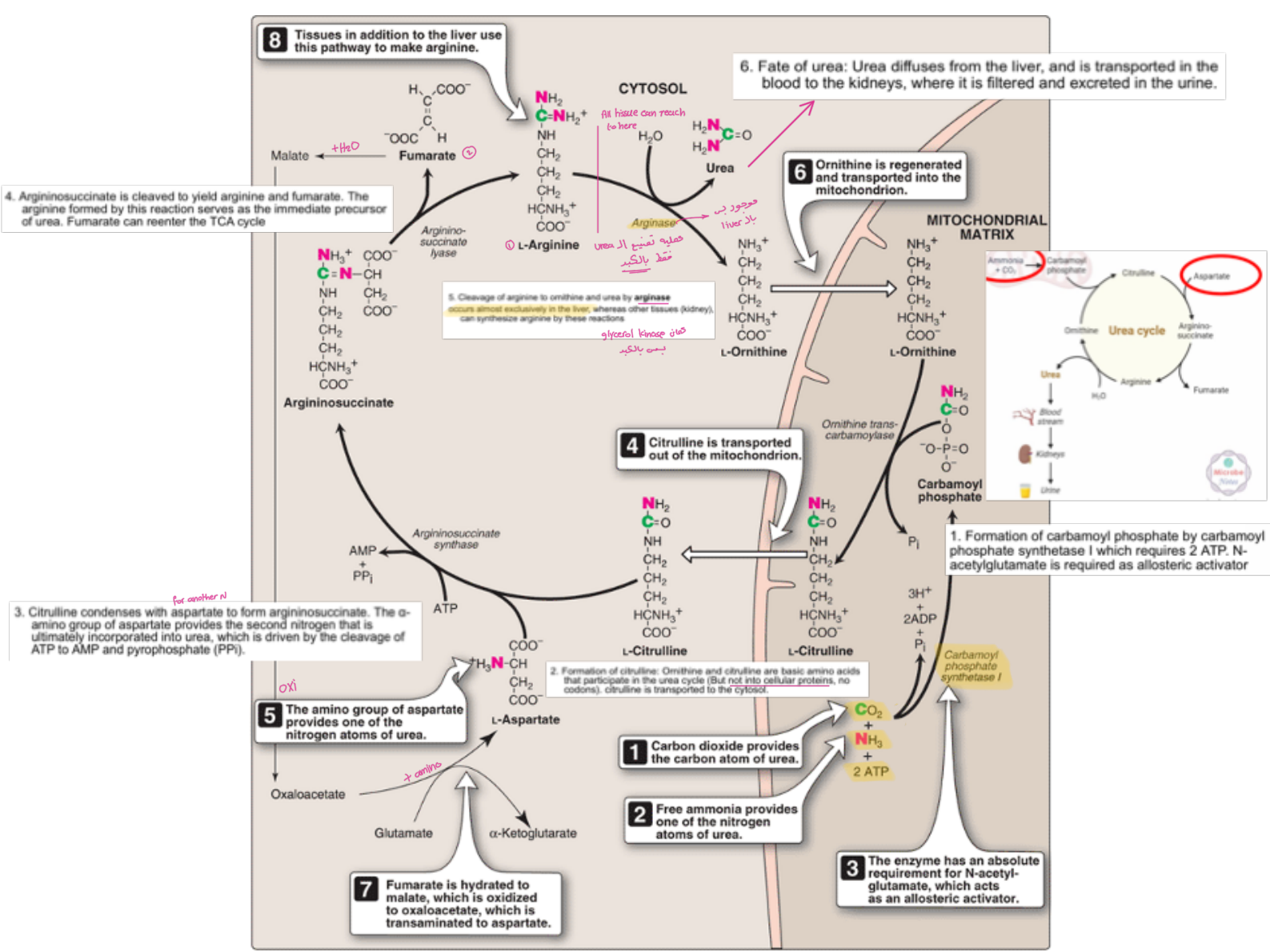
Urea is the major disposal form of amino groups derived from amino acids (90% of the nitrogen-containing components of urine).

One nitrogen of the urea molecule is supplied by free NH3, and the other nitrogen by aspartate, the carbon and oxygen of urea are derived from CO2.

Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

- Reactions of the cycle: On the scheme below




8 Tissues in addition to the liver use this pathway to make arginine.
6. Fate of urea: Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine.
CYTOSOL
All tissue can reach to here
Malate
+H2O
Fumarate
Urea
4. Argininosuccinate is cleaved to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea. Fumarate can reenter the TCA cycle
Arginino-succinate lyase
L-Arginine
Arginase
موجود ب liver بالـ
عملية تصنيع الـ urea فقط بالكبد
6 Ornithine is regenerated and transported into the mitochondrion.
MITOCHONDRIAL MATRIX
5. Cleavage of arginine to ornithine and urea by arginase occurs almost exclusively in the liver, whereas other tissues (kidney), can synthesize arginine by these reactions
glycerol kinase فقط بس بالكبد
L-Ornithine
L-Ornithine
Argininosuccinate
4 Citrulline is transported out of the mitochondrion.
Ornithine trans-carbamoylase
Carbamoyl phosphate
Argininosuccinate synthase
AMP + PPi
ATP
L-Citrulline
L-Citrulline
Pi
1. Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I which requires 2 ATP. N-acetylglutamate is required as allosteric activator
for another N
3. Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea, which is driven by the cleavage of ATP to AMP and pyrophosphate (PPi).
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
2. Formation of citrulline: Ornithine and citrulline are basic amino acids that participate in the urea cycle (But not into cellular proteins, no codons). citrulline is transported to the cytosol.
L-Aspartate
OXI
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
1 Carbon dioxide provides the carbon atom of urea.
CO2 + NH3 + 2 ATP
Oxaloacetate
+ amino
Glutamate
α-Ketoglutarate
2 Free ammonia provides one of the nitrogen atoms of urea.
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.
Ammonia + CO2
Carbamoyl phosphate
Citrulline
Aspartate
Ornithine
Urea cycle
Arginino-succinate
Urea
Arginine
Fumarate
H2O
Blood stream
Kidneys
Urine

UREA CYCLE

simple diffution

6. Fate of urea: Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine.

A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO2 and NH3 by bacterial urease. This ammonia is partly lost in the feces and is partly reabsorbed into the blood.

a b

In patients with kidney failure, plasma urea levels are elevated (hyperammonemia), promoting a greater transfer of urea from blood into the gut.

معلومة

Antibiotics

* Oral administration of **neomycin** reduces the number of intestinal bacteria responsible for this NH3 production.

Overall stoichiometry of the urea cycle

نواتج

Aspartate + NH_3 + CO_2 + 3ATP → Urea + fumarate + 2ADP + AMP + 2 Pi + PPi + 3 H_2O

مصدر اول لـ مصدر ثاني لـ

- the synthesis of urea is irreversible, with a large, negative ΔG.

هادد للعزاره

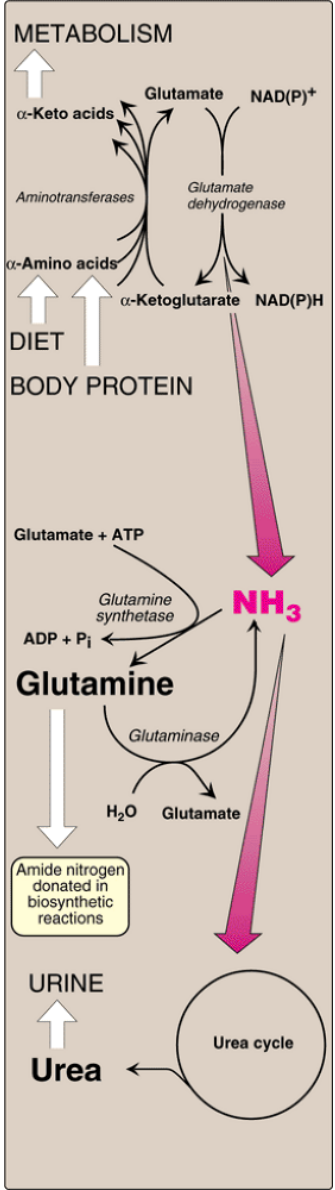
Regulation of the urea cycle

- N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I (the rate-limiting step in the urea cycle) (synthesized from acetyl CoA and glutamate using arginine as an activator).
- the intrahepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis.
- This leads to an increased rate of urea synthesis.

Metabolism of ammonia

- Slight increase in the concentration of urea in blood leads to hyperammonemia which is toxic to the CNS

- Sources of ammonia:
- → From amino acids: mainly in liver by the aminotransferase and glutamate dehydrogenase reactions
- → From glutamine: The kidneys form ammonia from glutamine by the action of renal glutaminase. Ammonia is also obtained from the hydrolysis of glutamine by intestinal glutaminase.
- → From bacterial action in the intestine: Ammonia is formed from urea by the action of bacterial urease in the lumen of the intestine.
- → From amines: Amines obtained from the diet, and monoamines that serve as hormones or neurotransmitters
- → From the catabolism of purines and pyrimidines



Transport of ammonia in circulation

لازم تكون عشان

- ① As **urea**: the most disposal form of ammonia which moves from liver to the kidney

or

- ② As **Glutamine**:
- Occurs primarily in the muscle and liver and nervous system.
- Circulating glutamine is removed by the kidneys and deaminated by glutaminase.

Hyperammonemia

- when the liver function is compromised, due either to genetic defects of the urea cycle, or liver disease, blood levels can rise above 1000 µmol/L.
- hyperammonemia is a medical emergency, because ammonia has a direct neurotoxic effect on the CNS (tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision).
- At high concentrations, ammonia can cause coma and death.

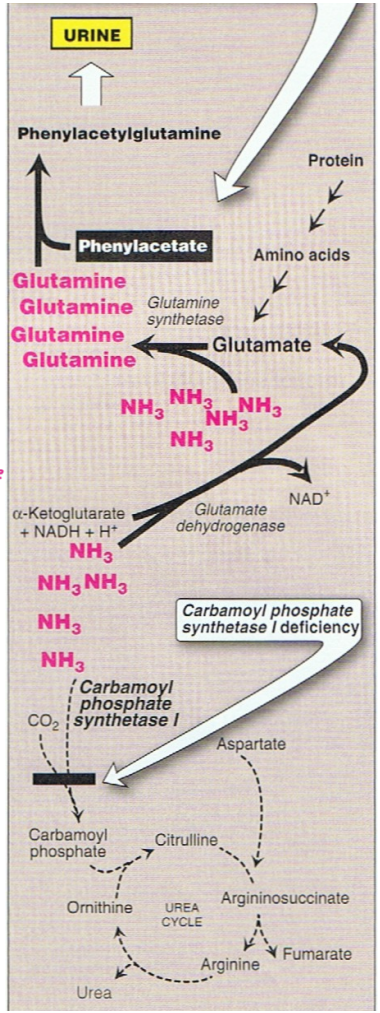
Hyperammonemia

* Abnormality in function

- **Acquired hyperammonemia**: It may be due to viral hepatitis, ischemia, or hepatotoxins. Cirrhosis of the liver caused by alcoholism, hepatitis, or biliary obstruction may result in formation of collateral circulation around the liver.

* genetic

- **Hereditary hyperammonemia**: Genetic deficiencies of each of the five enzymes of the urea cycle had an overall prevalence estimated to be 1 in 30,000 live births.
- Ornithine transcarbamoylase deficiency, which is X-linked, is the most common of these disorders, affecting males predominantly (males more)
- All of the other urea cycle disorders follow an autosomal recessive inheritance pattern. The failure to synthesize urea leads to hyperammonemia during the first weeks following birth leading to mental retardation
- Treatment includes:
  1. limiting protein in the diet
  2. administering compounds that bind covalently to amino acids, producing nitrogen-containing molecules that are excreted in the urine (phenylbutyrate given orally is converted to phenylacetate)



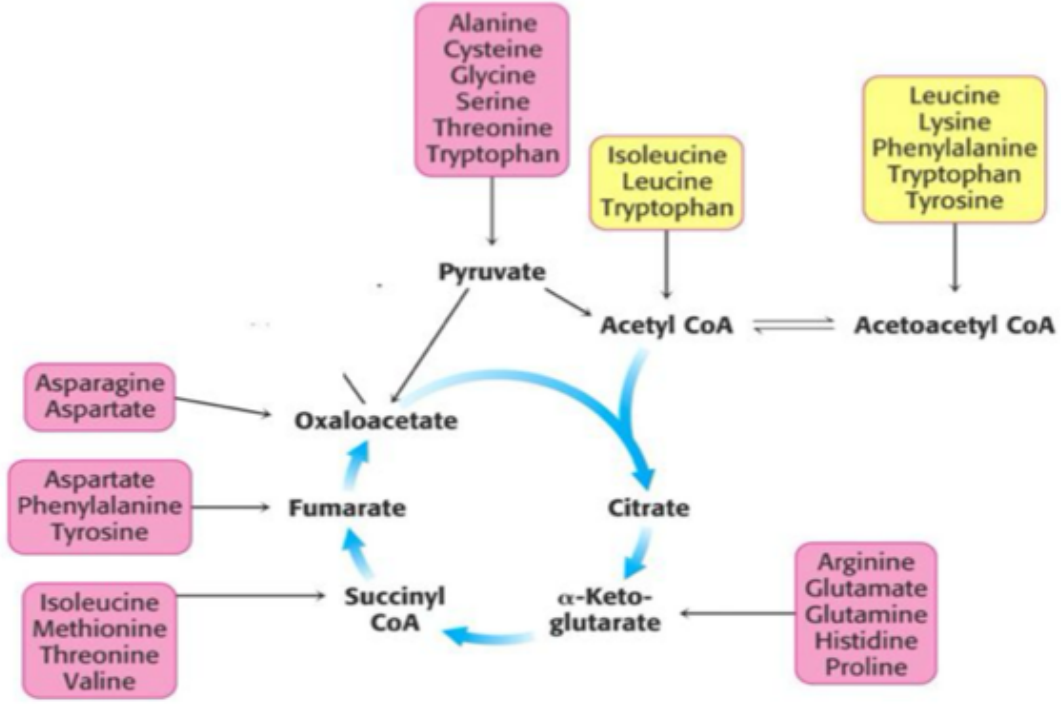
Take a break 💋

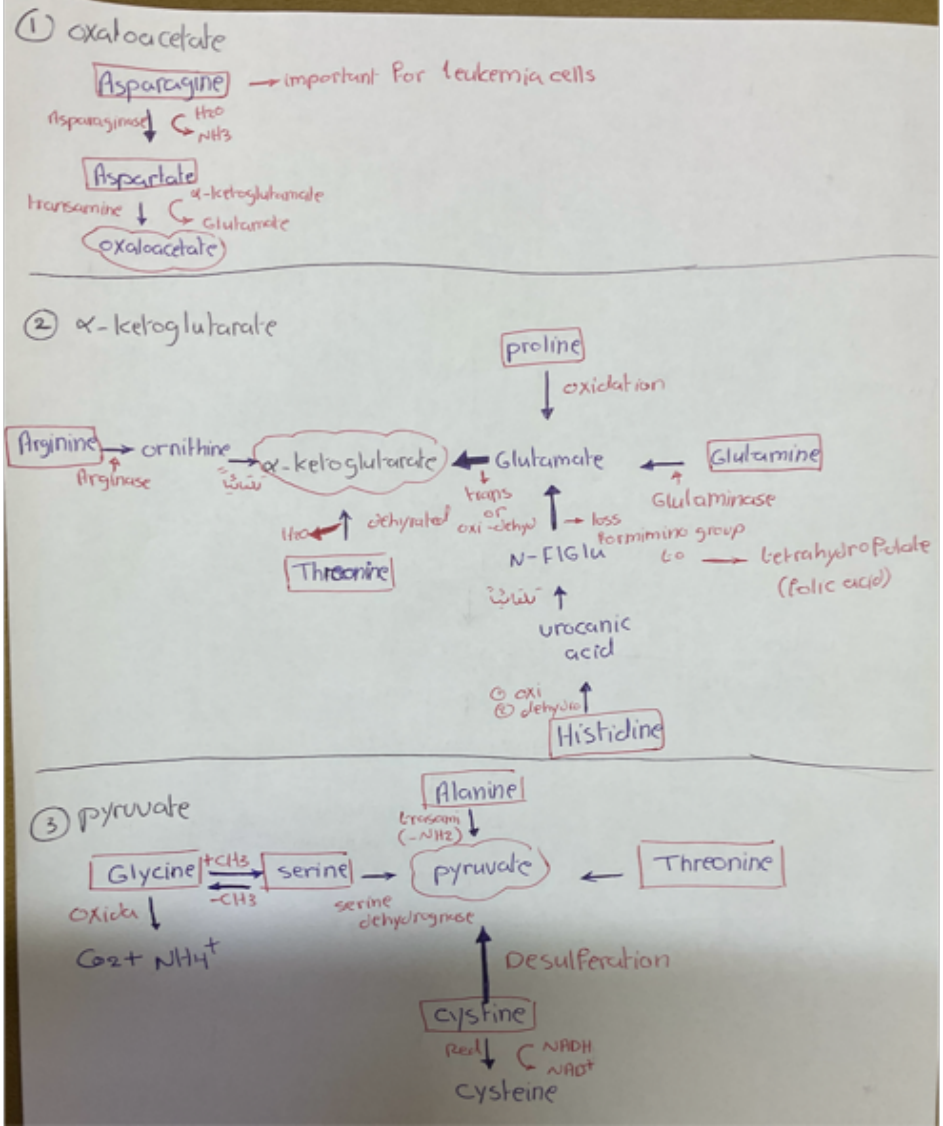
Catabolism of the carbon skeleton

من هون لآخر
التشابتر كتير
مصمم

Amino acid are catabolized to form:

oxaloacetate	5. fumarate
α-ketoglutarate	6. succinyl-CoA
pyruvate	7. acetyl-CoA and acetoacetyl CoA.




① oxaloacetate
Asparagine
important for leukemia cells
Asparaginase
Hro
NH3
Aspartate
α-ketoglutamate
transamine
Glutamate
oxaloacetate
② α-ketoglutarate
proline
oxidation
Arginine
ornithine
α-ketoglutarate
Glutamate
Glutamine
Arginase
transa
oxi-dehyd
Glutaminase
Hro
dehydrated
loss formimino group to
tetrahydrofolate (folic acid)
Threonine
N-FIGlu
urocanic acid
① oxi
② dehydro
Histidine
③ pyruvate
Alanine
transam (-NH2)
Glycine
+CH3
-CH3
serine
pyruvate
Threonine
Oxida
serine dehydrogenase
CO2 + NH4+
Desulferation
cystine
Red
NADH
NAD+
Cysteine

④ Fumarate

phynylalanine

phenylalanine hydroxylase → Tyrosine

Coa enzyme: —

① Tetrabiopterin → bihydro

② $O_2 \rightarrow H_2O$

metabolism of these two:

- Fumarate
- Acetoacetate

enzymes →

⑧ diffiction of these enzymes leads to:

① phenylketonuria
② Alkaptonuria
③ Albinism

⑤ succinyl CoA

Methionine → succinyl CoA

branched a.a: valine, isoleucine → succinyl CoA

succinyl CoA ← precursor of propionyl CoA ← α-ketoglutarate ← dehydration ($-H_2O$) ← Threonine

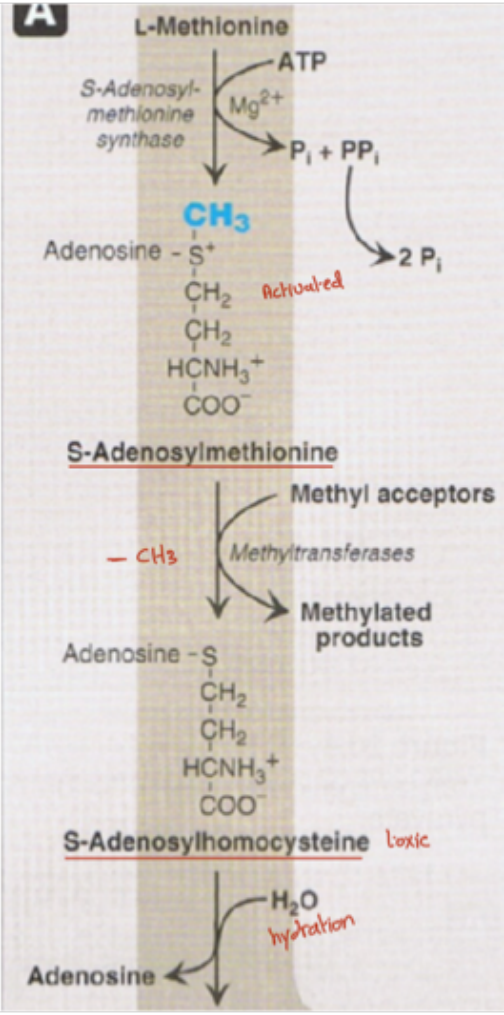
⑥ Acetyl CoA / acetoacetyl CoA

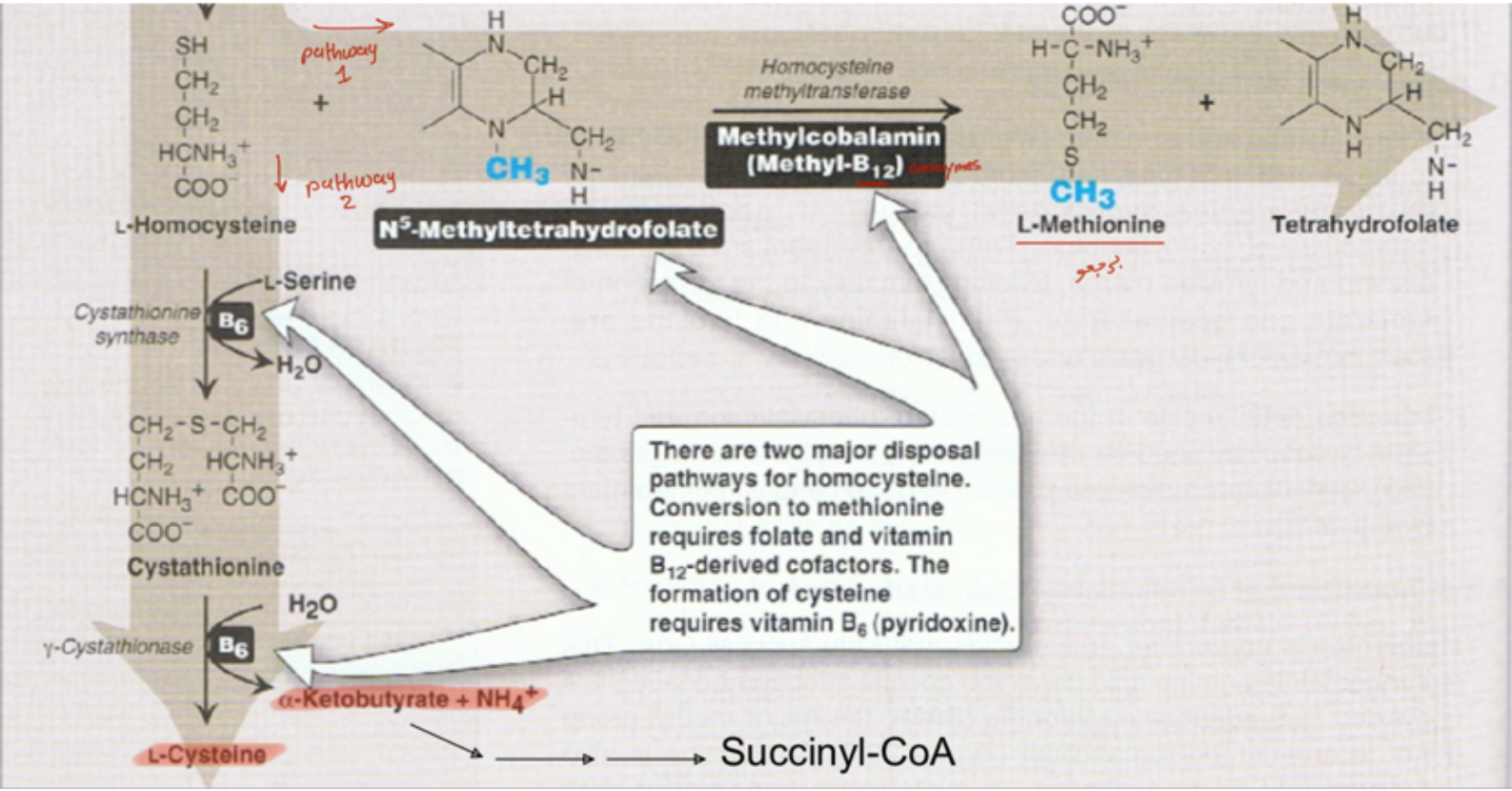
- Leucine (branched) → Acetyl CoA and acetoacetate
- isoleucine → acetyl CoA and propionyl CoA
  - valine
  - leucine
- lysine → - unusual to go under transamination → acetoacetyl CoA
- Tryptophan → Alanine and acetoacetate CoA

- **Methionine:** Methionine is one of four amino acids that form succinyl CoA. This sulfur-containing amino acid deserves special attention because it is converted to S-adenosylmethionine (SAM), the major methyl-group donor in one-carbon metabolism

- Methionine is also the source of homocysteine, a metabolite associated with atherosclerotic vascular disease.

Degradation of valine, isoleucine, and threonine also results in the production of succinyl CoA- a TCA cycle intermediate and glucogenic compound.



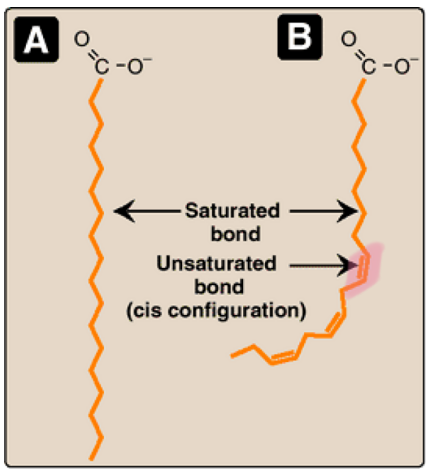

pathway 1
pathway 2
L-Homocysteine
N5-Methyltetrahydrofolate
Homocysteine methyltransferase
Methylcobalamin (Methyl-B12)
L-Methionine
Tetrahydrofolate
L-Serine
Cystathionine synthase
B6
H2O
Cystathionine
γ-Cystathionase
α-Ketobutyrate + NH4+
L-Cysteine
Succinyl-CoA
There are two major disposal pathways for homocysteine. Conversion to methionine requires folate and vitamin B12-derived cofactors. The formation of cysteine requires vitamin B6 (pyridoxine).

Lipid metabolism

Fatty acids
Saturation of fatty acids

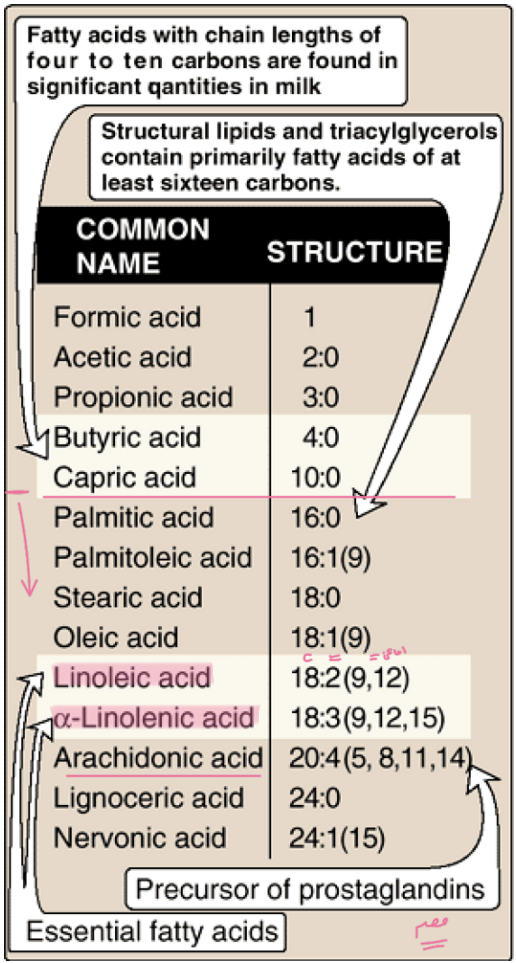
- Fatty acid chains (with no double bonds or one or more double bonds that are always in the cis configuration) and this causes fatty acid to kink at that position

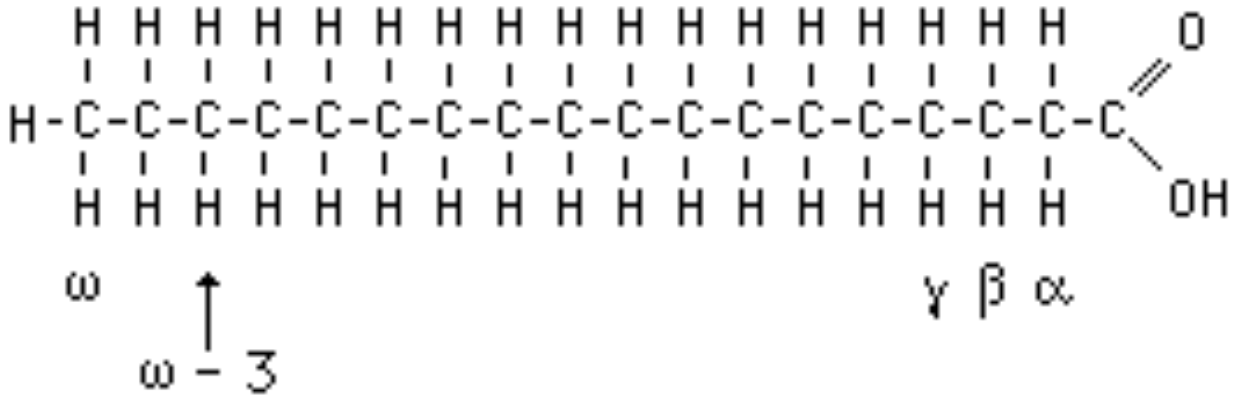
- Addition of double bond decreases the melting temperature (Tm) of a fatty acid, whereas increasing the chain length increases the Tm



Chain length of fatty acids

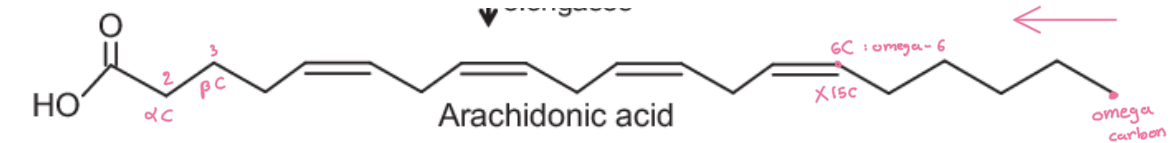
- The number before the colon indicates the number of carbons in the chain, and those after the colon indicate the numbers and positions of double bonds
- For example, arachidonic acid, 20:4(5, 8, 11, 14), is 20 carbons long ana double bonds (between carbons 5-6, 8-9, 11-12, and 14-15). The carbon to which the carboxyl group is attached (carbon 2) called the α-carbon, carbon 3 is the β-carbon. The carbon of the terminal methyl group is called ω-carbon regardless of the chain length
- Arachidonic acid is referred to as an ω-6 while linolenic acid, 18:3(9,12,15), is an ω-3 fatty acid.



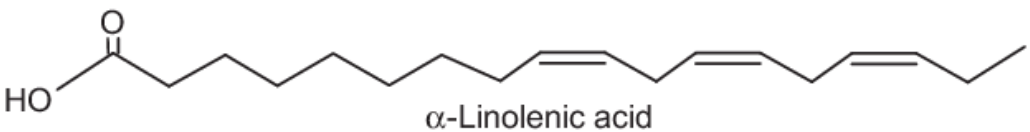


Arachidonic acid, 20:4(5, 8, 11, 14) is an ω-6 fatty acid [20 minus 14=6].

α-linolenic acid, 18:3(9,12,15), is an ω-3 fatty acid [18 minus 15=3].



ω-6 fatty acid



ω-3 fatty acid

Essential fatty acids

- Two fatty acids are dietary essentials in humans:
- Linoleic acid, which is the precursor of arachidonic acid, the substrate for prostaglandin synthesis
- Linolenic acid, the precursor of other ω -3 fatty acids important for growth development
- A deficiency of linolenic acid rest decreased vision and altered learning behaviors
- Arachidonic acid becomes essential if linoleic acid is deficient in the diet.

داخل الجسم

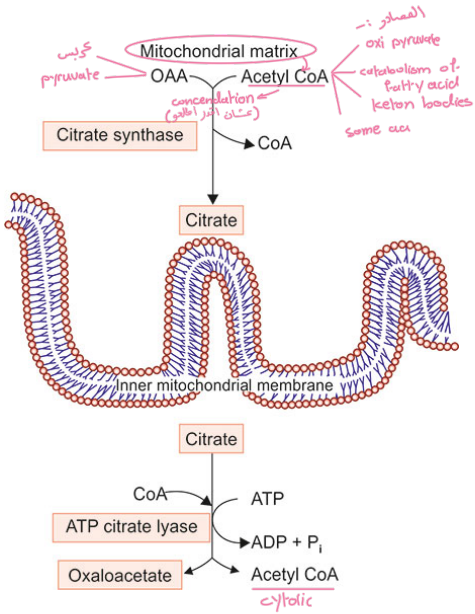
De novo synthesis of fatty acids

In humans, fatty acid synthesis occurs primarily in the **liver** and **lactating mammary glands** and, to a lesser extent, in **adipose tissue**.

The process incorporates carbons from acetyl CoA into the growing fatty acid chain, using ATP and reduced nicotinamide adenine dinucleotide phosphate (NADPH).

- Production of cytosolic acetyl CoA
- First acetate units is transferred from mitochondrial acetyl CoA to the cytosol. Mitochondrial acetyl CoA is produced by:
  - The oxidation of pyruvate
  - The catabolism of fatty acids
  - Ketone bodies
  - Certain amino acids

- The coenzyme A portion of acetyl CoA cannot cross the mitochondrial membrane and only the acetyl portion is transported to the cytosol. It does so in the form of citrate produced by the condensation of oxaloacetate (OAA) and acetyl CoA



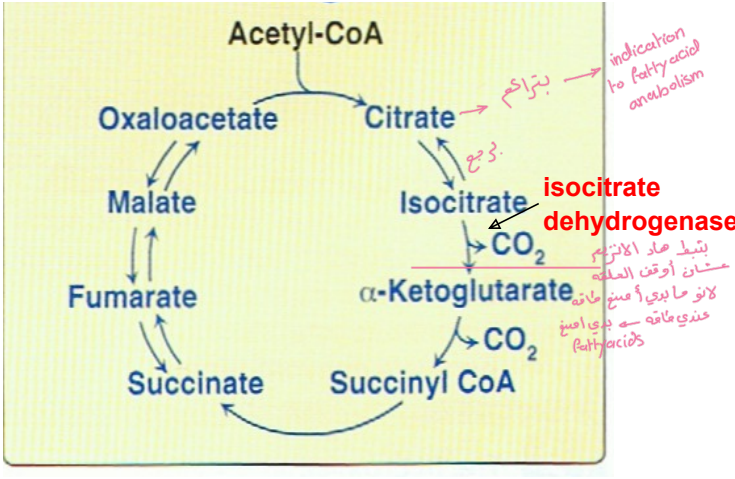
1. translocation of citrate from the mitochonderion to the cytosol

- The translocation of citrate from the mitochonderion to the cytosol, where it is cleaved by **ATP-citrate lyase** to produce cytosolic acetyl CoA and OAA, occurs when the mitochondrial substrate concentration is high.

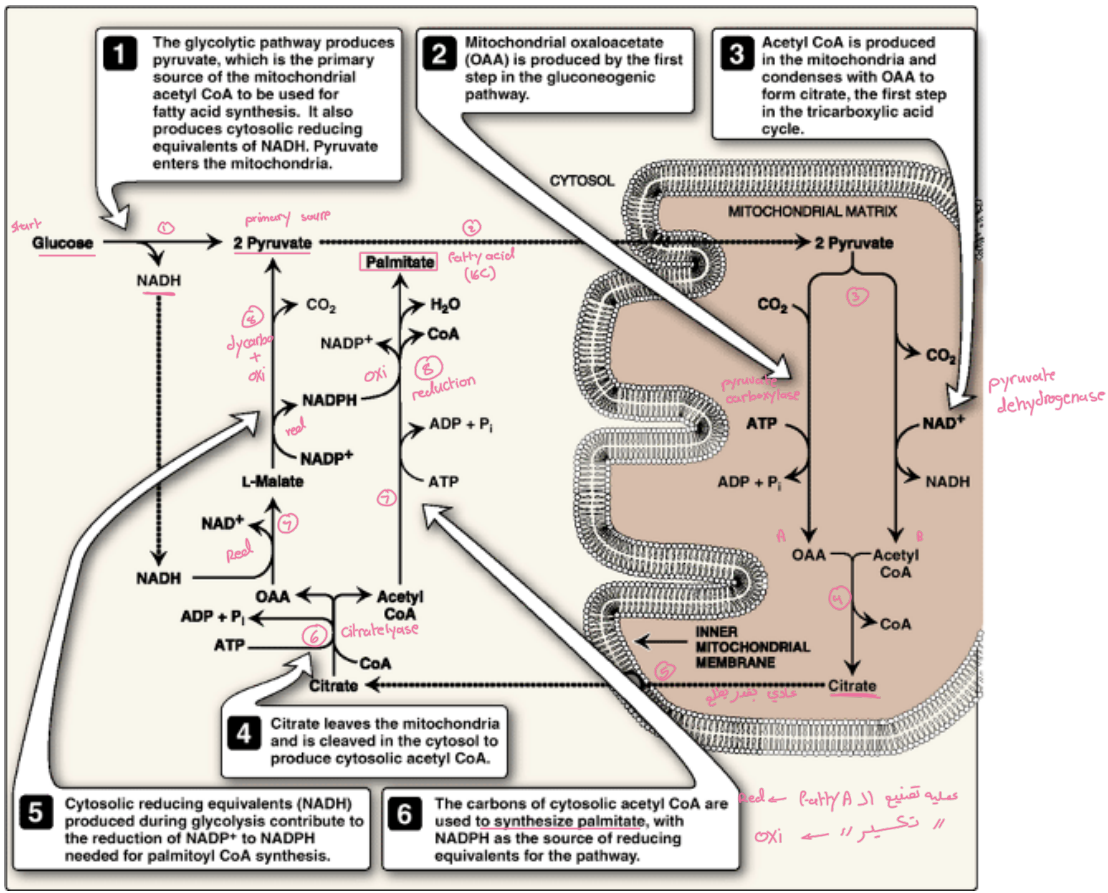
●This is observed when isocitrate dehydrogenase is inhibited by the presence of large amounts of ATP. causing citrate and isocitrate to accumulate.

●A large amount of ATP is needed for fatty acid synthesis

●The increase in both ATP and citrate enhances this pathway.



Source of cytosolic Acetyl coA



السلايد هاي مهمه

2. Carboxylation of acetyl CoA to form malonyl CoA

acetyl CoA ← Base ال تعنيع *

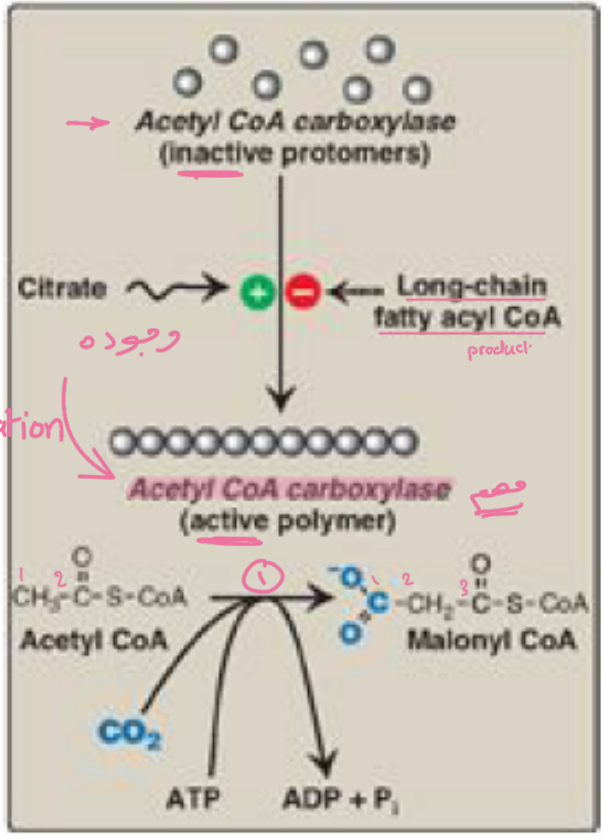
- The carboxylation of acetyl CoA to form malonyl CoA is catalyzed by acetyl CoA carboxylase and requires HCO3- and ATP and biotin coenzyme.

(2) soure: Co2

(3)

مهمين جدا

* fatty acid chain contain carboxyl group so I should add it



Regulation of acetyl CoA carboxylase

A

Short-term regulation of acetyl CoA carboxylase:

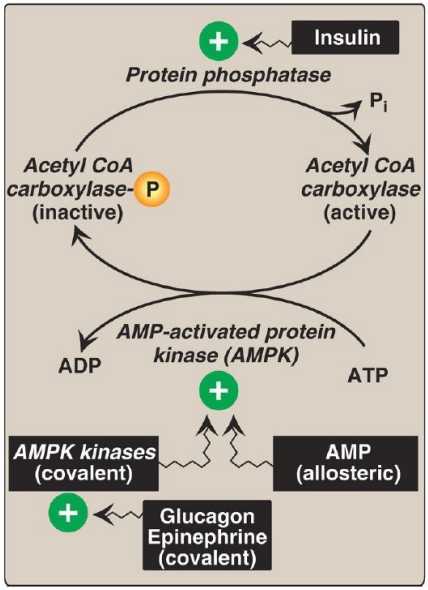
This carboxylation is both the **rate-limiting** and the regulated step in fatty acid synthesis

The **acetyl CoA carboxylase** is a dimer. Which is allosterically activated by citrate by polymerizing it.

The enzyme can be allosterically inactivated by

- Long-chain fatty acyl CoA (the end product of the pathway), which causes its depolymerization.
- Reversible phosphorylation in the presence of epinephrine and glucagon

In the presence of insulin, Acetyl CoA carboxylase is dephosphorylated and, so activated.



B

Long-term regulation of acetyl CoA carboxylase:

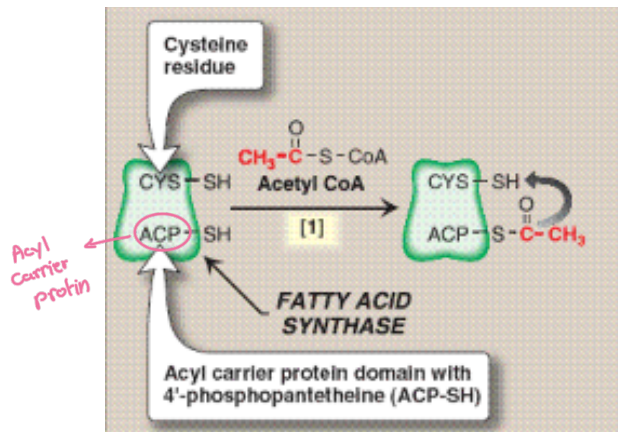
- Prolonged consumption of **high-calorie, high-carbohydrate diets** causes an increase in acetyl CoA carboxylase synthesis, thus increasing **fatty acid synthesis.**
- Conversely, a **low-calorie diet or fasting** causes a **reduction in fatty acid synthesis** by decreasing the synthesis of acetyl CoA carboxylase.

عملية تركيب بعض تفاعلات الـ Base الأول

Fatty acid synthase

للتفاعلات الـ Base الثاني :-

- The remaining series of reactions of fatty acid synthesis is catalyzed by the multifunctional, dimeric enzyme, **fatty acid synthase**.
- Each fatty acid synthase monomer is a multicatalytic polypeptide with seven different enzymatic activities plus a domain that covalently binds a molecule of 4'-phosphopantetheine, carries acetyl and acyl units on its terminal thiol (-SH group) during fatty acid synthesis



Steps of fatty acid synthesis

[1] A molecule of acetate is transferred from acetyl CoA to the -SH group of the ACP. Domain: Acetyl CoA-ACP acetyltransacylase

[2] This two-carbon fragment is transferred to the holding site, the thiol group of a cysteine residue on the enzyme.

[3] The now-vacant ACP accepts a three-carbon malonate from malonyl CoA. Domain: Malonyl CoA-ACP-transacylase

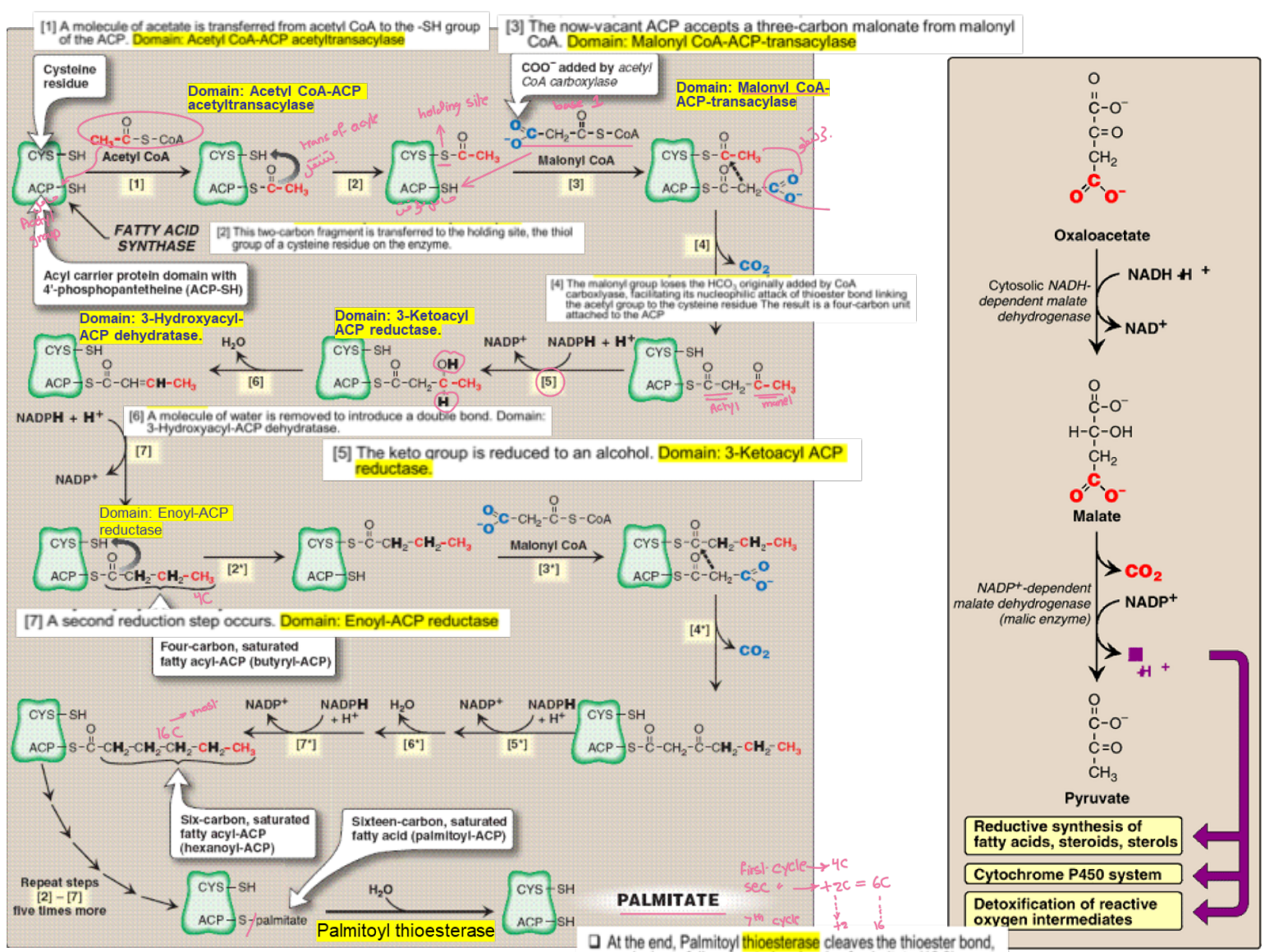
[4] The malonyl group loses the HCO_3 originally added by CoA carboxlyase, facilitating its nucleophilic attack of thioester bond linking the acetyl group to the cysteine residue The result is a four-carbon unit attached to the ACP

[5] The keto group is reduced to an alcohol. Domain: 3-Ketoacyl ACP reductase.

[6] A molecule of water is removed to introduce a double bond. Domain: 3-Hydroxyacyl-ACP dehydratase.

[7] A second reduction step occurs. Domain: Enoyl-ACP reductase

- At the end, Palmitoyl thioesterase cleaves the thioester bond, producing a fully saturated molecule of palmitate (16:0).


[1] A molecule of acetate is transferred from acetyl CoA to the -SH group of the ACP. Domain: Acetyl CoA-ACP acetyltransacylase
[3] The now-vacant ACP accepts a three-carbon malonate from malonyl CoA. Domain: Malonyl CoA-ACP-transacylase
Cysteine residue
Domain: Acetyl CoA-ACP acetyltransacylase
COO⁻ added by acetyl CoA carboxylase
Domain: Malonyl CoA-ACP-transacylase
Acetyl CoA
Malonyl CoA
[1]
[2]
[3]
FATTY ACID SYNTHASE
[2] This two-carbon fragment is transferred to the holding site, the thiol group of a cysteine residue on the enzyme.
Acyl carrier protein domain with 4'-phosphopantetheine (ACP-SH)
[4]
CO2
[4] The malonyl group loses the HCO3 originally added by CoA carboxylase, facilitating its nucleophilic attack of thioester bond linking the acetyl group to the cysteine residue The result is a four-carbon unit attached to the ACP
Domain: 3-Hydroxyacyl-ACP dehydratase.
Domain: 3-Ketoacyl ACP reductase.
H2O
[6]
NADP+
NADPH + H+
[5]
[6] A molecule of water is removed to introduce a double bond. Domain: 3-Hydroxyacyl-ACP dehydratase.
[7]
[5] The keto group is reduced to an alcohol. Domain: 3-Ketoacyl ACP reductase.
Domain: Enoyl-ACP reductase
[2*]
Malonyl CoA
[3*]
[4*]
CO2
[7] A second reduction step occurs. Domain: Enoyl-ACP reductase
Four-carbon, saturated fatty acyl-ACP (butyryl-ACP)
[7*]
[6*]
[5*]
Six-carbon, saturated fatty acyl-ACP (hexanoyl-ACP)
Sixteen-carbon, saturated fatty acid (palmitoyl-ACP)
Repeat steps [2] – [7] five times more
Palmitoyl thioesterase
PALMITATE
❑ At the end, Palmitoyl thioesterase cleaves the thioester bond, producing a fully saturated molecule of palmitate (16:0).
Oxaloacetate
Cytosolic NADH-dependent malate dehydrogenase
NADH + H+
NAD+
Malate
NADP+-dependent malate dehydrogenase (malic enzyme)
CO2
NADP+
NADPH + H+
Pyruvate
Reductive synthesis of fatty acids, steroids, sterols
Cytochrome P450 system
Detoxification of reactive oxygen intermediates

لمّا اصناع > 16C

Further elongation of fatty acids

- Palmitate can be further elongated by the addition of two-carbon units in the endoplasmic reticulum (**ER)** and **the mitochondria**. These organelles use separate enzymatic processes.

- The brain has additional elongation capabilities allowing it to produce the very-long-chain fatty acids (up to 24 C) that are required for synthesis of brain lipids.

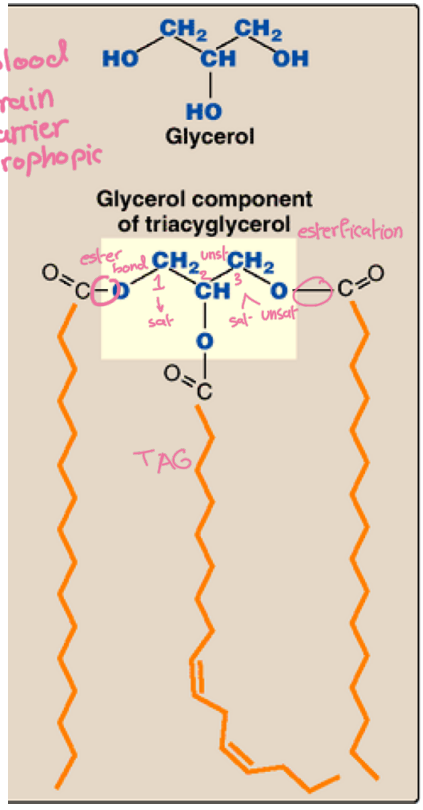
- Enzymes present in the **ER** are responsible for desaturating fatty acids (that is, adding cis double bonds). Termed **mixed-function oxidases**, the desaturation reactions require NADH and O2.

- We must have the polyunsaturated linoleic and linolenic acids provided in the diet.

Storage of fatty acids as components of triacylglycerols

- Mono-, di-, and triacyiglycerols consist of one, two, or three molecules of fatty acids are esterified to a molecule of glycerol through their carboxyl groups, resulting in a loss of negative charge and formation of 'neutral fat"
  - Fatty acid at C1 is usually saturated
  - Fatty acid at C2 is usually unsaturated
  - Fatty acid at C3 can be either

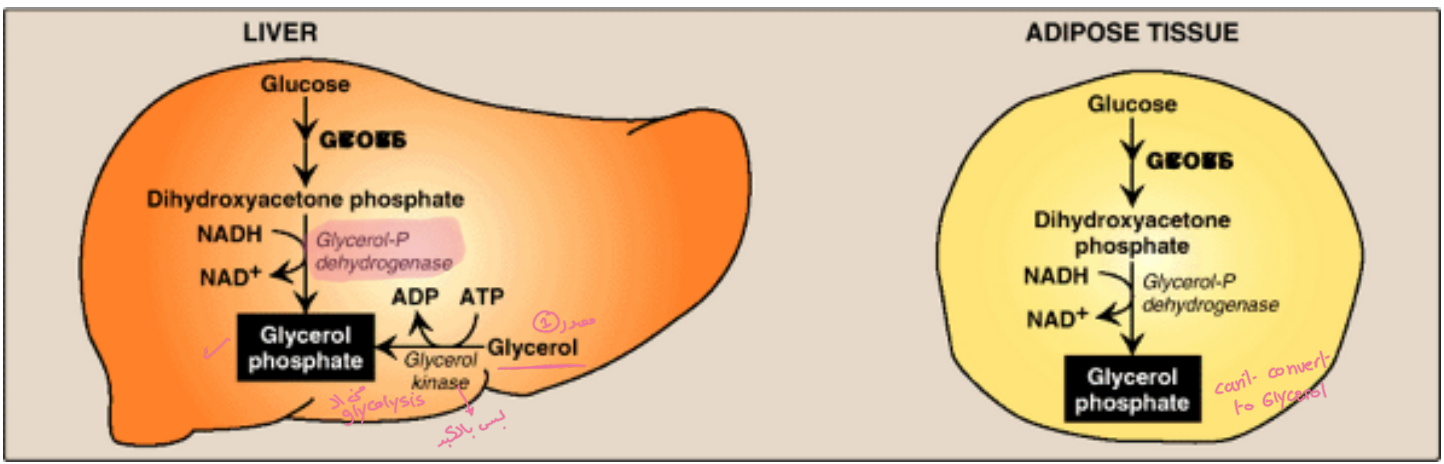
- If a species of acylglycerol is solid at room temperature, it is called a "fat", if liquid, it is called an "oil"



Storage of TAG

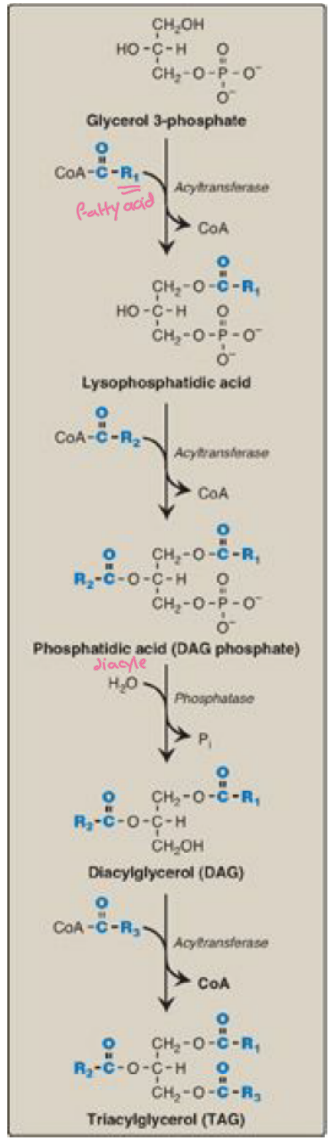
- TAGs are slightly soluble in water and cannot form stable micelles so they coalesce within adipocytes to form oily droplets that are nearly anhydrous.
- They act as the major energy reserve of the body.

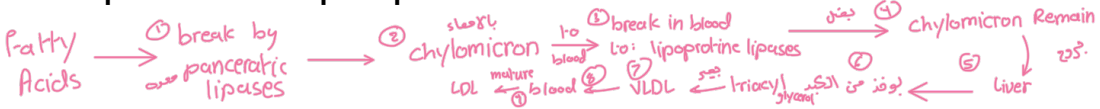
- Production of glycerol 3P



Synthesis of triacylglycerol

- Synthesis of glycerol phosphate from glucose during glycolysis in liver and adipose tissue
- Conversion of a free FA to its activated form (CoA)
- TAG is synthesized
- Different fates of TAG in the liver and adipose tissue
- In adipose tissue, TAG is stored in the cytosol of the cells in a nearly anhydrous form.
- → In liver, most are exported, packaged with cholesteryl esters, cholesterol, phospholipid, and protein (apolipoprotein B-100) to form lipoprotein particles called very low density lipoproteins (VLDL). VLDL are secreted into the blood where they mature and function to deliver the endogenously-derived lipids to the peripheral tissues.





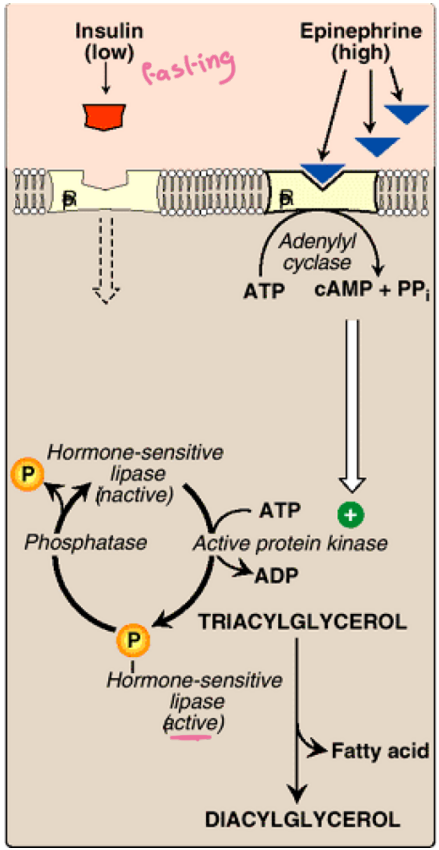
Mobilization of stored fat

- Release of fatty acids from TAG
- This process is initiated by hormone-sensitive lipase, which removes a fatty acid from carbon 1 and/or carbon 3 of the TAG.
- Additional lipases specific for diacylglycerol or monoacylglycerol remove the remaining fatty acids.

Mobilization of stored fat

- Activation of hormone-sensitive lipase (HSL): This enzyme is activated when phosphorylated by a 3',5 '-cyclic AMP-dependent protein kinase in the adipocyte upon binding of hormones (like epinephrine) to receptors on the cell membrane, and activation of adenylate cyclase

- The process is similar to that of the activation of glycogen phosphorylase :
- Because acetyl CoA carboxylase is inhibited upon phosphorylation, when the cAMP-mediated cascade is activated. fatty acid synthesis is turned off when TAG degradation is turned on.
- In the presence of high plasma levels of insulin and glucose, HSL is dephosphorylated (inactive)



Mobilization of stored fat

Fate of glycerol:

It cannot be metabolized by **adipocytes** because they **lack glycerol kinase**. Rather, glycerol is transported through the blood to the liver, where it can be phosphorylated, which can be used to form TAG in the liver; or can be converted to DHAP that can participate in glycolysis or gluconeogenesis.

Fate of fatty acids:

The free fatty acids move through the cell membrane of the adipocyte, and immediately bind to albumin in the plasma, enter cells, get activated to their CoA derivatives, and are oxidized for energy.

Active transport of fatty acids across membranes is mediated by a membrane fatty acid binding protein

plasma free fatty acids cannot be used for fuel by **erythrocytes**, which have no mitochondria, or by the **brain** because of the impermeable BBB

1 β-Oxidation of fatty acids

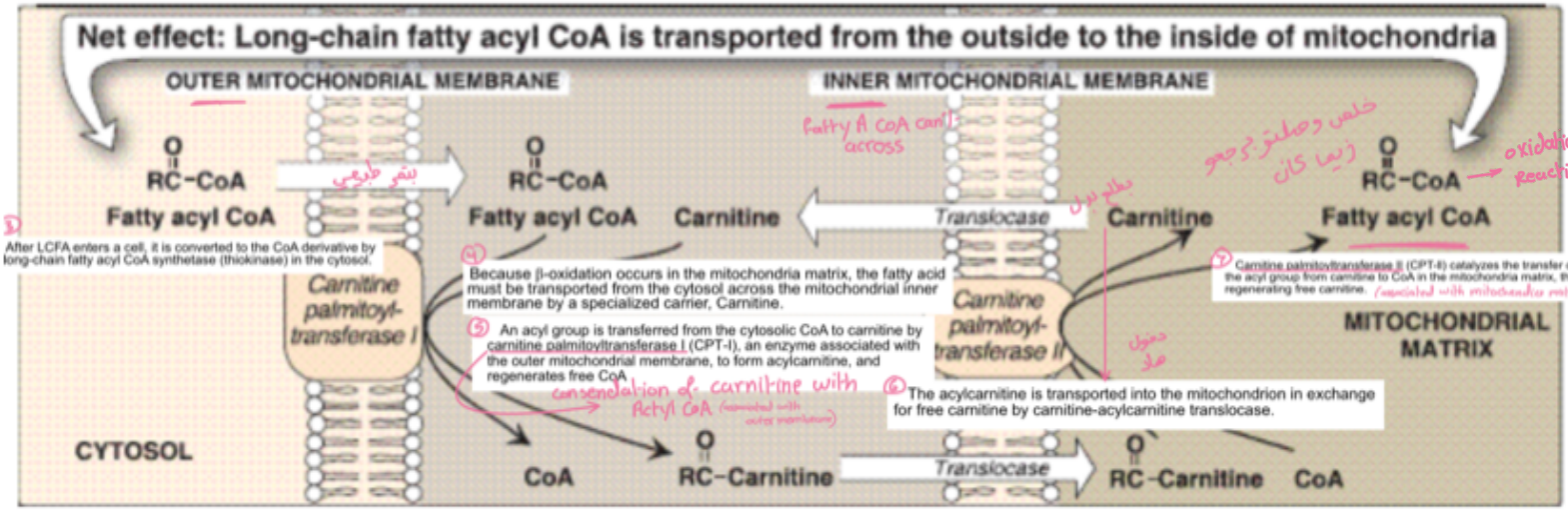
lipolysis

1. The major pathway for catabolism of saturated fatty acids is a mitochondrial pathway called β-oxidation, in which two-carbon fragments are successively removed from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and FADH2.

(two carbon I cut)

كل عمليه تقطيع

2. Transport of long-chain fatty acids (LCFA) into the mitochondria:



Inhibitor of the carnitine shuttle

1. Malonyl CoA inhibits CPT, thus preventing the entry of long-chain acyl groups into the mitochondrial matrix.

ذكيرنا ← تصنع ← ؟

2. When fatty acid synthesis is occurring in the cytosol (as indicated by the presence of malonyl CoA), the newly made palmitate cannot be transferred into the mitochondria and degraded

ما تصرم وتصنع بنفس الوقت

Carnitine

Sources:

from the diet (meat, diary products, nuts), synthesized from the amino acids lysine and methionine by an enzymatic pathway found in the liver and kidney but not in skeletal or heart muscle.

these tissues are totally dependent on carnitine provided by hepatocytes or the diet, and distributed by the blood.
(**Skeletal muscle** contains 97% of all carnitine in the body)

Additional functions:

a. The carnitine system also allows the export from the mitochondria of branched-chain acyl groups (such as those produced during the catabolism of the branched-chain amino acids).

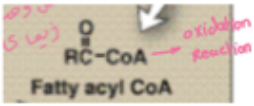
b. The carnitine system is involved in the trapping and excretion via the kidney of acyl groups that cannot be metabolized by the body.

Carnitine deficiencies

- result in a decreased ability of tissues to use LCFA as a metabolic fuel, can also cause the accumulation of toxic amounts of free fatty acids and branched-chain acyl groups in cells.

- Secondary carnitine deficiency occurs for many reasons:
  1) in patients with **liver disease** causing decreased synthesis of carnitine
  2) individuals suffering from **malnutrition** or those on strictly vegetarian diets
  3) in those with an **increased requirement** for carnitine as in pregnancy, severe infections, burns, or trauma
  4) in those undergoing **hemodialysis**, which removes carnitine from the blood

- Congenital deficiencies in one of the components of the carnitine palmatoyltransferase system, in tubular reabsorption of carnitine, or a deficiency in carnitine uptake by cells, can also cause carnitine deficiency.

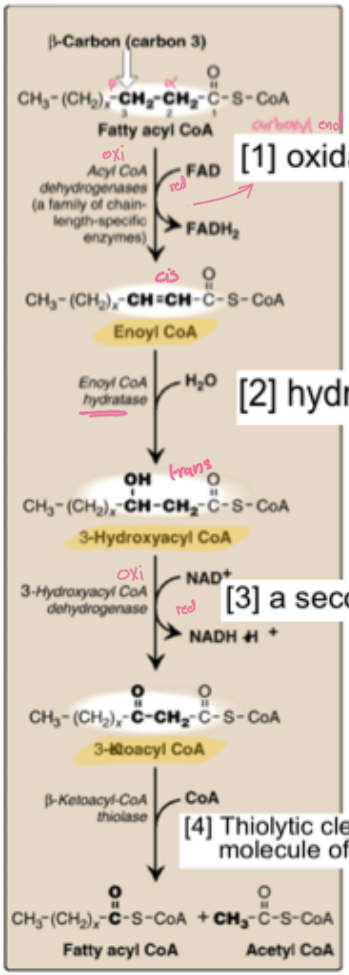


Reactions of β-oxidation

It consists of a sequence of four reactions that result in shortening the fatty acid chain by two carbons.

1# for sat. even No. of C Fatty acids

F.A breakdown



[1] oxidation that produces FADH2

[2] hydration step

[3] a second oxidation that produces NADH

[4] Thiolytic cleavage that releases a molecule of acetyl CoA.

These four steps are repeated for saturated fatty acids of even numbered carbon chains (n16), each cycle producing an acetyl group plus one NADH and one FADH2

palmetic : 7 cycles

7 NADH = 2.5 * 7 = 17.5
7 FADH2 = 1.5 * 7 = 10.5
Tot. ATP = 28

16C → 8 Actyle CoA → كربس

8 * 10 = 80

28 + 80 = 108 ← palmeticsl من تكسير ATP

Actyl CoA

* The final thiolytic cleavage produces two acetyl groups.

* Acetyl CoA is a positive allosteric effector of pyruvate carboxylase, thus, linking fatty acid oxidation and gluconeogenesis.

Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency

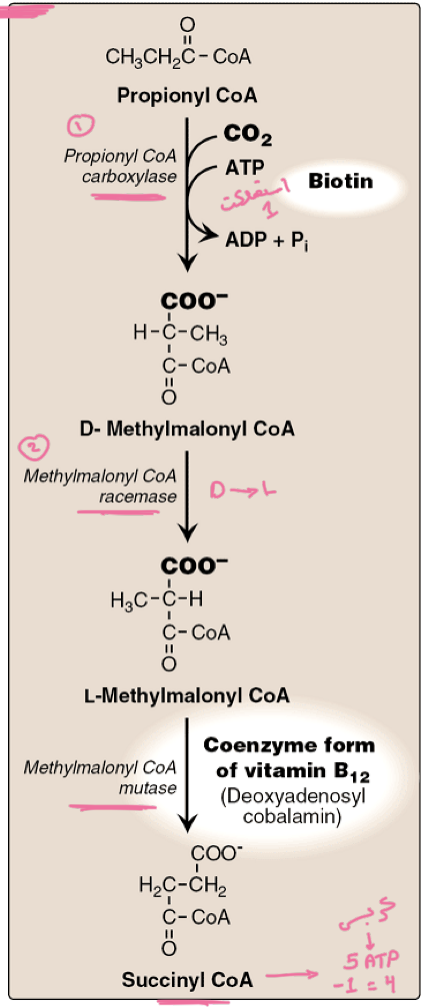
Acyl CoA dehydrogenases (a family of chain-length-specific enzymes)

- In mitochondria, there are four fatty acyl CoA dehydrogenase species, each of which has a specificity for either short-, **medium-**, long-, or very-long-chain fatty acids.
- MCAD deficiency is:
  - an autosomal, recessive disorder جين متنحي
  - one of the most common inborn errors of metabolism. المواليد الجدد
  - causes a decrease in fatty acid oxidation and severe hypoglycemia (no full energetic benefit from fatty acids and so must now rely on glucose).
- Treated by a carbohydrate-rich diet.
- Infants are particularly affected by MCAD deficiency, because they rely for their nourishment on milk, which contains primarily MCADS
- MCAD dehydrogenase deficiency has been identified as the cause of sudden infant death syndrome (SIDS) or Reye's syndrome

حليب فيو carb

2 # Oxidation of fatty acids with an odd number

- It oxidizes two carbons at a time (producing acetyl CoA) until the last three carbons (propionyl CoA).
- (Propionyl CoA is also produced during the metabolism of certain amino acids)
- This compound is carboxylated to methylmalonyl CoA by propionyl CoA carboxylase (requires biotin), which is then converted to succinyl CoA by methylmalonyl CoA mutase (requires vitamin B12).
  (Succinyl CoA can enter TCA cycle)
- ✡ A genetic error in the mutase or vitamin B12 deficiency causes methylmalonic acidemia and aciduria in addition to developmental retardation.

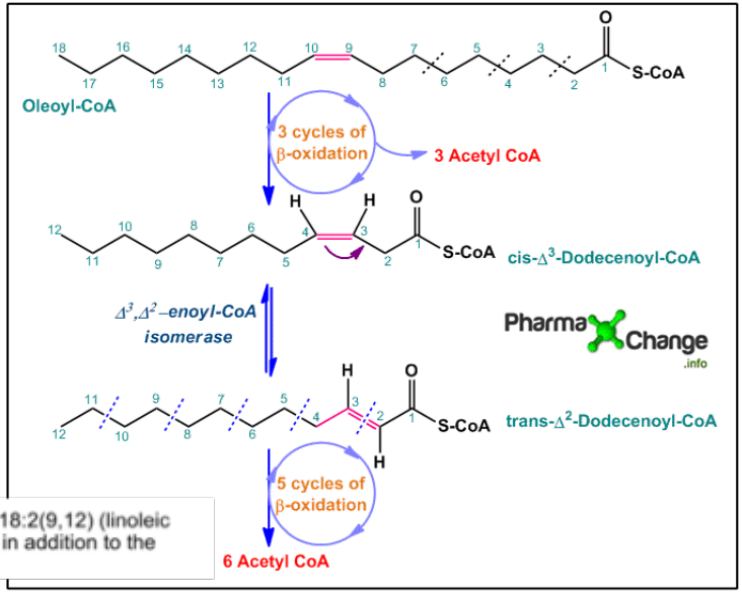


* first step → hydration

3 # Oxidation of unsaturated fatty acids

unsat- ↓ no need to first step ↓ No FADH2 released ↓ less energy

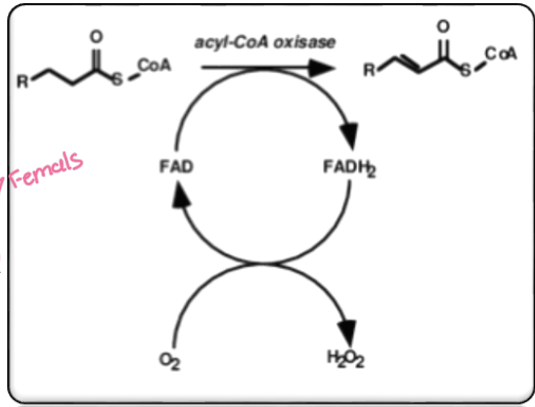
- The oxidation of unsaturated fatty acids provides less energy than that of saturated fatty acids because they are less highly reduced and, therefore, fewer reducing equivalents can be produced from these structures.
- Oxidation of monounsaturated fatty acids, such as 18:1(9) (oleic acid) requires one additional enzyme, **3,2-enoyl CoA isomerase** (converts the 3-cis derivative obtained after **three rounds** of p-oxidation to the 2-trans derivative that can serve as a substrate for the hydratase)



Oxidation of polyunsaturated fatty acids, such as 18:2(9,12) (linoleic acid) requires an **NADPH-dependent reductase** in addition to the isomerase.

Oxidation in the peroxisome

- Very-long-chain fatty acids (VLCFA), twenty carbons long or longer, undergo a preliminary β-oxidation in **peroxisomes**. The shortened fatty acid is then transferred to a mitochondrion for further oxidation.
- In contrast to mitochondrial β-oxidation, the initial dehydrogenation in peroxisomes is catalyzed by an **FAD-containing acyl CoA oxidase.**
- The FADH2 produced is oxidized by molecular oxygen, which is reduced to H2O2. The H2O2 is reduced to H2O by catalase
- The genetic defects Zellweger (cerebrohepatorenal) syndrome (a defect in peroxisomal biogenesis in all tissues) and X-linked adrenoleukodystrophy (a defect in peroxisomal activation of VLCFA) lead to accumulation of VLCFA in the blood and tissues.

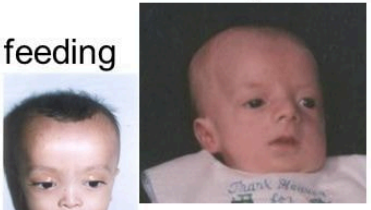


Peroxisomal Disorders

Zellweger Syndrome Cerebro-hepato-renal syndrome

Clinical signs

- Typical and easily recognized dysmorphic facies.
- Progressive degeneration of Brain/Liver/Kidney, with death ~6 mo after onset.
- Hypotonic, seizures and poor feeding
- Distinctive facies.
- Retinal dystrophy,
- hearing loss, severe DD

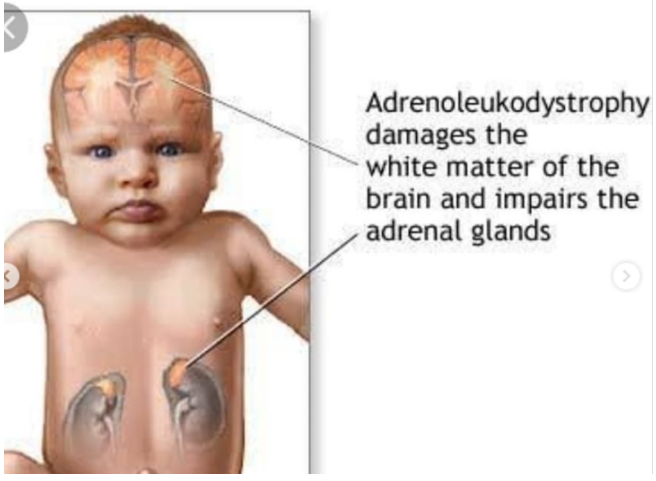


Diagnosis

- Biochemical, serum Very Long Chain Fatty Acids- VLCFAs
- Gene test

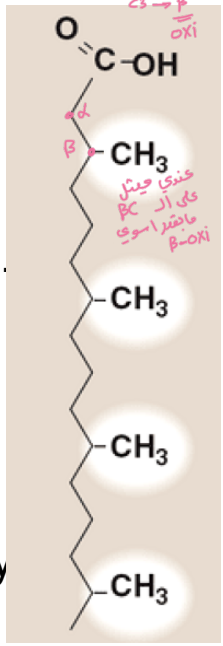
●The genetic defects Zellweger (cerebrohepatorenal) syndrome (a defect in peroxisomal biogenesis in all tissues)

●and X-linked adrenoleukodystrophy (a defect in peroxisomal activation of VLCFA) lead to accumulation of VLCFA in the blood and tissues.



2 α-Oxidation of fatty acids

- The branched-chain fatty acid (phytanic acid) is not a substrate for acyl CoA dehydrogenase due to the methyl group on its third carbon
- Instead, it is hydroxylated at the α-carbon by **fatty acid α -hydroxylase**.
- The product is decarboxylated and then activated to its CoA derivative, which is a substrate for the enzymes of β-oxidation.
- **Refsum disease** is a rare, autosomal recessive disorder caused by a deficiency of α-hydroxylase. Leading to the accumulation of phytanic acid in the plasma and tissues.
- The symptoms are primarily neurologic, that treated by dietary restriction to halt disease progression



موضوع جديد و الأخير ك

Ketone bodies

① مهمين للدماغ
② مو تبطين بالكبد

مخططا

- Liver mitochondria can convert acetyl CoA derived from fatty acid oxidation into the ketone bodies, acetoacetate and 3-hydroxy-butyrate.

β-fatty oxi → Acetyl CoA → Liver → keton bodies

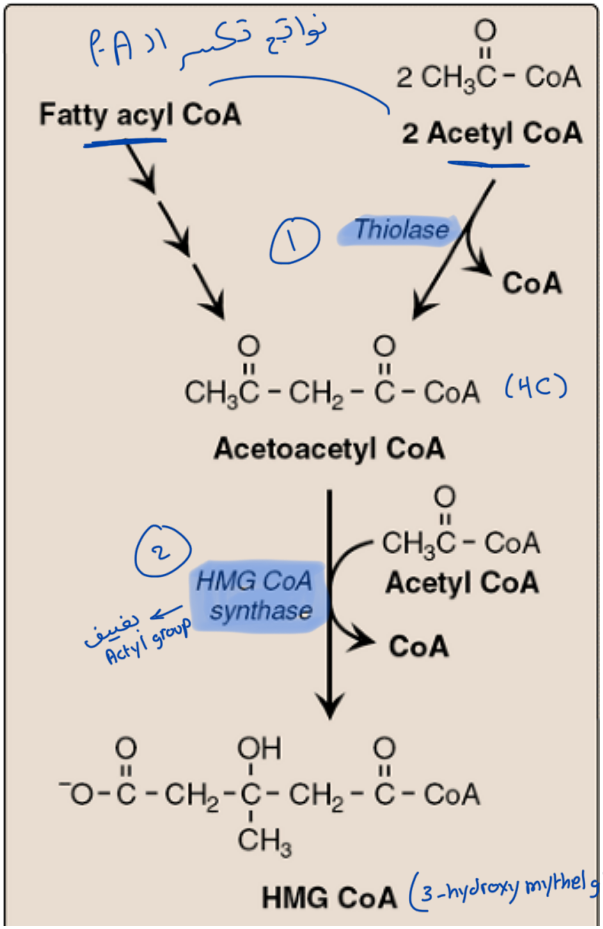
- Peripheral tissues possessing mitochondria can oxidize 3-hydroxybutyrate to acetoacetate, which can be reconverted to acetyl CoA, thus producing energy for the cell.

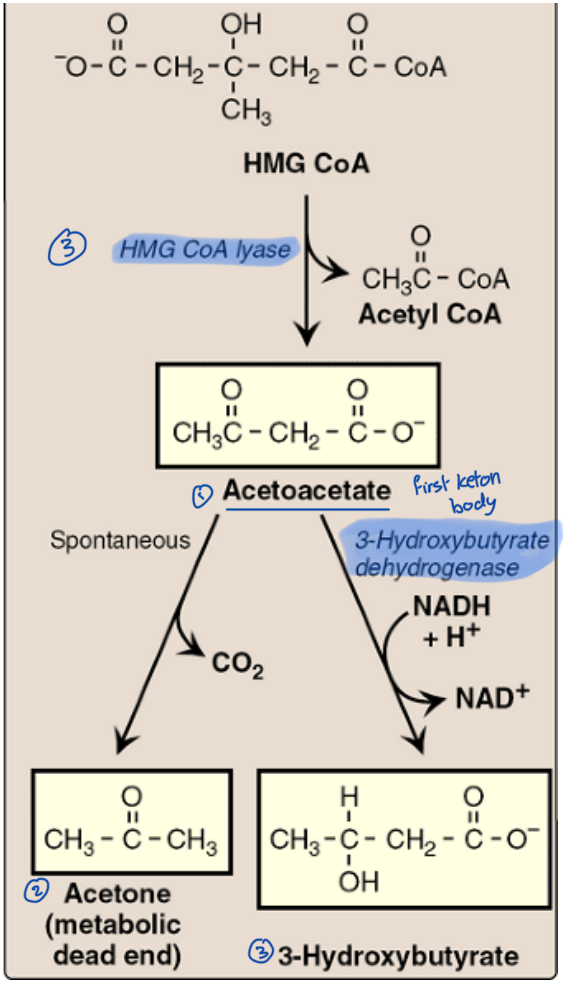
- Unlike fatty acids, ketone bodies can be utilized by the brain and, therefore, are important fuels during a fast.

ما بقدر يستفيد منهم

- The liver lacks the ability to degrade ketone bodies, and so synthesizes them specifically for the peripheral tissues.

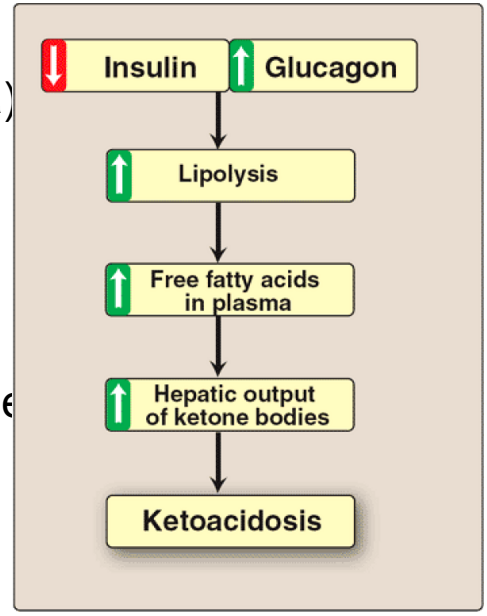
Synthesis of ketone bodies by the liver





Ketoacidosis

- Ketoacidosis occurs when the rate of formation of ketone bodies is greater than their rate of use, as seen in cases of uncontrolled, type 1 (insulin-dependent) diabetes mellitus.
- their levels begin to rise in the blood (ketonemia) and eventually in the urine (ketonuria).
- In such individuals, high fatty acid degradation produces excessive amounts of acetyl CoA.
- It also depletes the NAD+ pool and increases the NADH pool, which slows the TCA cycle



no polymers

Metabolism of phospholipids and cholesterol

* This chapter include

1. Biosynthesis of membrane phospholipids
2. Synthesis of sphingomyelin
3. Synthesis of PE, PC and PS
4. Synthesis of PI
5. Synthesis of PGH2
6. Cholesterol synthesis
7. Synthesis of Bile acids

1

Phospholipids

charghed / uncharged

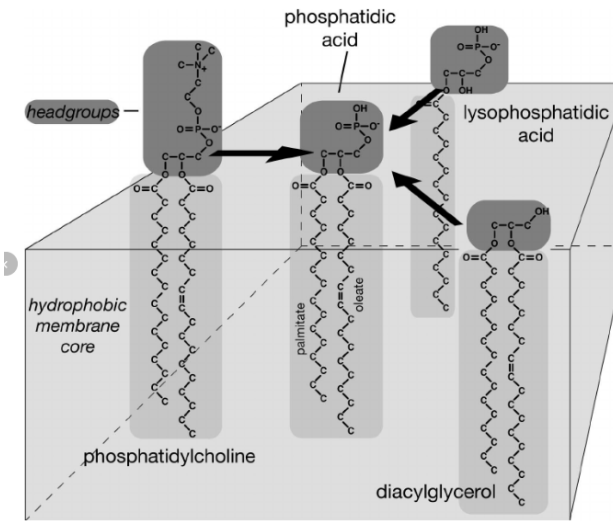
- Are polar, ionic compounds composed of an alcohol that is attached by a phosphodiester bridge to either diacylglycerol or sphingosine (amphipathic)
- Phospholipids are the predominant lipids of cell membranes that function as a **reservoir for intracellular messengers** and for some proteins, they serve as **anchors to cell membranes**.

مرس ← تثبت

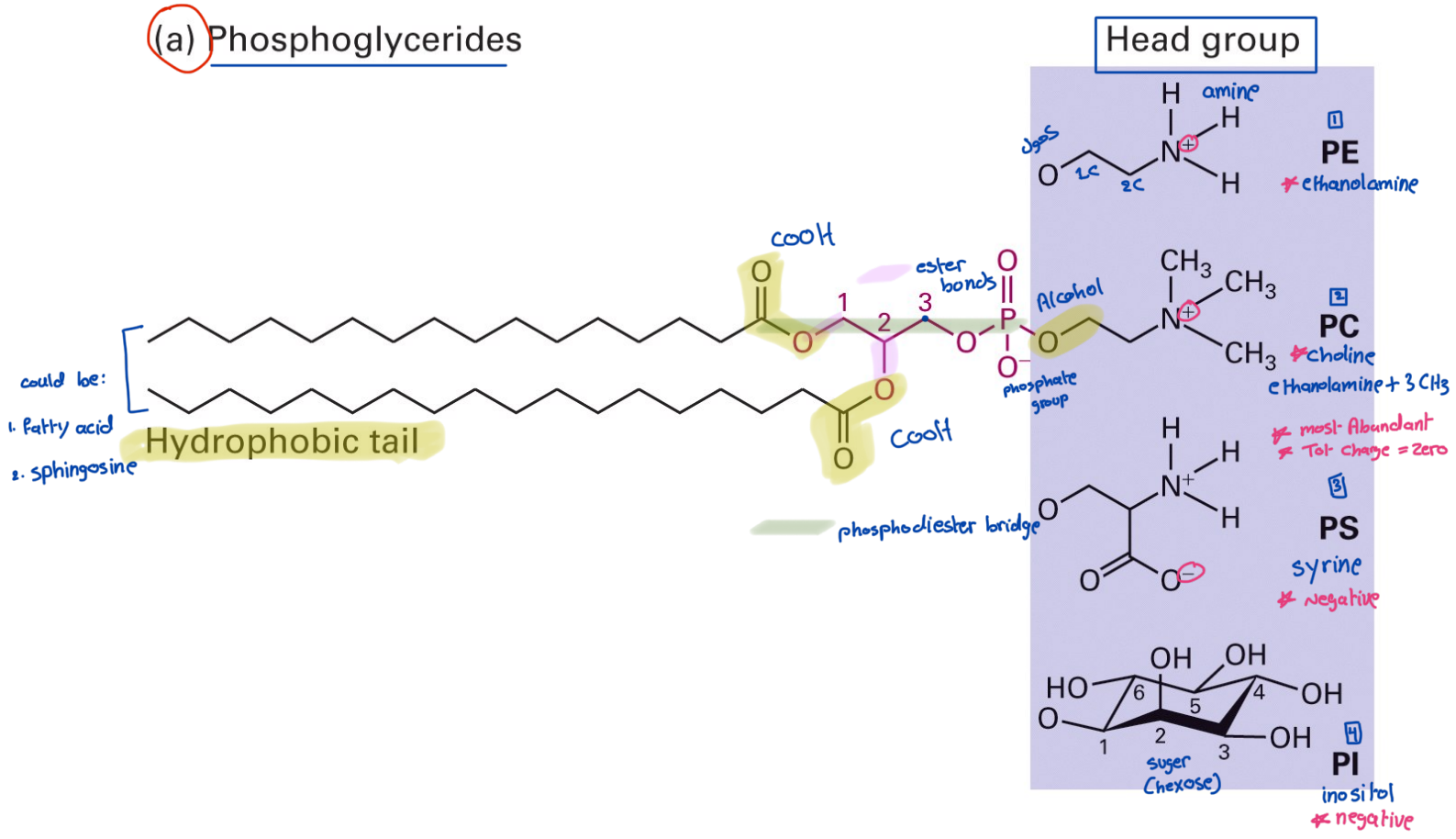
New type phospholipids :- ← في انهم بكونو cell membrane

- ☆ Nonmembrane-bound phospholipids serve additional functions in the body, as components
  1. of **lung surfactant** and essential components
  2. of **bile** that aid in the **solubilization of cholesterol**

عشان اتخلص منو لازم أذيبو بالـ bile



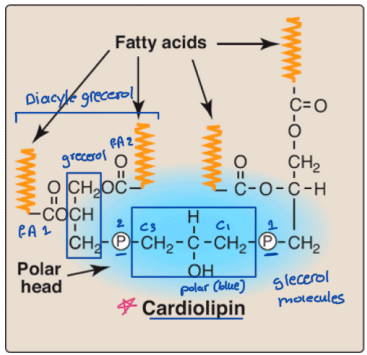
Phospholipids



Acyle group	Actyle group
C=O ✓	C=O ✓
so many carbons	only two carbon

الأنواع الجديده هي

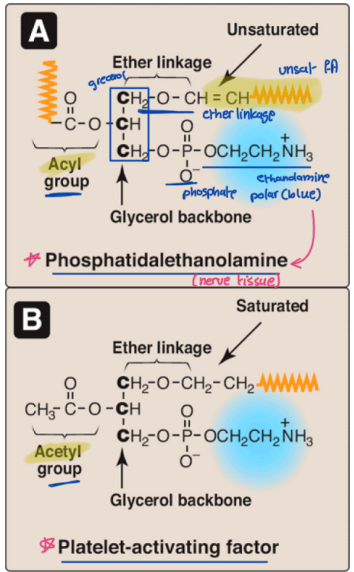
Phospholipids :-



1. **Cardiolipin:** cardiolipin is virtually exclusive to the inner mitochondrial membrane, where it is required for the maintenance of certain respiratory complexes

2. **Plasmalogens:** when an unsaturated alkyl group attached by an ether linkage to the core glycerol molecule, a plasmalogen is produced. phosphatidalethanolamine (abundant in nerve tissue, phosphatidalcholine (abundant in heart muscle) is the other quantitatively significant ether lipid in mammals.

choline



3. **Platelet-activating factor (PAF):** is an unusual ether glycerophospholipid, with a saturated alkyl group in an ether link to carbon 1 and an acetyl residue at carbon 2

toxic function unless it's in normal amounts

It binds to surface receptors, triggering potent thrombotic and acute inflammatory events. PAF activates inflammatory cells and mediates hypersensitivity, acute inflammatory, and anaphylactic reactions. It causes platelets to aggregate and degranulate, and neutrophils and alveolar macrophages to generate superoxide radicals

Biosynthesis of membrane phospholipids

- Synthesis of membrane lipids requires in general :
  - Synthesis of backbone molecule (glycerol or sphingosine)
  - Attachment of F.A to the backbone by ester or amide linkage.
  - Addition of hydrophilic head group through phosphodiester linkage.
  - Alteration or exchange of head group to yield final phospholipids.
- PL Synthesis occur in smooth **endoplasmic reticulum** then goes to **Golgi apparatus** and then to membranes of organelles or the plasma membrane, or are secreted from the cell by exocytosis
- All cells except mature RBC can synthesize phospholipid

(b) Sphingophospholipids

Ceramide + choline = sphingomyelin → neurons

- The backbone of sphingomyelin is the amino alcohol sphingosine, rather than glycerol .

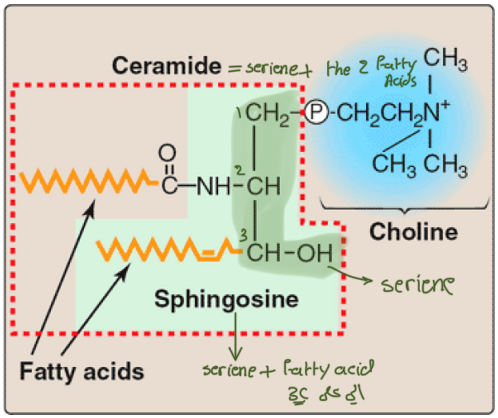
serine

Not glycerol

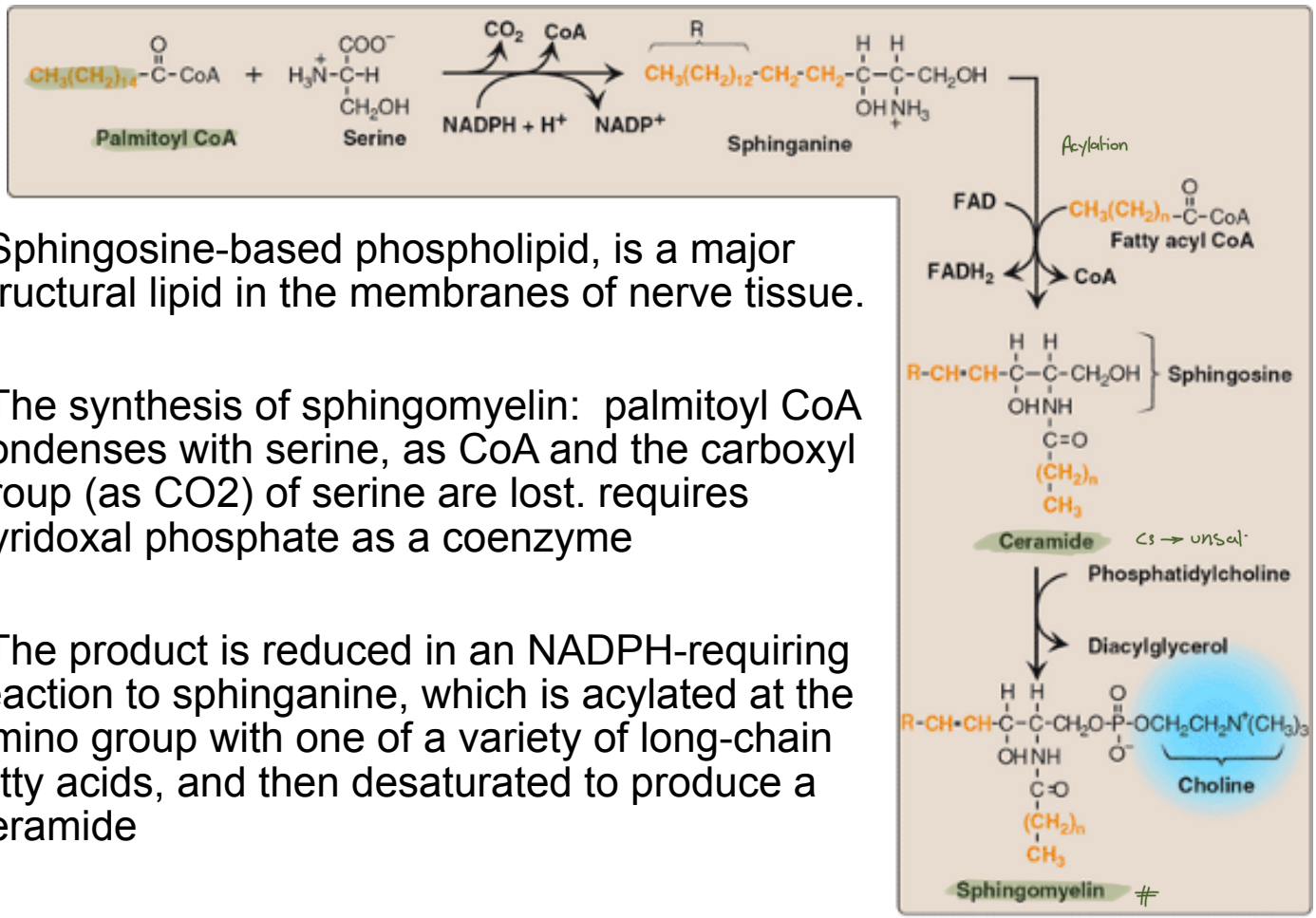
- A long-chain fatty acid is attached to the amino group of sphingosine through an amide linkage, producing a ceramide, which can also serve as a precursor of **glycolipids**. The alcohol group at carbon 1 of sphingosine is esterified to phosphorylcholine, producing sphingomyelin, the only significant sphingophospholipid in humans.

تشكيل

- Sphingomyelin is an important constituent of the **myelin of nerve fibers** that insulates and protects neuronal fibers of the central nervous system



Synthesis of sphingomyelin



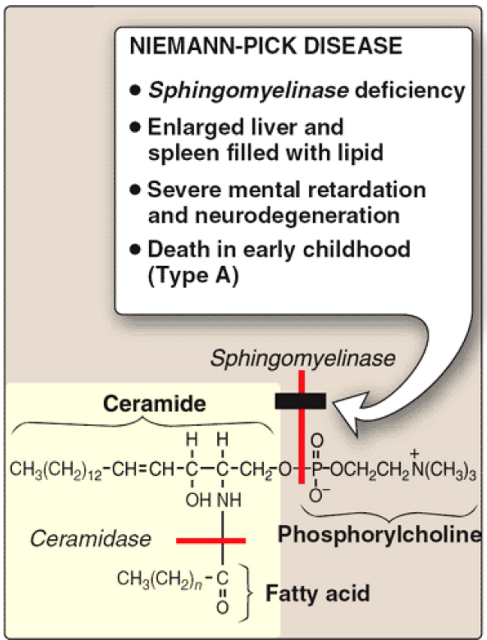
- Sphingosine-based phospholipid, is a major structural lipid in the membranes of nerve tissue.
- The synthesis of sphingomyelin: palmitoyl CoA condenses with serine, as CoA and the carboxyl group (as CO2) of serine are lost. requires pyridoxal phosphate as a coenzyme
- The product is reduced in an NADPH-requiring reaction to sphinganine, which is acylated at the amino group with one of a variety of long-chain fatty acids, and then desaturated to produce a ceramide

Degradation of sphingomyelin

- Sphingomyelin is degraded by the lysosomal sphingomyelinase.

- Ceramides appear to be involved in the response to stress, and sphingosine inhibits protein kinase C

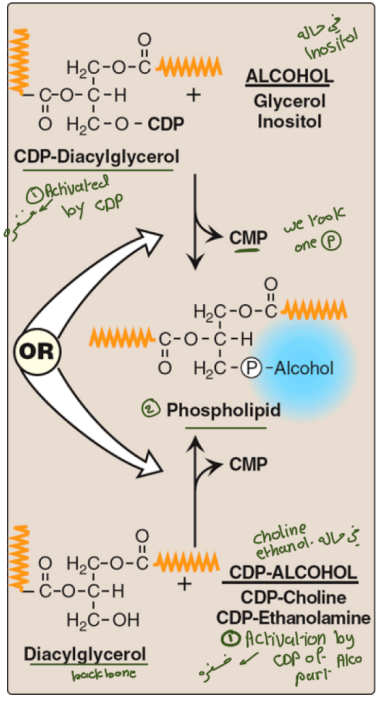
Protein Kinase C (PKC) is a family of enzymes that act as intracellular messengers by phosphorylating proteins, which changes their activity and function. PKC plays a crucial role in various cellular processes, including cell growth, differentiation, proliferation, and immune responses.



3

Synthesis of PE and PC

- PC and PE are the most abundant phospholipids in most eukaryotic cells. Choline and ethanolamine are obtained either from the ① diet or from the ② turnover of the body's phospholipids.



- ★ **Synthesis from preexisting choline and ethanolamine**: by phosphorylation of choline or ethanolamine by kinases, followed by conversion to the activated form, CDP-choline or CDP-ethanolamine. Then, choline-phosphate or ethanolamine-phosphate is transferred from the nucleotide (CMP) to a molecule of diacylglycerol

- The reutilization of choline is important because, as humans can synthesize choline de novo, the amount made is insufficient for our needs.

- dipalmitoylphosphatidylcholine (DPPC) made and secreted by Type II pneumocytes, is the major lipid component of **lung surfactant**. Surfactant serves to decrease the surface tension of this fluid layer, reducing the pressure needed to reinflate alveoli, thereby preventing alveolar collapse. Lung maturation can be accelerated by giving the mother glucocorticoids shortly before delivery.

★ inhibition phospholipase A2

Synthesis of PE, PC and PS

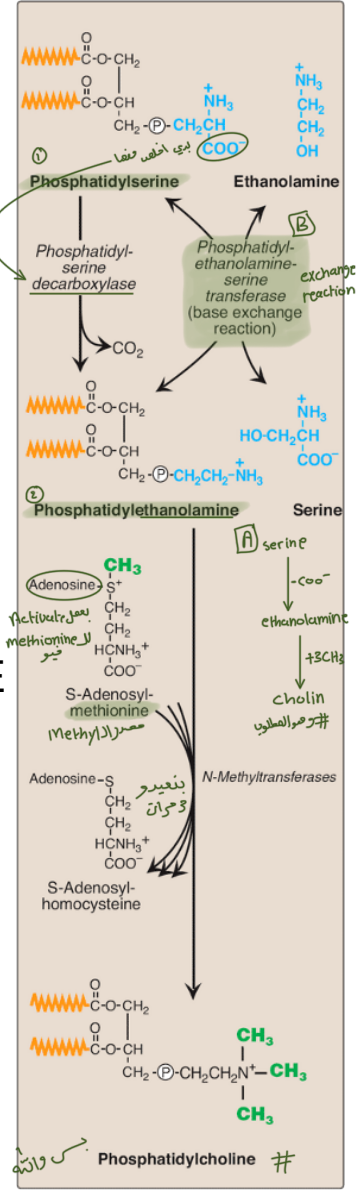
تحويلات لازم تعلمهم

Serien ⟶ Cholin

- **Synthesis of PC from PS in the liver**: To provide the needed PC (secreted in bile), PS is decarboxylated to PE by PS decarboxylase, an enzyme requiring pyridoxal phosphate as a cofactor. PE then undergoes three methylation steps to produce PC

⟶ membrane synthesis

- Phosphatidylserine (PS): provided by the base exchange reaction, in which the ethanolamine of PE is exchanged for free serine to produce the PS required for membrane synthesis



إذاً كيف بحصل على هدول الانواع من الـ PL :-

1. diet ⟶ Free choline / Etha. ⟶ synthesis
2. interconversions
3. exchange reactions

Synthesis of PI

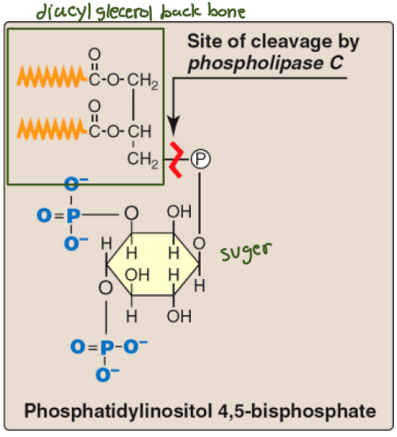
PI is synthesized from free inositol and CDP-diacylglycerol

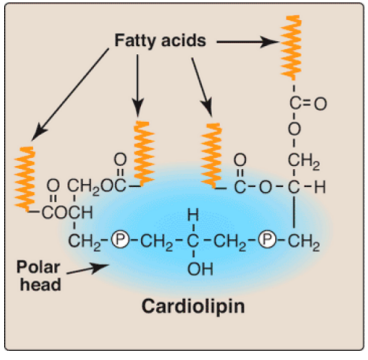
PI is an unusual phospholipid in that it often contains stearic acid on carbon 1 and arachidonic acid on carbon 2 of the glycerol

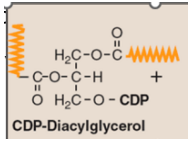
PI serves as a reservoir of arachidonic acid in membranes and, thus, provides the substrate for prostaglandin synthesis when require

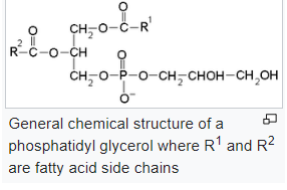
Phosphatidylglycerol is a precursor of cardiolipin. It is synthesized by a two-step reaction from CDP-diacylglycerol and glycerol 3-phosphate.

Cardiolipin is synthesized by the transfer of diacylglycerophosphate from CDP-diacylglycerol to a preexisting molecule of phosphatidylglycerol.



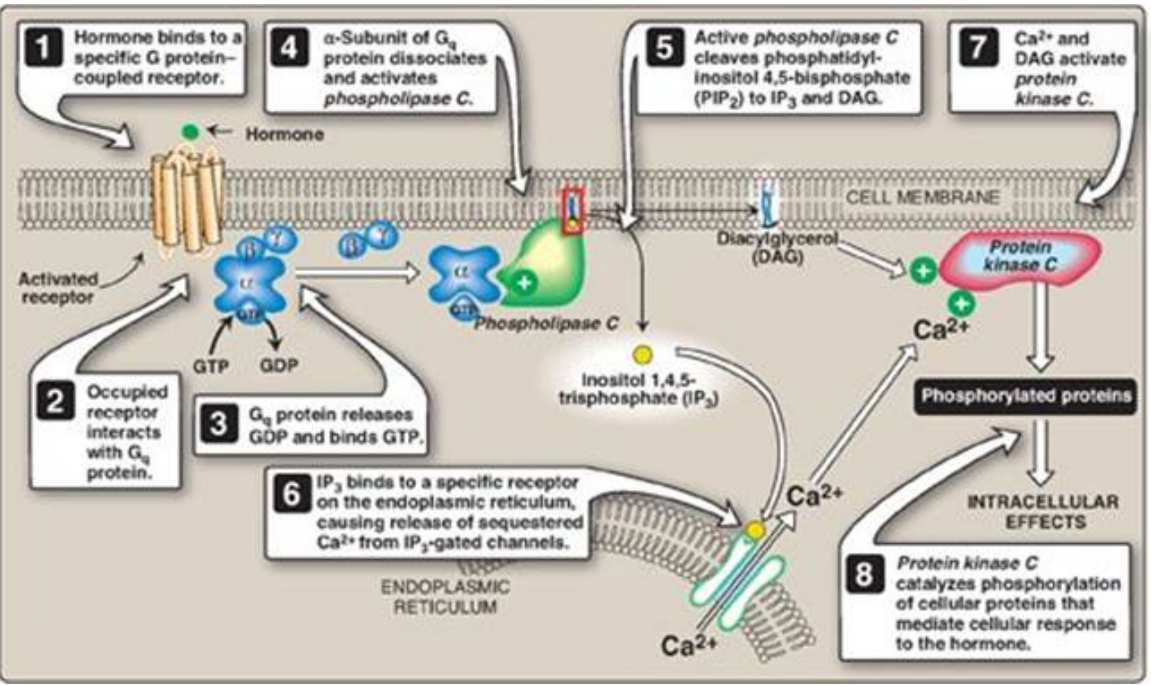


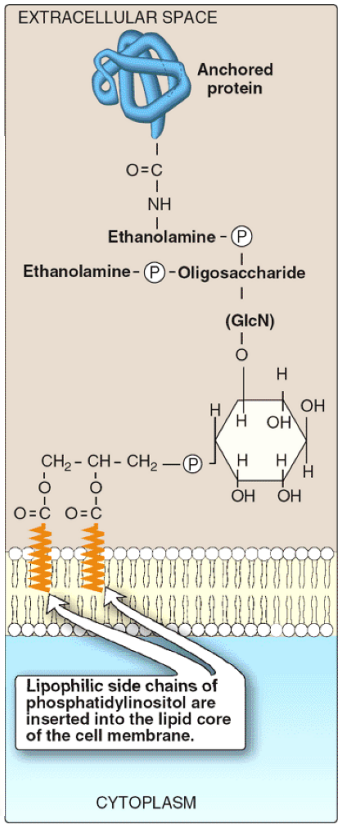



General chemical structure of a phosphatidyl glycerol where R^1 and R^2 are fatty acid side chains

Role of PI

- PI in signal transmission across membranes
- PI in membrane protein anchoring



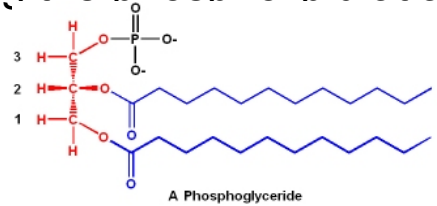


5 Degradation of phosphoglycerides

performed by phospholipases found in all tissues and pancreatic juice

Some toxins and venoms have phospholipase activity, and several pathogenic bacteria produce phospholipases that dissolve cell membranes and allow the spread of infection.

Phospholipases hydrolyze the phosphodiester bonds of phosphoglycerides, with each enzyme cleaving the phospholipid at a specific site.

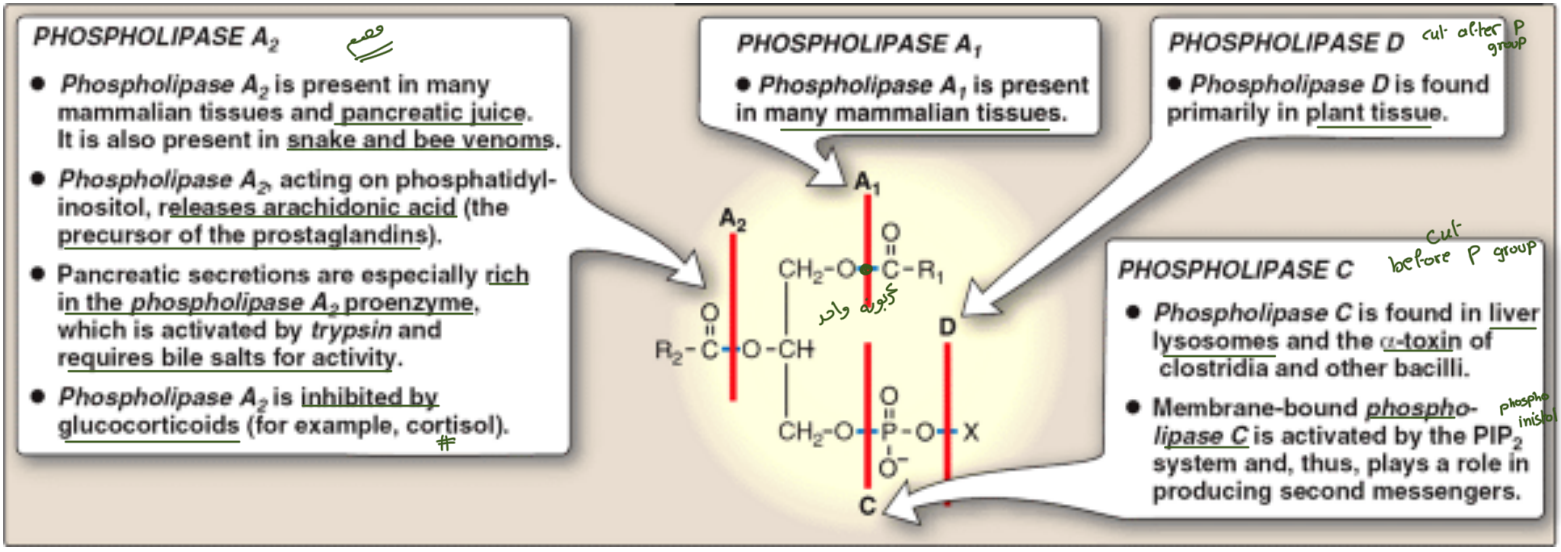


A Phosphoglyceride

Phospholipases release molecules that can serve as messengers (DAG and IP3), or that are the substrates for synthesis of messengers (arachidonic acid).

phospholipases A1 and A2 remove specific fatty acids from membrane-bound phospholipids; these can be replaced with alternative fatty acids using fatty acyl CoA transferase. This mechanism is used as one way to create the unique lung surfactant, DPPC and to insure that carbon 2 of PI (and sometimes of PC) is bound to arachidonic acid

Degradation of phosphoglycerides

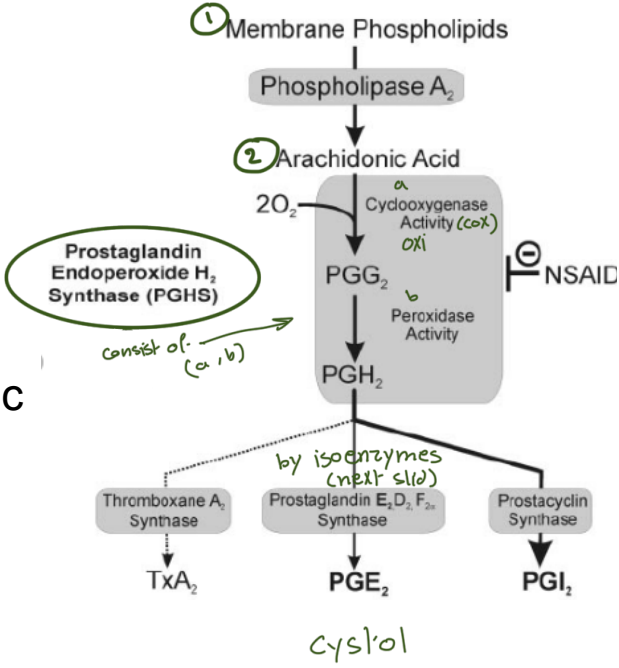


6

prostaglandens

1 Synthesis of PGH2 → cyclic

The first step in the synthesis of prostaglandins is the oxidative cyclization of free arachidonic acid to yield PGH2 by prostaglandin endoperoxide synthase (PGH synthase). Arachidonic acid → PGH2



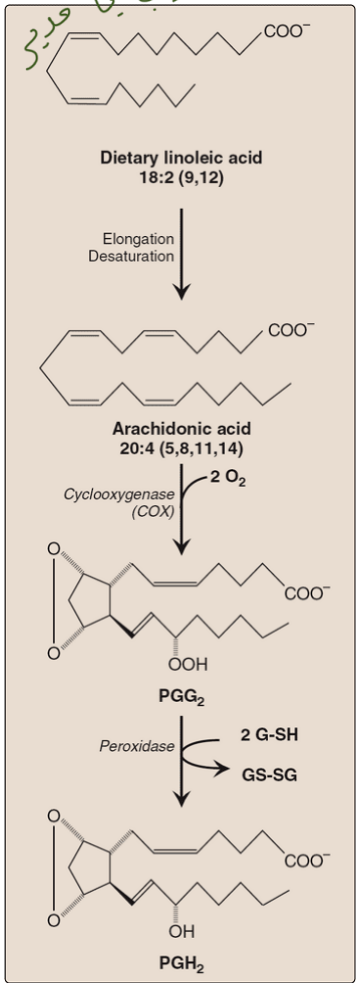
This enzyme is an endoplasmic reticulum membrane-bound protein that has two catalytic activities:

- fatty acid cyclooxygenase (COX), which requires two molecules of O2, and
- peroxidase, which is dependent on reduced glutathione

PGH2 is converted to a variety of prostaglandins and thromboxanes, by cell-specific synthases.

Isozymes of PGH synthase

- Two isozymes of the synthase are known.
  - COX-1 is made constitutively in most tissues, and is required for maintenance of healthy gastric tissue, renal homeostasis, and platelet aggregation.
  - COX-2 is inducible in a limited number of tissues in response to products of activated immune and inflammatory cells.
- The increase in prostaglandin synthesis subsequent to the induction of COX-2 mediates the pain, heat, redness, and swelling of inflammation, and the fever of infection.



Inhibition of prostaglandin synthesis

- The synthesis of prostaglandins can be inhibited by a number of unrelated compounds. For example, cortisol (a steroidal anti-inflammatory agent) inhibits phospholipase A2 activity and so, the precursor of the prostaglandins is not available.

- Aspirin, indomethacin, and phenylbutazone (all nonsteroidal anti-inflammatory agents [NSAIDS]) inhibit both COX-1 and COX-2 and so, prevent the synthesis of the parent prostaglandin, PGH2.

- Aspirin's toxicity is due to the systemic inhibition of COX-1, leading to damage to the stomach and the kidneys, and impaired clotting of blood.

- Inhibitors specific for COX-2 (e.g. celecoxib) were designed to reduce pathologic inflammatory processes while maintaining the physiologic

Fuctions of COX-1

2 Leukotrienes → linear

- Leukotrienes are linear molecules produced by the lipoxygenase pathway from arachidonic acid

pathway مختلف

- Neutrophils contain 5-lipoxygenase, which converts arachidonic acid to 5-hydroxy-6,8,11,14 eicosatetraenoic acid (5-HPETE) which is converted to a series of leukotrienes.

- Lipoxygenases are not affected by NSAIDS. Leukotrienes are mediators of allergic response and inflammation.

simply such as prostaglandins

- Inhibitors of 5-lipoxygenase and leukotriene receptor antagonists are used in the treatment of asthma

↓

consl-

القصبة الهوائية

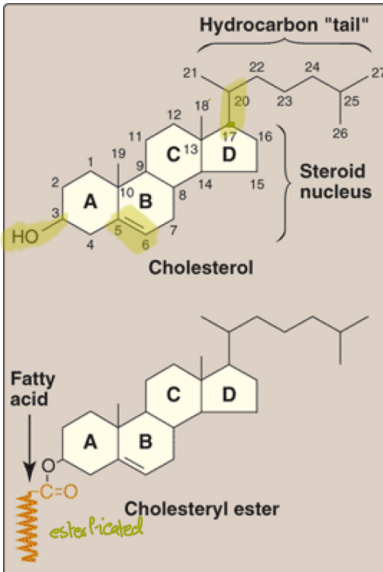
7

Cholesterol

- cholesterol is a structural component of all cell membranes, modulating their fluidity,

- In specialized tissues, cholesterol is a precursor of bile acids, steroid hormones, and vitamin D

- Cholesterol is a very hydrophobic compound. It consists of four fused hydrocarbon rings (A, B, C, and D, called the "steroid nucleus"), and it has an eight-carbon, branched hydrocarbon chain attached to C-17 of the D ring. Ring A has a hydroxyl group at C-3, and ring B has a double bond between C-5 and C-6



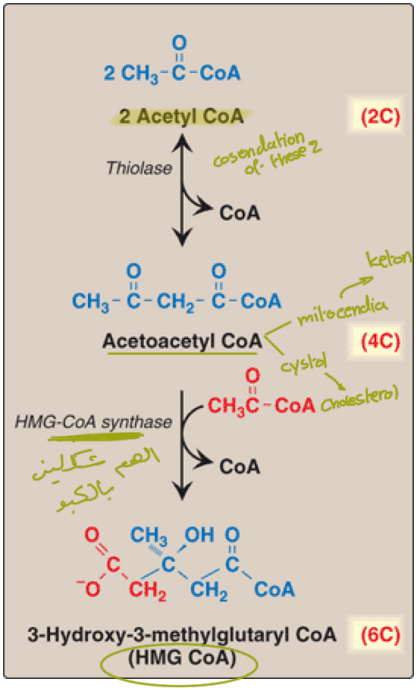
Cholesterol synthesis

- Cholesterol is synthesized by all tissues in humans, although liver, intestine, adrenal cortex, and reproductive tissues, including ovaries, testes, and placenta, make the largest contributions to the body's cholesterol pool.

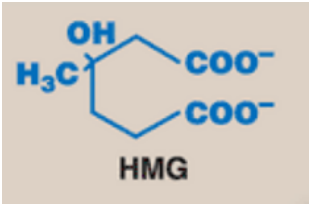
- Synthesis occurs in the cytoplasm, with enzymes in both the cytosol and the membrane of the endoplasmic reticulum.

- The first two reactions in the cholesterol synthetic pathway are similar to those in the pathway that produces ketone bodies. They result in the production of HMG CoA

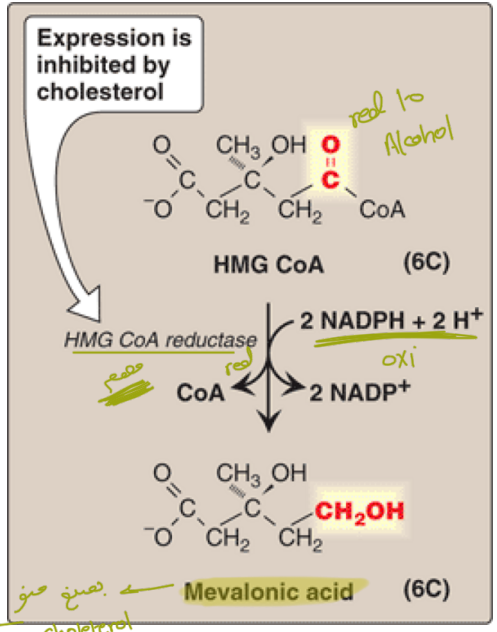
- Liver parenchymal cells contain two isoenzymes of HMG CoA synthase



Cholesterol synthesis



- The next step, the reduction of HMG CoA to mevalonic acid, is catalyzed by HMG CoA reductase, and is the rate-limiting and key regulated step in cholesterol synthesis.
- It occurs in the cytosol, uses two molecules of NADPH as the reducing agent, and releases CoA, making the reaction irreversible
- HMG CoA reductase is an intrinsic membrane protein of the endoplasmic reticulum (ER), with the enzyme's catalytic domain projecting into the cytosol



limiting step

Regulation of cholesterol synthesis

- HMG CoA reductase, the rate-limiting enzyme, and is subject to different metabolic control:
- ① **Sterol-dependent regulation of gene expression**: Expression of the HMG CoA reductase gene is controlled by the transcription factor, SREBP (sterol regulatory element–binding protein that is bound to ER membrane) that binds DNA at the cis-acting sterol regulatory element (SRE) of the reductase gene. SREBP is associates with a second ER membrane protein SCAP (SREBP cleavage–activating protein).

transcription factor (SREBP) → بترتبط بـ protien (SCAP) ↓ complex يروح ← ER ← Golgi ← cleavage تقطيع ← stimulate DNA gene HMGCOA reductase expression ← Thus ← stimulating cholestrol synthesis

- When sterol levels in the cell are low, the SREBP-SCAP complex is sent out of the ER to the Golgi. Where it generates a soluble fragment that enters the nucleus and functions as a transcription factor. This results in increased synthesis of HMG CoA reductase and cholesterol synthesis. If sterols are abundant, it results in the retention of the SCAP-SREBP in the ER, leading to down-regulation of cholesterol synthesis.

- ② **Sterol-accelerated enzyme degradation**: The reductase itself is an integral protein of the ER membrane. When sterol levels in the cell are high, the reductase binds to insig proteins. This binding leads to ubiquitination and proteasomal degradation of the reductase.

HMG reductase (integral protien on ER membrane) Sterol↑ → بترتبط بـ insing proteins → التتبيع ① Ubiquitination ② proteasomal degradation] of- HMG reductase

Regulation of cholesterol synthesis

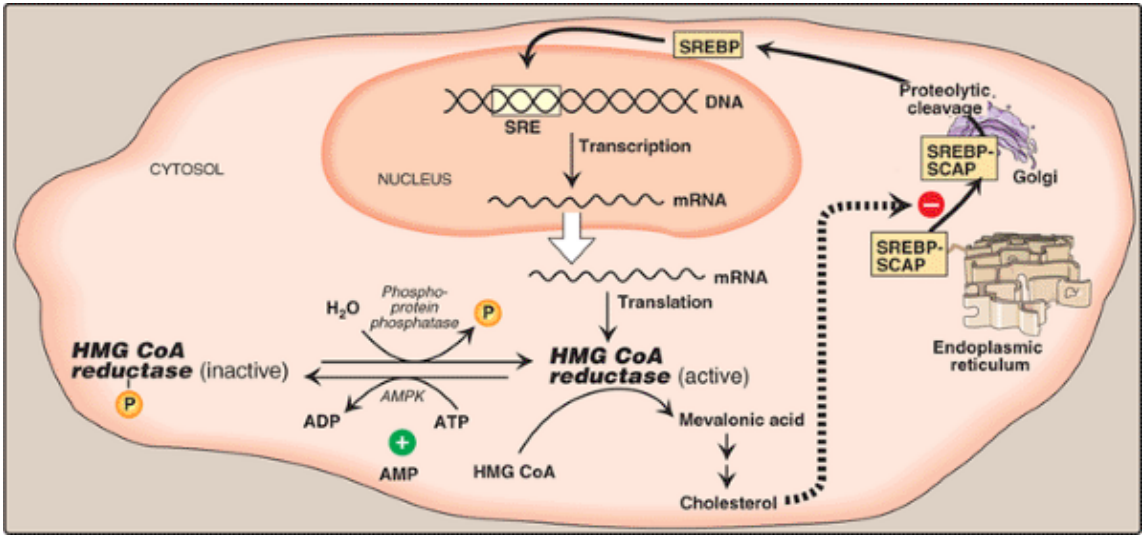
- (3) **Sterol-independent phosphorylation/dephosphorylation**: HMG CoA reductase activity is controlled covalently through the actions of AMP–activated protein kinase (AMPK), and a phosphoprotein phosphatase. The phosphorylated form of the enzyme is inactive, so cholesterol synthesis, is decreased when ATP availability is decreased.

covalently ↓ hormone not sterol

(1) (2)

ATP ↑ → phosphorilation (inhibition)

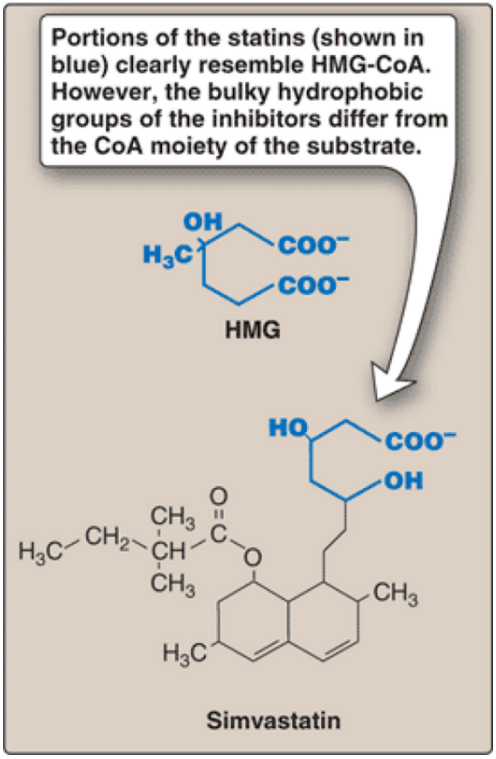
- (4) **Hormonal regulation**: The amount and the activity of HMG CoA reductase is up-regulated by insulin and down-regulated by glucagon.



Drug Inhibitors of cholesterol synthesis

The statin drugs (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) are structural analogs of HMG CoA, and are (or are metabolized to) reversible, competitive inhibitors of HMG CoA reductase.

They are used to decrease plasma cholesterol levels in patients with hypercholesterolemia



Degradation of Cholesterol

- The ring structure of cholesterol cannot be metabolized to CO_2 and H_2O in humans but the intact sterol nucleus is eliminated from the body by conversion to bile acids and bile salts, which are excreted in the feces, and by secretion of cholesterol into the bile, which transports it to the intestine for elimination.

- Some of the cholesterol in the intestine is modified by bacteria before excretion. The primary compounds made are the isomers coprostanol and cholestanol, which are reduced derivatives of cholesterol.

✱ Last But not least :

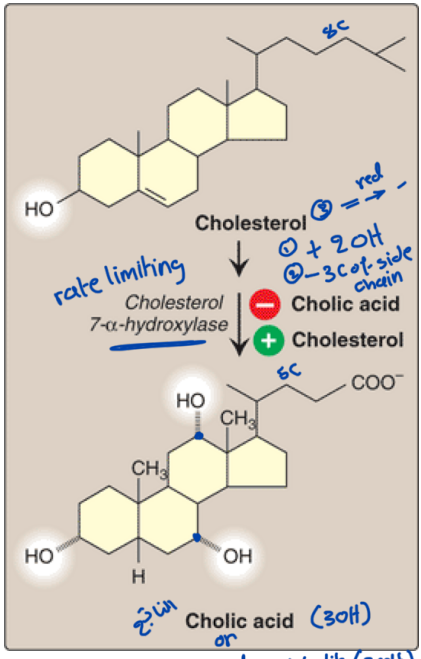
Synthesis of Bile acids

- Bile acids are synthesized in the liver by a multistep, multiorganelle pathway in which hydroxyl groups are inserted at specific positions on the steroid structure, the double bond of the cholesterol B ring is reduced, and the hydrocarbon chain is shortened by three carbons, introducing a carboxyl group at the end of the chain

- The most common resulting compounds, cholic acid (a triol) and chenodeoxycholic acid (a diol), are called "primary" bile acids.

- The rate-limiting step in bile acid synthesis is the introduction of a hydroxyl group at carbon 7 of the steroid nucleus by cholesterol-7-α-hydroxylase, an ER-associated cytochrome P450 (CYP) enzyme found only in liver

- The enzyme is down-regulated by cholic acid and up-regulated by cholesterol



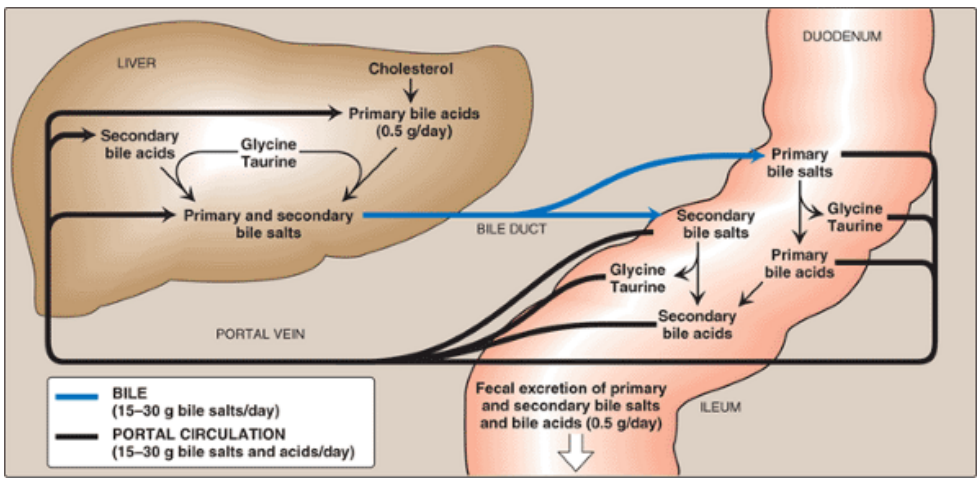
Enterohepatic circulation of bile salts

- Bile salts secreted into the intestine are efficiently reabsorbed (greater than 95%) and reused. The mixture of primary and secondary bile acids and bile salts is absorbed primarily in the ileum. They are actively transported from the intestinal mucosal cells into the portal blood, and are efficiently removed by the liver parenchymal cells.

- Bile acids are carried in blood by albumin as a noncovalent complex

- The liver converts both primary and secondary bile acids into bile salts by conjugation with glycine or taurine, and secretes them into the bile to the duodenum where some are converted to bile acids, and their subsequent return to the liver as a mixture of bile acids and salts

- Bile acid sequestrants, such as cholestyramine, and dietary fibers bind bile acids in the gut, prevent their reabsorption, and so promote their excretion



A sours of energy

Glycogen metabolism

→ branched polysaccharride glucose units
(homo)

Glycogen

- # Blood glucose can be obtained from three sources: diet, degradation of glycogen and gluconeogenesis.
- Glycogen is a rapidly mobilized form of glucose which is stored in both liver and kidney to raise blood glucose during early stages of fast.
- When glycogen stores are depleted, glucose is produced from amino acids in specific tissues.
- Glycogen works as fuel for synthesis of ATP during muscle contraction

Structure and function of glycogen

- 400 g make up 1-2% of muscle weight but 100 g make up 10% of liver

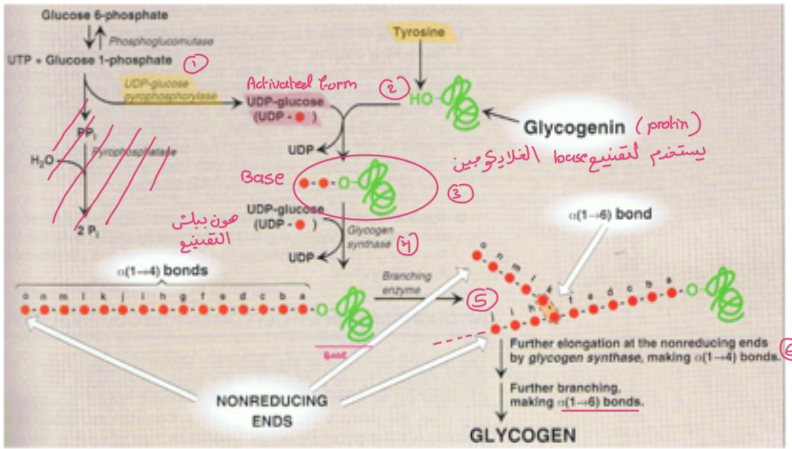
- Glycogen is a branched chain homopolysaccharides made of α-D-glucose linked together by α (1-4) glycosidic bond in the linear chain and α-(1-6) glycosidic bond in the branches.

- Fluctuation in glycogen stores: muscle glycogen is not affected by short fast (days) but decreased in prolonged fasting.

Glycogenesis

Occurs in the cytosol and requires energy supplied by ATP and UTP

A. Synthesis of UDP-glucose: from glucose 1-phosphate and UTP by **UDP-glucose pyrophosphorylase**

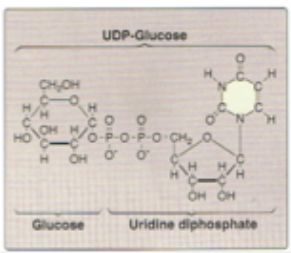


B. Synthesis of a primer to initiate glycogen synthesis: **Glycogen synthase** is responsible for making the α(1- 4) linkages in glycogen. This enzyme cannot initiate chain synthesis using free glucose as an acceptor of a molecule of glucose from UDP-glucose (only elongation).

C. Elongation of glycogen chains by glycogen synthase

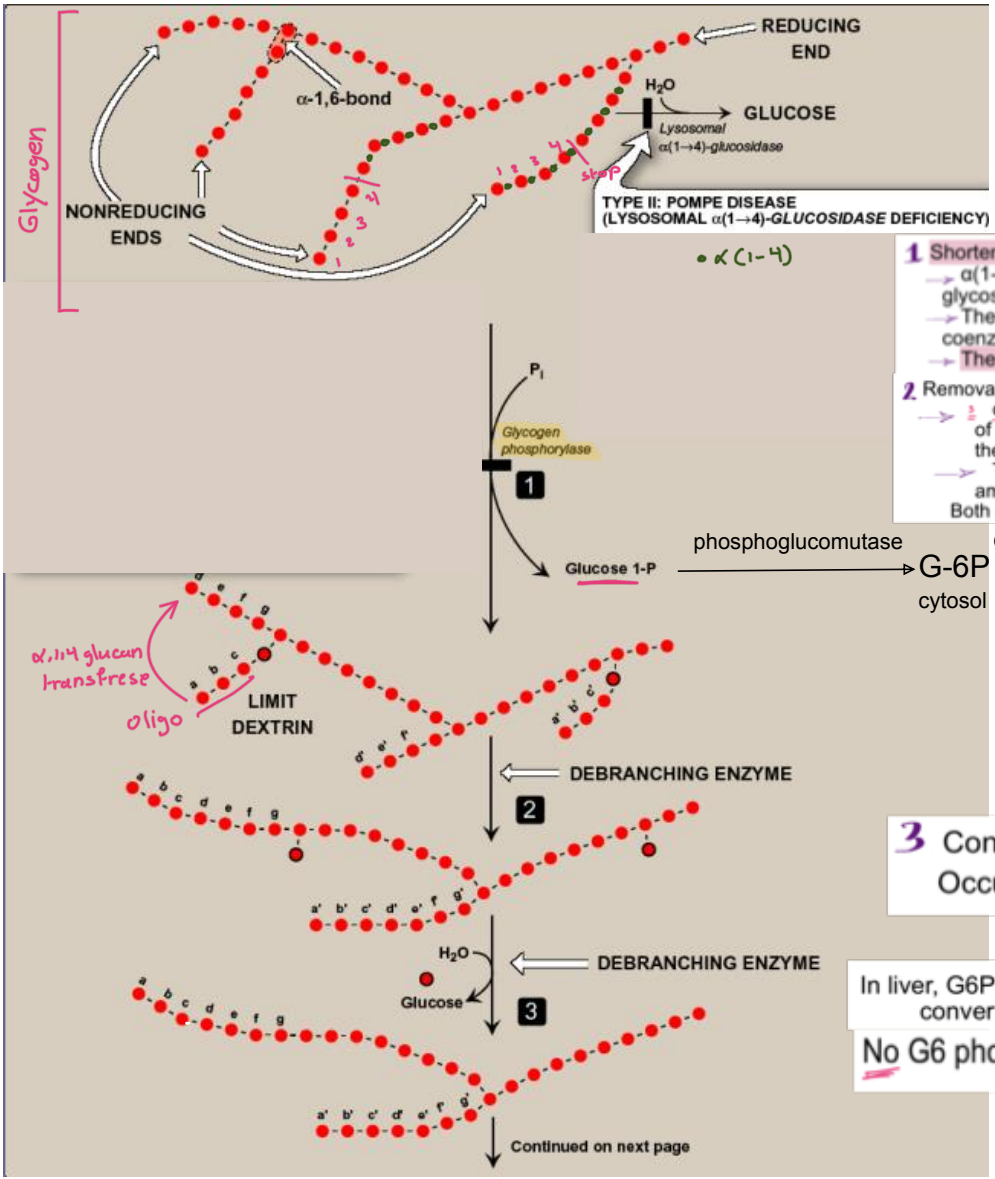
D. Formation of branches in glycogen: branches are present almost every glycosyl residues which has more solubility than unbranched and increase the number of non-reducing ends where Glu-UDP can be added and this will accelerate the rate of glycogenesis.

Branching occurs by branching enzyme **(amylo α(1-4) □ α(1-6) transglucosidase)** followed by elongation using glycogen synthase



glycogenolysis

- From breaking of α(1-4) produce glucose 1-phosphate
- Breaking of α(1-6) release free glucose



• α(1-4)

1. Shortening of the chains:
   - α(1-4) is cleaved by **glycogen phosphorylase** until four glycosyl units remain on each chain before branch point
   - The enzyme utilize pyridoxal phosphate which is required as coenzyme
   - The resulting structure is called limit dextrin
2. Removal of branches: it involves two enzymes:
   - oligo α(1-4)-> (α(1-4) glucan transferase: removes the three of the four glycosyl residues at a branch. Then it transfers them to the nonreducing end of another chain.
   - The remaining α(1-6) single glucose residue is removed by amylo- α(1-6) glucosidase activity

Both enzymes are called debranching enzyme.

phosphoglucomutase

G-6P
cytosol

G6P translocase

G-6P
ER

G6-phosphatase

glucose

3 Conversion of glucose 1-phosphate to G6P: Occurs in cytosol by phosphoglucomutase.

In liver, G6P is translocated in ER by G6P translocase and then converted to glucose by G6phosphatase.

No G6 phosphatase in muscle so G6P enter glycolysis

معلومه كالعاده

glycogenolysis

- Lysosomal degradation of glycogen

small amount of glycogen is continuously degraded by the lysosomal enzyme α(1-4) glucosidase.

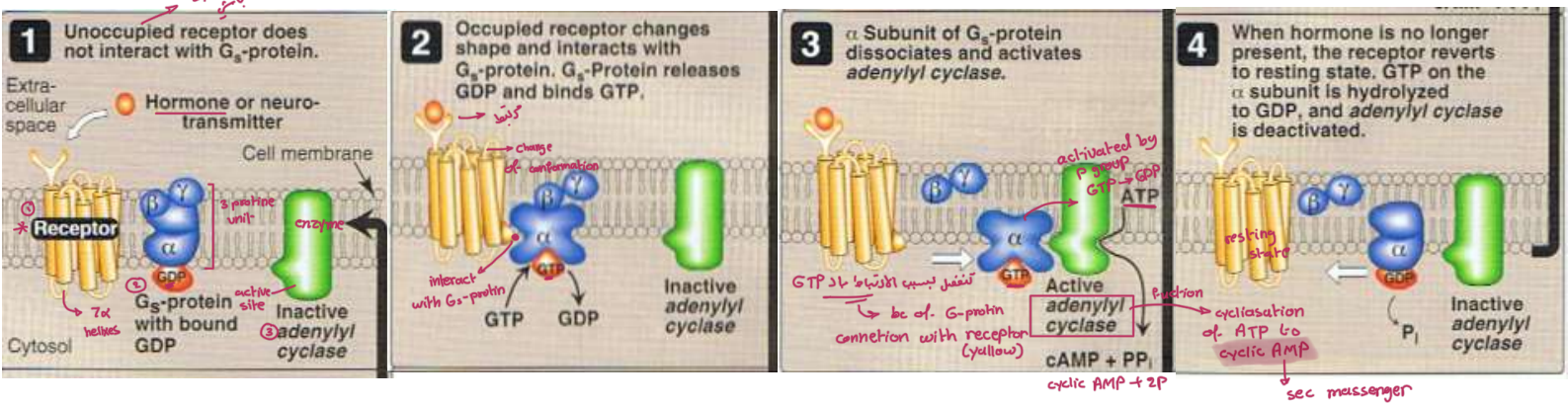
deficiency in this enzyme causes accumulation of glycogen in vaccuole in cytosol (glycogen storage disease type II (pompe disease))

comblication : hypoglycemia / hepatomegaly / liver problems
lactic acidosis / Growth faliure

Regulation of metabolism

Adenylyl cyclase

① Glucagon (hormon)
② ep/nor·ep (Neurotransmiters)
③ corticohormones (hormon)



1. GTP-dependent regulatory proteins (Gs and Gi-proteins)
2. Protein kinases: phosphorylates different proteins and enzymes
3. Dephosphorylation of proteins: Phosphatases reverse the effect of kinases.

Regulation of Glycogen metabolism

* product of Adenyly cyclase pathway

- cAMP Integrates the Regulation of Glycogenolysis & Glycogenesis
- The principal enzymes controlling glycogen metabolism- glycogen phosphorylase and glycogen synthase are regulated by allosteric mechanisms and covalent modifications due to reversible phosphorylation and dephosphorylation of enzyme protein kinase in response to hormone action

- cAMP is formed from ATP by **adenylyl cyclase** at the inner surface of cell membranes and acts as an intracellular **second messenger** in response to hormones such as **epinephrine, norepinephrine,** and **glucagon**

- cAMP is hydrolyzed by **phosphodiesterase,** so terminating hormone action, in liver, insulin increases the activity of phosphodiesterase

insuline → stimulat proline phosphotase

suger → glycogen ← Active ← dephosphor of glycogen syntheis

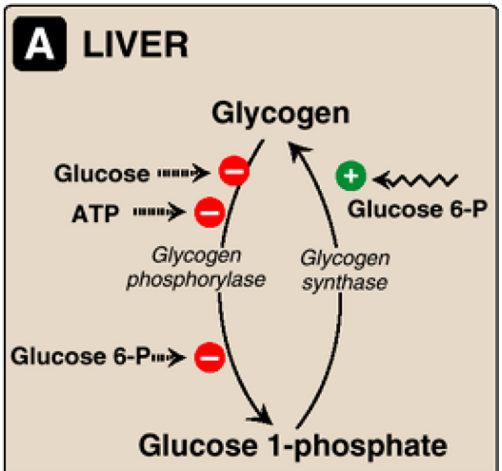
يتم تصنيع ال Glycogen

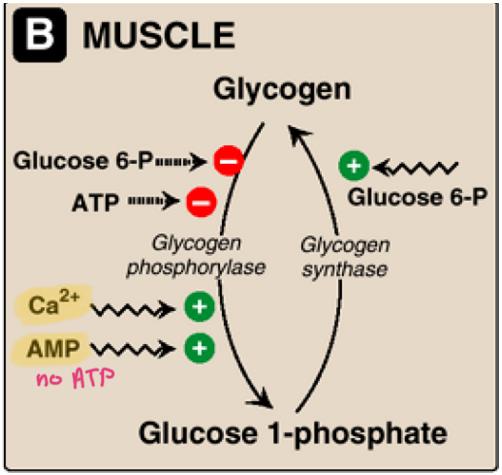
Regulation

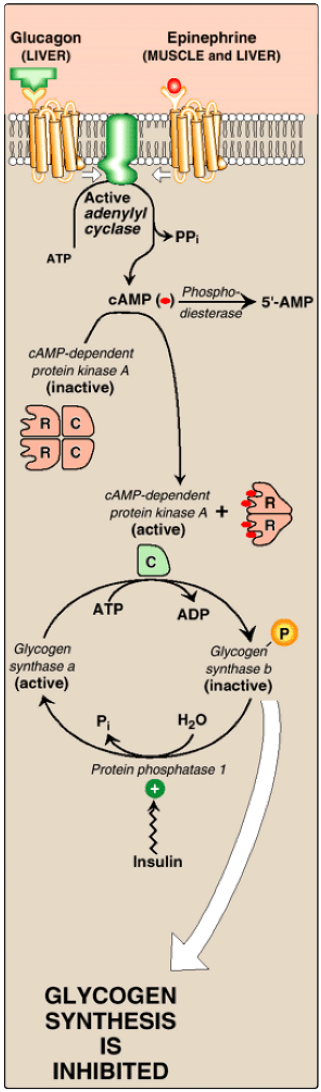
- when muscle glycogen phosphorylase b is bound to glucose, it cannot be allosterically activated by AMP

وجود

- In the muscle, insulin indirectly inhibits the enzyme by increasing the uptake of glucose, leading to an increased level of glucose 6-phosphate-a potent allosteric inhibitor of glycogen phosphorylase

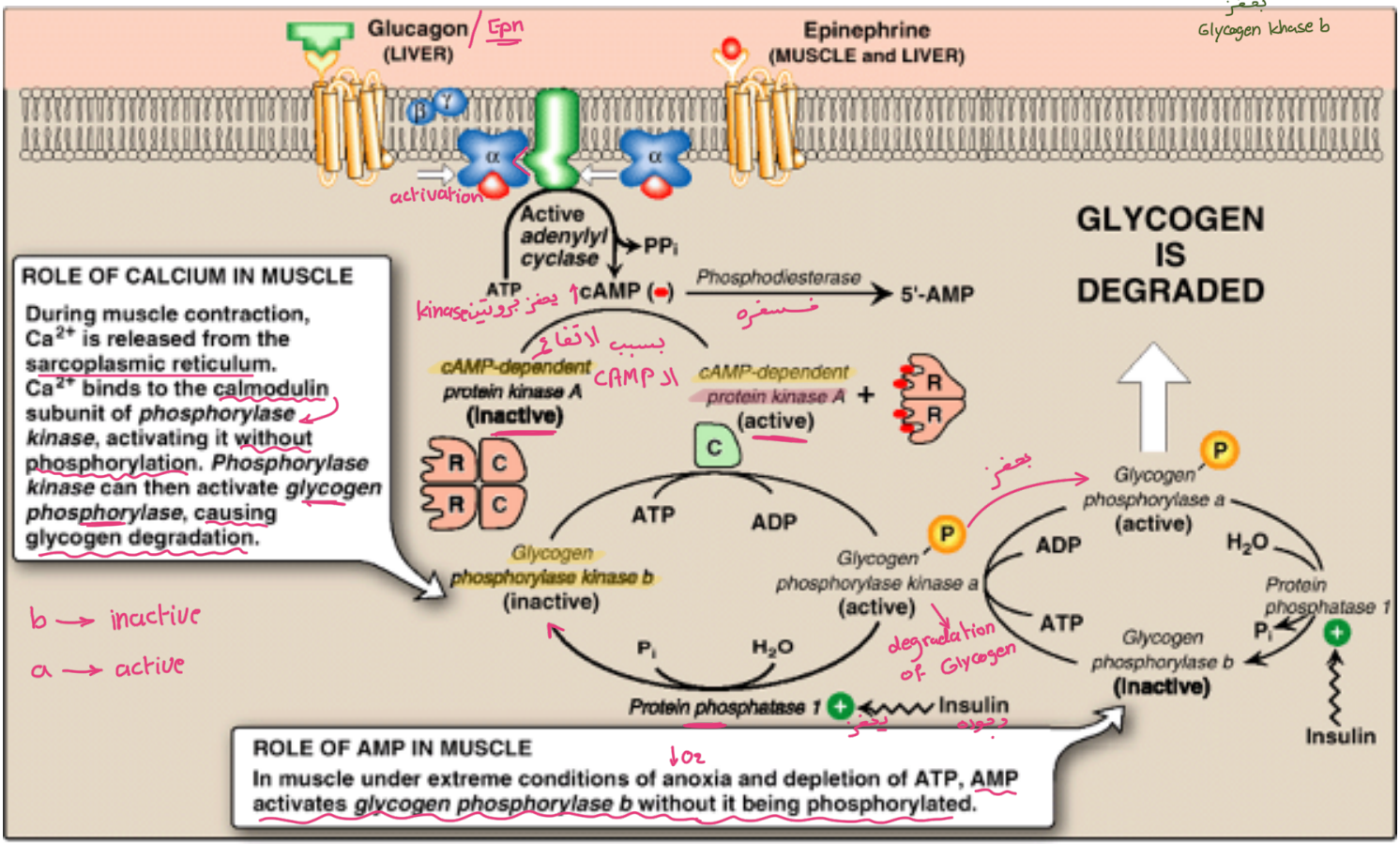






Regulation

stimulation of Glycogen phosphorase
- direct: phosphorilation, ↑AMP
- indirect: Ca^{+} يعزز Glycogen kinase b



Glycogen storage diseases

- They result either in formation of glycogen that has an abnormal structure, or in the accumulation of excessive amounts of normal glycogen in specific tissues as a result of impaired degradation.
- A particular enzyme may be defective in a single tissue, such as the liver, or the defect may be more generalized, affecting liver, muscle, kidney, intestine, and myocardium.
- The severity of the glycogen storage diseases (GSDs) ranges from fatal in infancy to mild disorders that are not life-threatening

Integration of metabolism

Metabolic Adaptation

* Fatty acids and triacylglycerols is break down during fasting stages

Fed State Blood glucose ~ 6 mM. Liver and muscle make glycogen. Liver uses amino acids and fatty acids. Triaclyglycerols stored in adipose cells.

For protien synthesis ←

مرحلة تخزين

بيجو من تكسير البروتينات اللي معمله

6 -12 hrs Blood glucose ~ 4.5 mM. Liver uses muscle amino acids to make and export glucose. Triacylglycerols split and the glycerol is used by the liver to make glucose. Fatty acids used by liver and muscle.

short- fasting

glucagensis + gluconyogenysis

تكسير جلايكوجين — تصنيع جـ

الأحماض الكبيره

1-3 days Carbohydrate reserves depleted. Muscle rapidly degraded to amino acids. Triacylglycerols used.

ما في مصادر لصناعة الـ glucose

main sours of energy

bul- don't use it- → brain

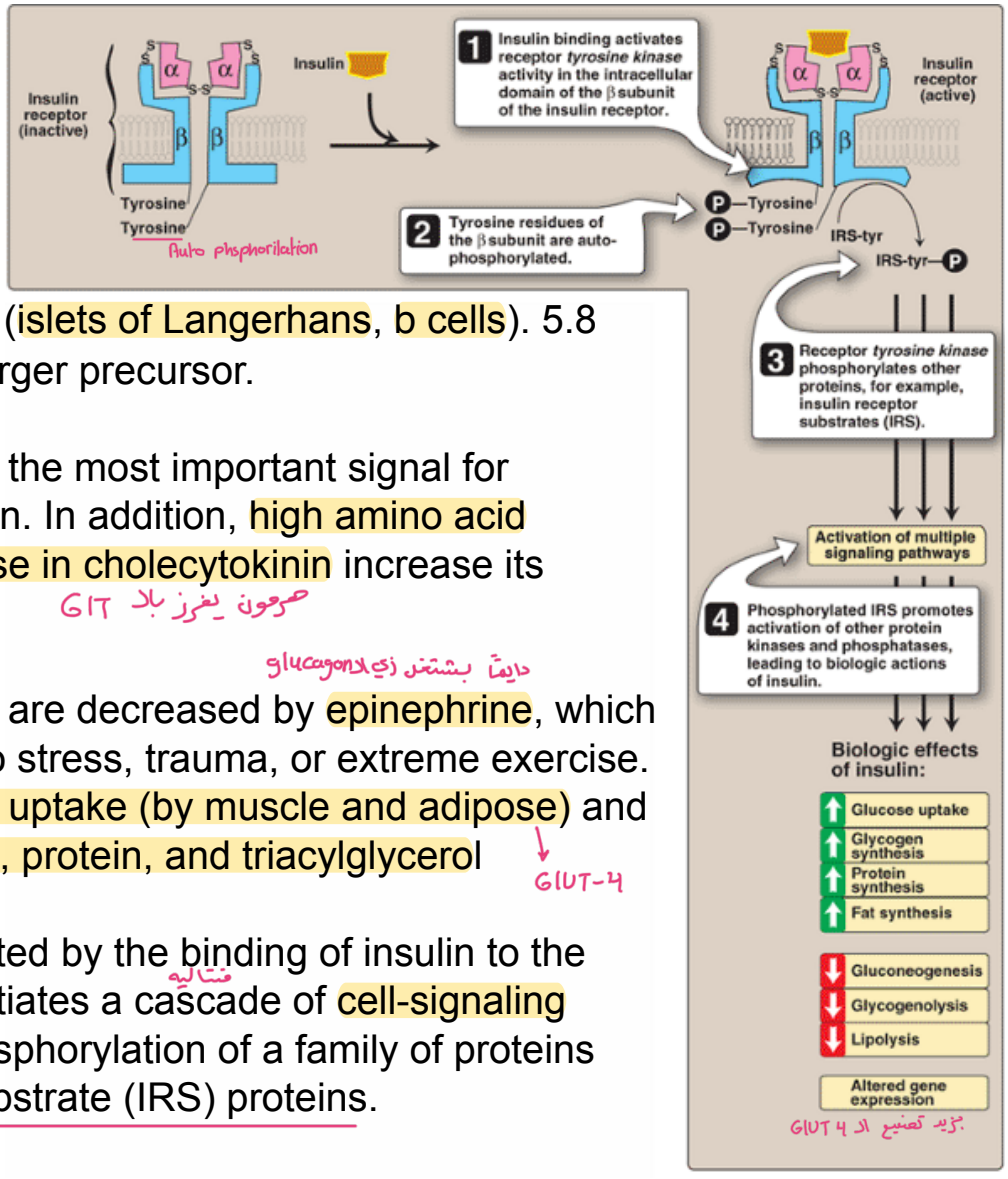
3 days Starvation Liver makes ketone bodies (Citric acid cycle slows). The switch to ketone body production is coordinated with a decrease in the rate of protein degradation in muscle.

الاعتماد الكلي على Fatty acids الـ

↓ Live breakit- ketons bodies

كرتبط

✡Insulin



- Synthesized in pancreas (islets of Langerhans, b cells). 5.8 kDa protein, cut from a larger precursor.

- A rise in blood glucose is the most important signal for increased insulin secretion. In addition, high amino acid concentration and increase in cholecytokinin increase its secretion

- Its synthesis and release are decreased by epinephrine, which is secreted in response to stress, trauma, or extreme exercise. Insulin increases glucose uptake (by muscle and adipose) and the synthesis of glycogen, protein, and triacylglycerol

- These actions are mediated by the binding of insulin to the insulin receptor, which initiates a cascade of cell-signaling responses, including phosphorylation of a family of proteins called insulin receptor substrate (IRS) proteins.

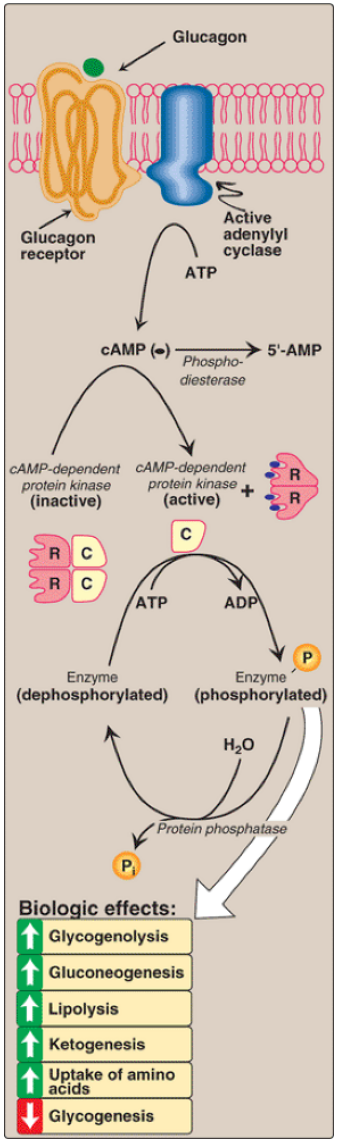
Glucagon

- Glucagon is a polypeptide hormone secreted by the α cells of the pancreatic islets. Glucagon, along with epinephrine, cortisol, and growth hormone (the "counter-regulatory hormones"), opposes many of the actions of insulin.

- Glucagon acts to maintain blood glucose during periods of potential hypoglycemia. Glucagon increases glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, and uptake of amino acids. by the liver عشان يصنع glucose

- Glucagon secretion is stimulated by low blood glucose, amino acids, and epinephrine. Its secretion is inhibited by elevated blood glucose and by insulin.

- Glucagon binds to high-affinity receptors of Hepatocytes primary target liver and adipose tissue



Hypoglycemia

- Hypoglycemia is characterized by:
  - Central nervous system symptoms, including confusion, aberrant behavior, or coma
  - A simultaneous blood glucose level equal to or less than 40 mg/dl
  - Resolution of these symptoms within minutes following the administration of glucose.

- Hypoglycemia most commonly occurs in patients receiving insulin treatment with tight control.

- The consumption and subsequent metabolism of **ethanol** inhibits gluconeogenesis, leading to hypoglycemia in individuals with depleted stores of liver glycogen. Alcohol consumption can also increase the risk for hypoglycemia in patients using insulin.

Epinephrine

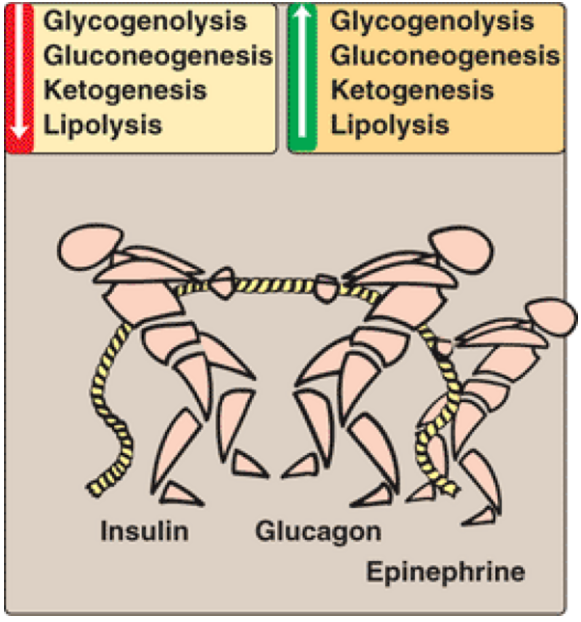
- Epinephrine is a Catecholamine, When released from presynaptic nerve endings, serves as neurotransmitter.

- When released from adrenal medulla, acts as hormone. Signals glucose limitation.

- Main targets muscle and adipose tissue.

●Inhibits insulin secretion and stimulates glucagon secretion.

●Part of "flight or fight" response.



Major hormones controlling fuel metabolism in mammals

	Glucagon	Epinephrine
Insulin stimulates **glucose uptake** **glycolysis** **glycogenesis** **triacylglycerol synthesis** **protein, DNA, RNA synthesis**	**cAMP** **glycogenolysis** **gluconeogenesis** **triacylglycerol hydrolysis**	**cAMP** **triacylglycerol hydrolysis** **glycogenolysis**
Inhibits Gluconeogenesis lipolysis protein degradation	glycogenesis glycolysis	glycogenesis

↑ Amino acid (↑ الدم) → insuline : to ↑ protien synthesis of aa
↑ Amino acid (↑ بعض) → Glucagon : to stimulate gluconyogenesis using the aa

Main Purpose	Action	Type	Process
⚡ Energy production	Glucose → Pyruvate + ATP	🔽 **Break Glucose**	**Glycolysis**
🏦 Glucose storage	Glucose → Glycogen	🔼 **Build Glycogen**	**Glycogenesis**
🩸 Raise blood glucose	Non-carbs → Glucose	🔼 **Build Glucose**	**Gluconeogenesis**
🚨 Provide glucose when needed	Glycogen → Glucose	🔽 **Break Glycogen**	**Glycogenolysis**

Enzymatic changes in the fed state

- Availability of the substrate
- a Allosteric effect
- For example, glycolysis in liver is stimulated after meal by elevation in fructose 2,6-bisphosphate which is an allosteric activator of phosphofructokinase-1
- b Regulation of enzymes by covalent modification
- In the fed state, most of the enzymes regulated by covalent modification are in the dephosphorylated form and are active (exceptions: are glycogen phosphorylase, fructose 2,6-bisphosphatase-2, and hormone-sensitive lipase of adipose tissue, which are inactive in their dephosphorylated state).
- Induction and repression of enzyme synthesis
- For example, in the fed state, elevated insulin levels result in an increase in the synthesis of key enzymes involved in anabolic metabolism

In fed state

- After ingestion of the meal, absorptive state took 2-4 hr where an increase in glucose, amino acids and TAG in blood is observed
- As a response pancreas will increase the secretion of insulin and drop the release of glucagon by islets of langerhans
- During the absorptive state, all tissues use glucose as a feul

In fed state

- In liver: اعلاه تجديد
  - It starts glycogenesis to replinish glycogen store.
  - Replaces any needed hepatic proteins
  - Increase TAG synthesis, which are packaged as very low density lipoprotein (VLDL) and exported to the perepheral tissue

- In resting skeletal muscles
  - Increase protein synthesis to replace protein degraded since the previous meal

- In adipose tissue
  - Increase the TAG synthesis and storage

- In brain
  - It uses glucose extensively as feul

In fast state (starvation)

- Decrease in blood glucose, aa, and TAG levels leading to decrease in insulin secretion and increase in glucagon and epinephrine release

- For the liver, adipose, skeletal muscles, and brain, their are two priorities:
- (1) Need to maintain adequate plasma level of glucose to sustain energy metabolism of the brain and other glucose-requiring tissues (RBC)
- (2) Need to mobilize fatty acids from adipose tissue and ketone bodies from liver to to supply energy to the other tissues

In fast state (starvation)

- In liver, this is accomplished by:
  - Glycogenolysis
  - Initiate gluconeogenesis using both increased fatty acid oxidation as source energy and supply acetyl coA for synthesis of ketone bodies
- Adipose tissues: will degrade stored TAG to fatty acids and glycerol that move to the liver
- Muscles:
  - start using fatty acids and ketone bodies as feul
  - Muscle proteins are degraded to supply amino acids for the liver to use in gluconeogenesis
- Brain can use glucose (short fasting) and ketone bodies (long fasting) as feul

Diabetes mellitus (DM)

- A disease characterized by elevation of fasting blood glucose caused by relative or absolute deficiency of insulin

- The leading cause of adult blindness, renal failure, heart attacks and strokes.

- Can be of two types:
- Type 1 DM: insulin dependent DM, usually during childhood, autoimmune, stimulated by environmental (viral) or genetic (low)
- Type 2 DM: non insulin dependent DM, old people, genetic reasons mainly.

Type 1 diabetes mellitus (DM)

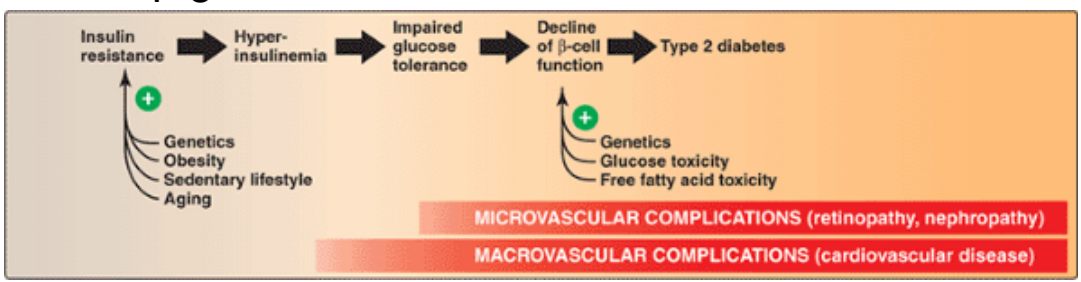
- Hyperglycemia and ketoacidosis

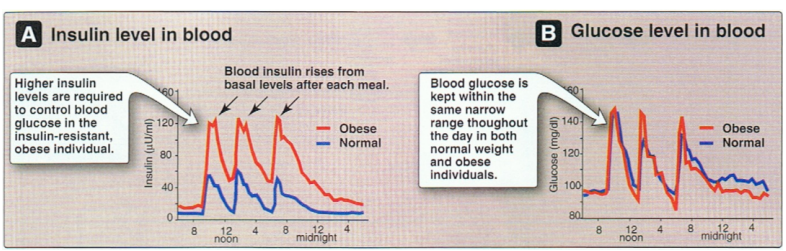
- Type 1 DM compared to fasting
  - Insulin level
  - Blood glucose level
  - Ketosis
  - hypertriacylgycerolemia

Type 2 diabetes mellitus (DM)

- Insulin resistance alone will not lead to Type 2 diabetes. But it develops in insulin-resistant individuals who show impaired β-cell function.

- Insulin resistance and subsequent risk for the development of Type 2 diabetes is commonly observed in the **elderly**, and in individuals who are **obese**, **physically inactive**, or in the 3–5% of **pregnant women** who develop gestational diabetes.





علم الطاقه الحيويه

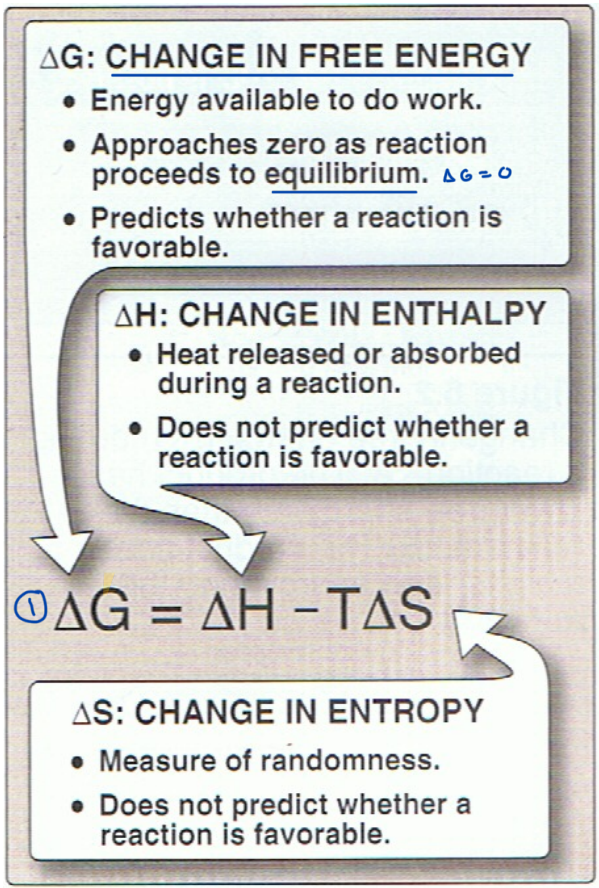
Bioenergetic and oxidative phosphorylation

Bioenergetics

- Is the study of energy changes accompanying biochemical reaction which explains why some reactions occur while others not

- Biological systems conform to the general laws of thermodynamics

- The free energy (G) predicts the direction in which the reaction will spontaneously proceed



Free energy change

- The sign of ΔG predicts the direction of the reaction

طارد

- Case 1 : -ΔG: there is a net loss of energy, the reaction goes sponatneously (Exergonic)
- Case 2 : + ΔG: there is a net gain of energy, reaction needs energy to preceed (energonic)

عاقب

- Case 3 : ΔG is zero: reactants are in equilibrium
- The ΔG of the forward reaction is equal in magnitude but opposite in sign to that of the back reaction
- ΔG depends on the concentration of the reactants and products at constant temperature and pressure

② $$\Delta G = \Delta G^{o} + RT \ln \frac{[B]}{[A]}$$

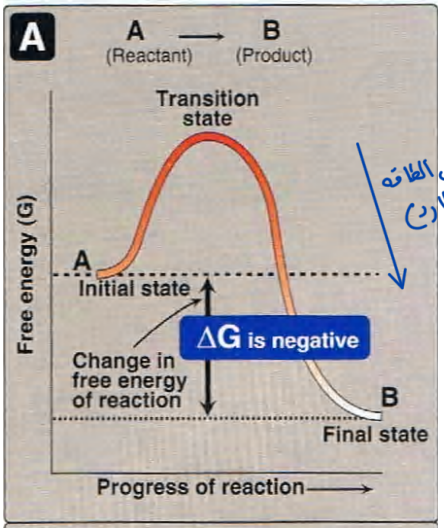
where

ΔGo is the standard free enrgy → بظروف قياسيه

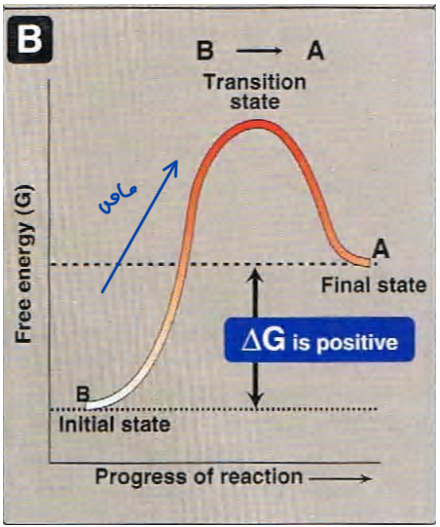
T is the absolute temperature (Ko)

R the gas constant (1.987cal/mol.degree)

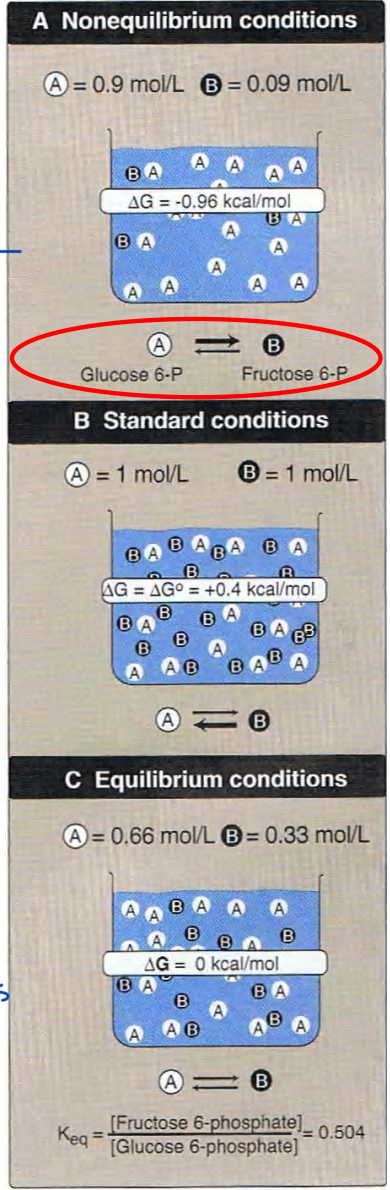
[A] and [B] are actual conc. of reactants and products



نقل الطاقة (طارد)



صاعد



ΔG- تفاعل / ع

ΔG+ backwards

backwards = afterwards

Standard free energy change, ΔGo

- The energy change when the reactants and products are at concentration of 1 mol/L
- ΔGo can predict the direction of the reaction only under standard conditions (ΔG = ΔGo) but not under physiological conditions
- At equilibrium Keq = [B]/[A] and ΔG = 0 so:

$$\Delta G^o = -RT \ln K_{eq}$$

This equation allows some simple predictions:

If $K_{eq} = 1$, then $\Delta G^o = 0$	$A \rightleftharpoons B$
If $K_{eq} > 1$, then $\Delta G^o < 0$	$A \rightharpoonup B$
If $K_{eq} < 1$, then $\Delta G^o > 0$	$A \leftharpoondown B$

- ΔGo of consecutive reactions are additive
- ΔGs of a pathway are additive

A → B → C → D

- As far as the sum of ΔGs of the pathway reaction is negative, reaction proceeds even if the ΔG of the individual reaction is positive

ATP as energy carrier

If the reaction or process has +ΔG (as movement of ions against concentration gradient across cell membrane), it can be coupled with the spontaneous hydrolysis of ATP to ADP and Pi

Reactions are coupled through common intermediate

A + B → C + D

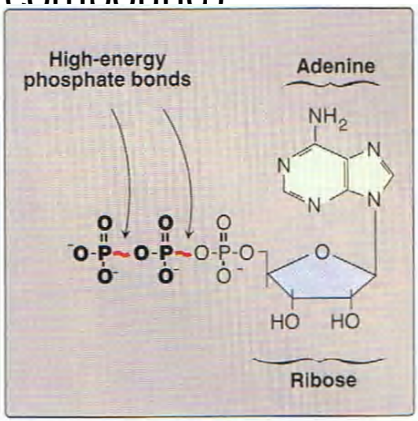
ATP ⇌ ADP ⇌ AMP (−P / +P)

Energy carried by ATP (high energy phosphate compound)

ATP → ADP + Pi AMP + Pi

ΔGo for each hydrolysis = -7300 cal/mol

ATP → ADP + P + energy



Electron transport chain

الموضوع الأهم بعد التشابتر

- In the metabolism of glucose to CO2 and water, many metabolic intermediates donate electrons to specific coenzymes (NAD+ and FAD) to form energy rich reduced coenzymes NADH and FADH2

نواتج الـ meta للغلوكوز

NAD: Nicotinamide adenine dinucleotide

FAD: Flavin adenine dinucleotide

أمامك

- The reduced form (NADH and FADH2) donate a pair of electrons to special set of electron carriers (Electron transfer chain)

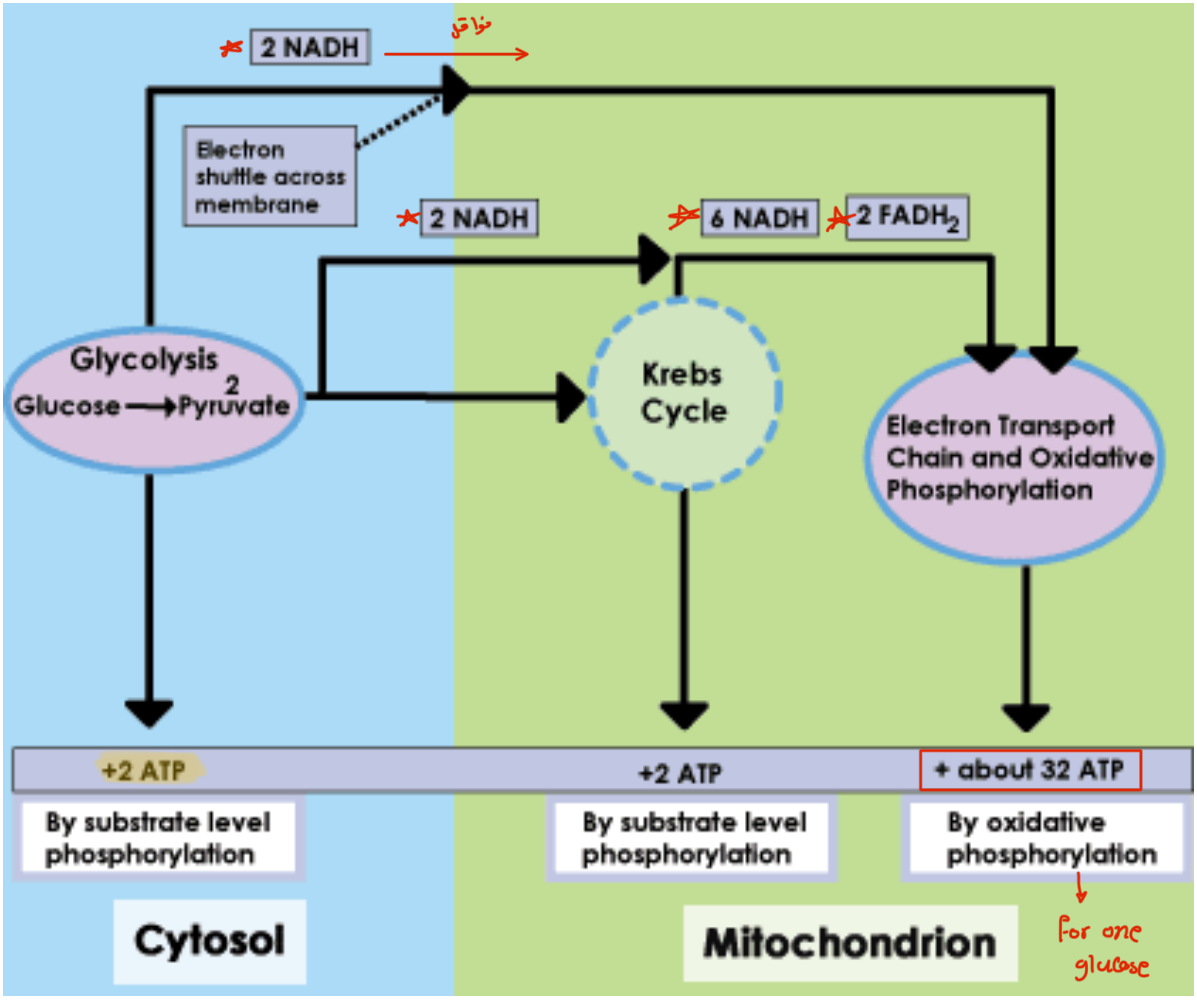
تدفعه

- The flow of electrons leads to the loss of of free energy which can be captured and stored by the production of ATP from ADP and Pi (oxidative phosphorylation)

القبض عليها

ADP + فسفره : الفسفرة التأكسدية

to ATP



اذاً :
المدخلات :

2.5x 4 = 10
=

****في ما يلي تلخيص لنواتج التنفس الخلوي بمراحله جميعها التحلل الغلاكولي / تفاعلات اكسده البيروفيت الى اسيتايل مرافق انزيم-أ / والتفاعلات التي تحدث في حلقه كريبس لجزيء غلوكوز واحد

6جزيئات من CO_2

4 جزيئات منATP

10جزيئات منNADH

2 من $FADH_2$

المرحله الثانيه من التنفس الهوائي وهي الفسفره التاكسديه ويطلق عليها ايضا سلسله نقل الالكترون والاسموزيه الكيميائيه

**هي عباره عن مجموعه من المكونات معظمها بروتينات ناقله وانزيمات

** اهميتها تستقبل هذه السلسله الالكترونات الناتجه من اكسده NADH و$FADH_2$ ثم تنقلها من بروتين ناقل الى اخر

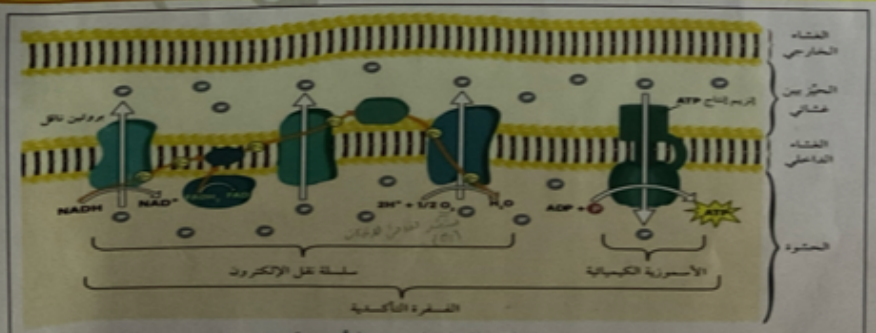
** في نهايه هذه السلسله تصل هذه الالكترونات الى مستقبلها النهائي وهو الاكسجين ثم تتحد معه ومع البروتونات ليتكون الماء

**يؤدي انتقال الالكترونات الناتجه من اكسدة NADH و$FADH_2$ الى الاكسجين خلال سلسلة نقل الاكترون الى ضخ البروتونات(H^+) من الحشوه الى الحيز بين الغشائي

والنتيجه فرق في تركيز البروتونات بين الحيز بين غشائي والحشوه

**بعد ذلك تعود البروتونات (H^+) نتيجه لفرق التركيز على جانبي غشاء الميتوكندريا الداخلي الى داخل الحشوه عن طريق انزيم انتاج ATP في عمليه تسمى الاسموزيه الكيميائيه وتحدث فيها فسفرة جزيئات ADP الى ATP

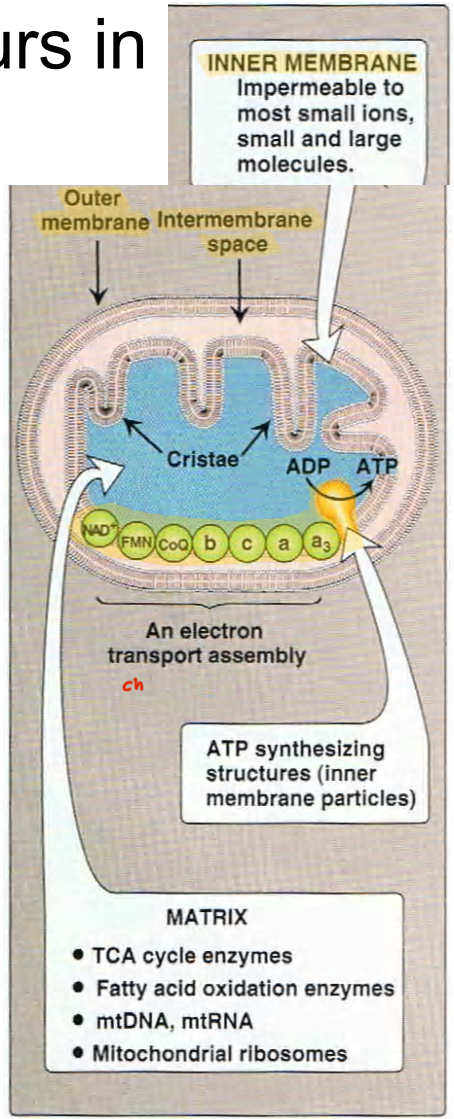
ملاحظه يطلق على عمليه انتاج ATP عن طريق سلسله نقل الالكترون والاسموزيه الكيميائيه اسم الفسفره التاكسديه



الشكل (38): الفسفرة التأكسدية.

Oxidative phosphorylation occurs in mitochondrion

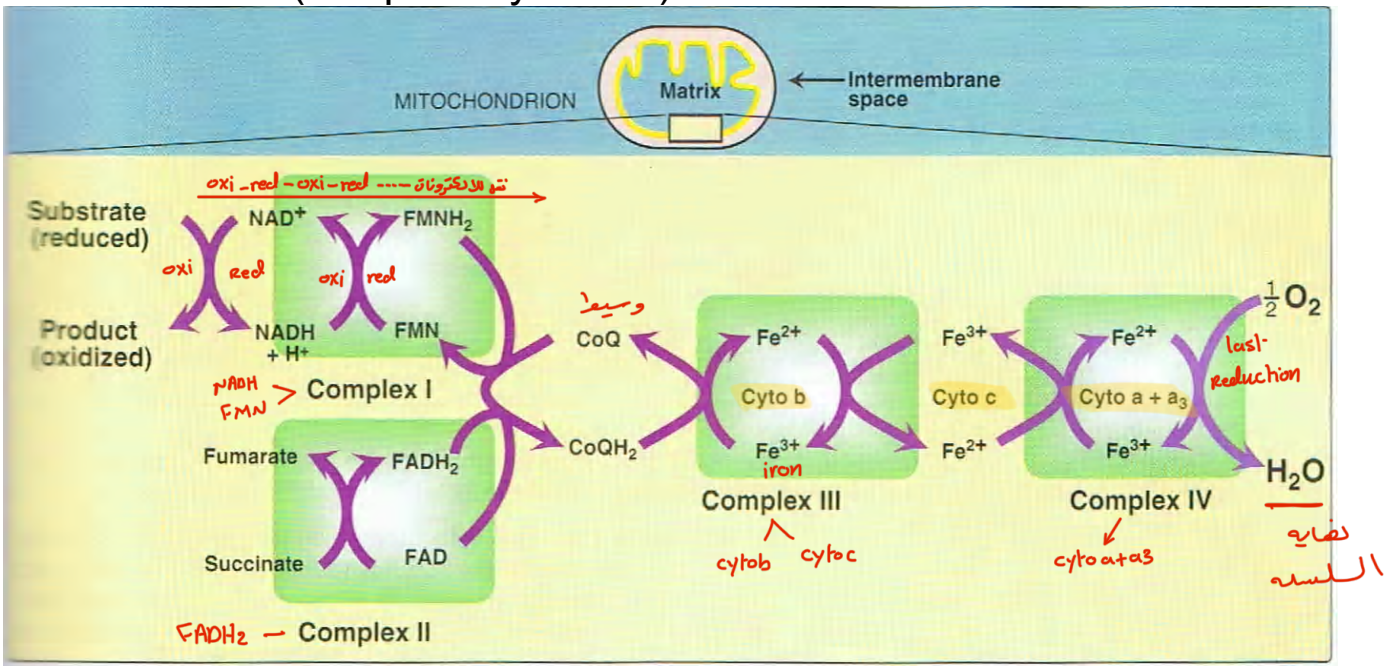
- The outer membrane is permeable for most of substances
- Oxidative phosphorylation occurs in the inner membrane of mitochondrion
- ATP synthesizing structures are present at the end of the e- transport assembly
- Different enzymes for TCA cycle, fatty acid oxidation, mtDNA, mtRNA and ribosomes are present in the matrix.



Organization of the chain

- Present in the inner mitochondrial membrane

- Consist of 5 separate enzyme complexes until e- combine with O2 to form water (Respiratory Chain)



Reactions of the electron transport chain

All components of this chain are proteins except coenzyme Q

Some of them contain metals (iron and copper) to function

1. Formation of NADH: needs dehydrogenase which transfers 2e- and one proton to form NADH + H+
2. NADH dehydrogenase: NADH + H+ is complexed with NADH dehydrogenase which has tightly bound flavin mononucleotide (FMN) which accept 2e- and 2 H+ to become FMNH2
   NADH dehydrogenase has iron-sulfur center necessary for the transfer of H+ to coenzyme Q
3. Coenzyme Q: is quinone derivative which can accept hydrogen atoms from FMNH2 and from FADH2.

Reactions of the electron transport chain

cyto: b/c

4. Cytochromes: the rest of electron transfer chain are cytochromes with heme group (iron)

5. Cytochrome a + a3 (cytochrome oxidase)

Fe

- is electron carrier in which the heme iron has a free ligand that can react directly with molecular O2 to produce water
- contain bound Cu atoms required for complex reaction to occur

التفاصيل مهمه

6. Site specific inhibitor:

Some compounds prevent passage of e- by binding one of the components of the chain which blocks oxidation/reduction and inhibit ATP synthesis

Release of free energy

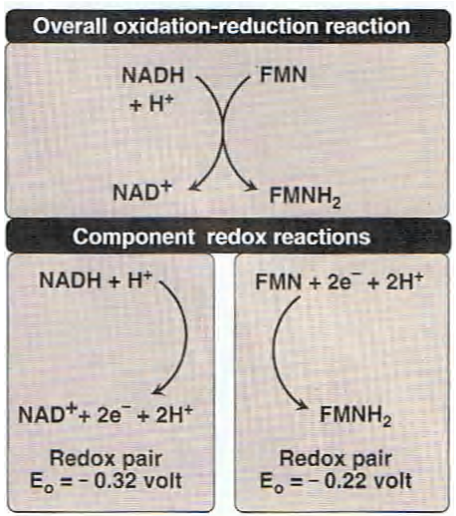
- Free energy is released as electrons are transferred along the electron transport chain from an electron donor (reducing agent or reductant) to an electron acceptor (oxidizing agent or oxidant)

- The electrons can be transferred in different forms, for example, as hydride ions, as hydrogen atoms, or as electrons

- Oxidation of one compound is always accompanied by reduction of a second substance.

- Redox pairs differ in their tendency to lose electrons, which is a characteristic of a particular redox pair, quantitatively specified by a constant, E0 (the standard reduction potential) in volts

Redox pair	E_o
$NAD^+/NADH$	-0.32
$FMN/FMNH_2$	-0.22
Pyruvate/lactate	-0.19
Cytochrome c Fe^{3+}/Fe^{2+}	+0.07
$1/2\ O_2/H_2O$	+0.82



Standard reduction potential (E0)

- The standard reduction potentials of various redox pairs can be listed to range from the most negative Eo to the most positive.
- The more negative the standard reduction potential of a redox pair, the greater the tendency of the reductant member of that pair to lose electrons.
- The more positive the Eo, the greater the tendency of the oxidant member of that pair to accept electrons.
- So electrons flow from the pair with the more negative Eo to that with the more positive Eo.

NADH and FADH2

- Oxidation of one mole of NADH results in free energy sufficient to produce 2.5 ATP

- Oxidation of one mole of FADH2 and FMN results in free energy sufficient to synthesize 1.5 ATP

ATP synthase (ATPase)

- The enzyme complex ATP synthase synthesizes ATP, using the energy of the proton gradient generated by the electron transport chain.

- The chemiosmotic hypothesis proposes that after protons have been transferred to the cytosolic side of the inner mitochondrial membrane. they reenter the mitochondrial matrix by passing through a channel in the ATP synthase complex, resulting in the synthesis of ATP from ADP + Pi and, at the same time, dissipating the pH and electrical gradients.

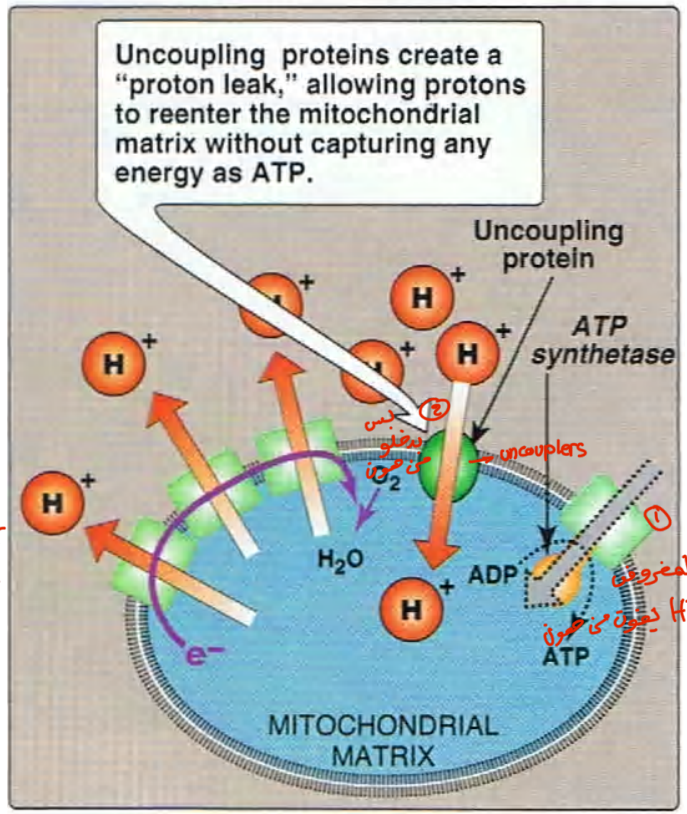
- Oligomycin binds to the stalk of ATP synthase, closing the H channel, and preventing reentry of protons into the mitochondrial matrix leading to stop in electron transport

- Electron transport and phosphorylation are tightly coupled processes and inhibition of phosphorylation inhibits oxidation.

فصل العصلية

Uncouplers of oxidative phosphorylation

- Are substance that inhibit the oxidative phosphorylation by ETC.
- They dissociate oxidation from phosphorylation
- The oxidation of hydrogen with O2 to form water proceed while there is no conversion of ADP to ATP
- The free energy librated during reaction is librated as heat leading to increase in body temperature.
- Billirubin, high Ca level, hyperthyroidism, toxins from bacteria, some drugs (warfarin, aspirin) and 2,4-dinitrophenol.



Drugs that inhibit ETC

- CO, CN-, sodium azide inhibit the cytochrome oxidase which is fatal
- Rotenone used insecticide
- Amytal as hypnotic
- Antimycin A as antibiotic