

Metabolism of phospholipids and cholesterol

constituent
of cell
membrane

polar
ionic
negative or neutral

stay familiar with these facts ★ قبل لدخل الشاير

1. DPPC = lung surfactant.
2. Sphingomyelin = myelin sheath.
3. Cardiolipin = inner mitochondrial membrane.
4. PI = arachidonic acid reservoir + signaling.
5. COX-1 = gastric/kidney/platelets.
6. COX-2 = inflammation.
7. Cortisol inhibits phospholipase A₂.
8. NSAIDs inhibit COX. 1+2
9. HMG-CoA reductase = rate-limiting enzyme of cholesterol synthesis.
10. Cholesterol 7α-hydroxylase = rate-limiting enzyme of bile acid synthesis. ★ only liver ★

- حكي الدكتوراة

- سنوات

- good luck -

By raneem Al-syouf

Phospholipids

alc ohol back bone (glycerol / sphingosine) + (P) group

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

سجل

1- reservoir for intracellular messengers

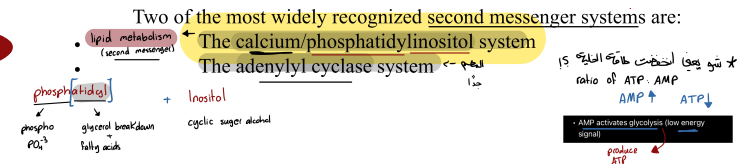
2- Anchor to cell membrane

membrane bounded

3- components of lung surfactant

4- essential component of bile → (phospholipids)

5- solubilization of cholesterol
+ bilirubin (excretion)



Function of phospholipids, except:

Lung surfactant

Bile

Anchor cell membrane

Intercellular messengers

Cell cell recognition (الجواب)

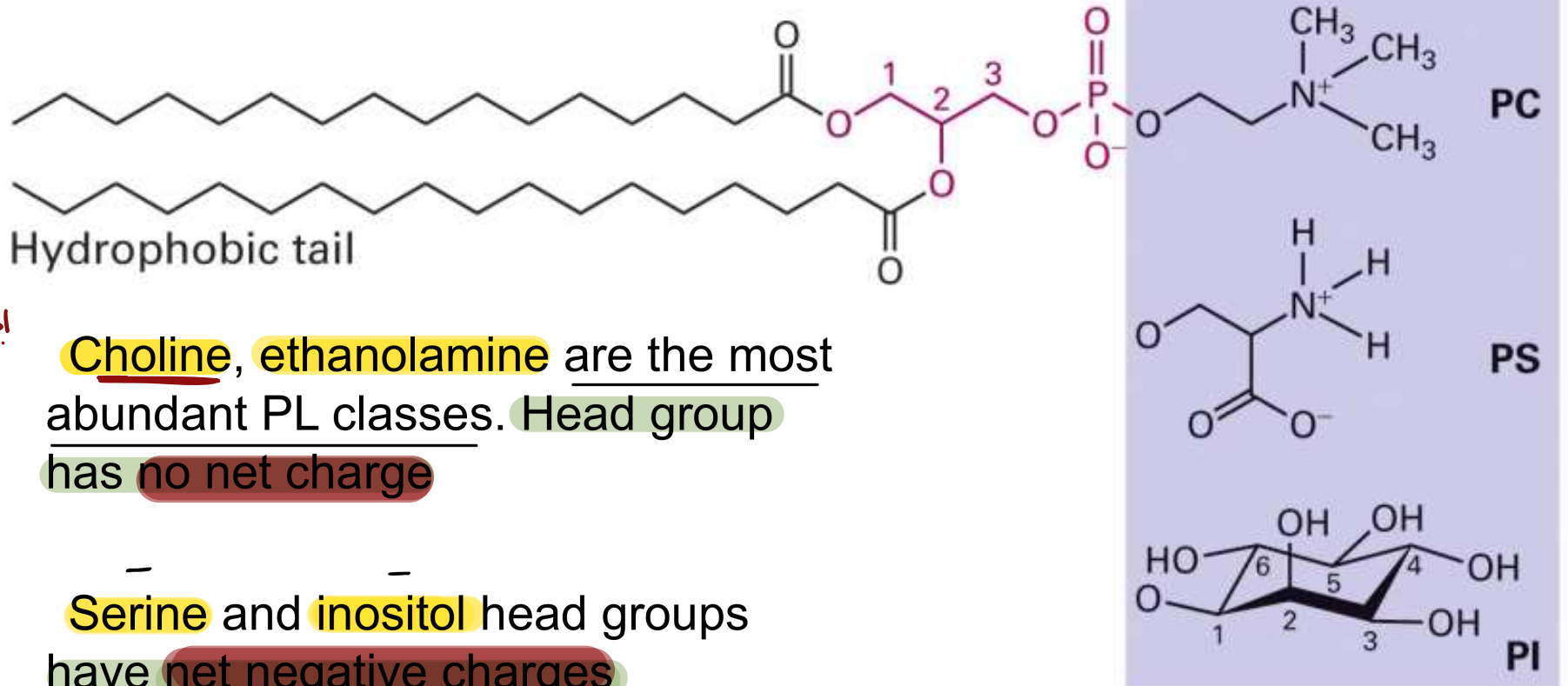
non bound membrane

Phospholipids

(a) Phosphoglycerides

most abundant?

- choline
- ethanolamine



second

Choline, ethanolamine are the most abundant PL classes. Head group has no net charge

Serine and inositol head groups have net negative charges

phosphatidylinositol

Phospholipids

Exam point:

Cardiolipin is required for normal mitochondrial oxidative phosphorylation

Function & responsible for the cytochrome enzymes of oxidative phosphorylation

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

ether PL

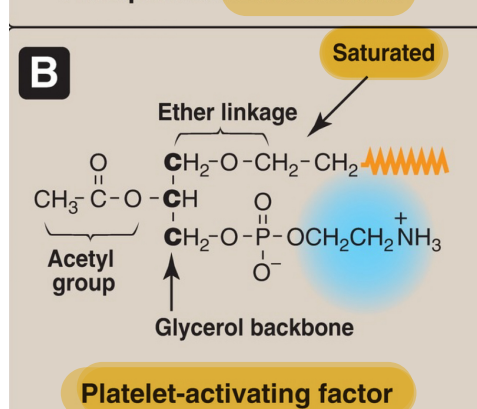
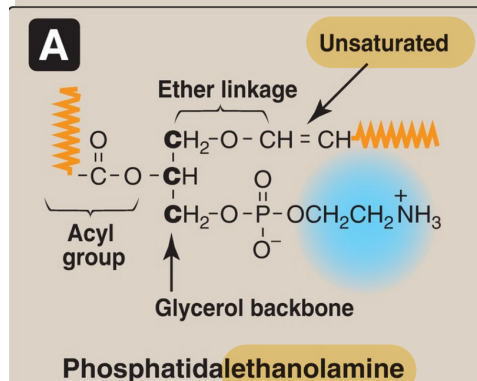
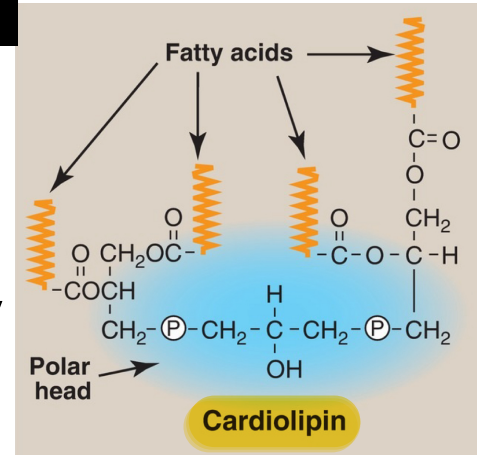
- **Plasmalogens:** when an **unsaturated** alkyl group attached by an **ether linkage** to the core glycerol molecule, a **plasmalogen** is produced. **phosphatidylethanolamine** (abundant in nerve tissue, **phosphatidylcholine** (abundant in heart muscle) is the other quantitatively significant ether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

- **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

carbon 1 → saturated alkyl group

carbon 2 → acetyl group

- 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



Functions

PAF is a powerful inflammatory mediator.

It:

- Causes **platelet aggregation**. ✓
- Causes **platelet degranulation**. ✓
- Activates **neutrophils** and **macrophages**. ✓
- Stimulates production of **superoxide radicals**.
- Mediates:
 - Acute inflammation
 - Hypersensitivity reactions
 - Anaphylaxis

Compound	Location/Function
Cardiolipin	Inner mitochondrial membrane; oxidative phosphorylation
Plasmalogens	Ether phospholipids in nerve tissue and heart muscle
PAF	Potent inflammatory mediator; platelet aggregation and anaphylaxis

Which phospholipid is found almost exclusively in the inner mitochondrial membrane and is required for oxidative phosphorylation?

- A. Phosphatidylcholine
- B. Cardiolipin
- C. Sphingomyelin
- D. Platelet-activating factor

Answer: B. Cardiolipin

Sphingophospholipids

sphingomyelin *(myelin sheath of nerves) protection*

- The backbone of sphingomyelin is the amino alcohol sphingosine, rather than glycerol. *(logic)*

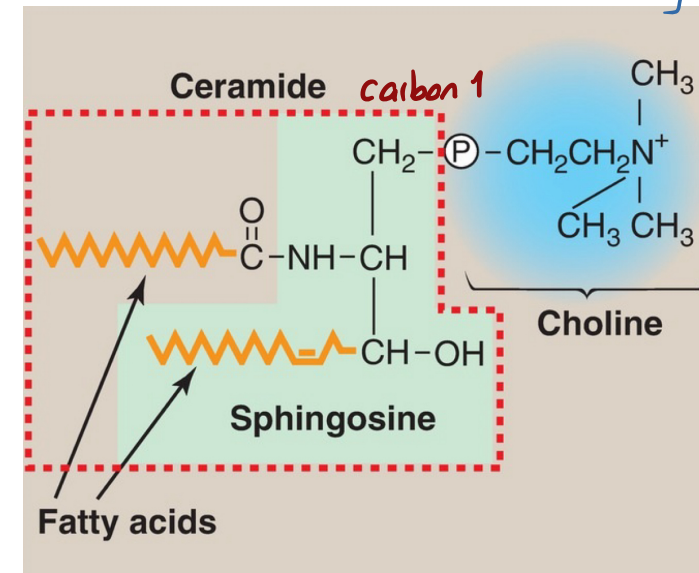
Sphingosine + Fatty acid = Ceramide

- 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.

C_1
Ceramide + Phosphorylcholine = Sphingomyelin

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

لوراكت
تسبب
dementia



3. The only significant sphingophospholipid in humans is:

- A. Cerebroside
- B. Ganglioside
- C. Ceramide
- D. Sphingomyelin

Answer: D. Sphingomyelin

→ can be synthesised in all organs EXCEPT
mature RBCs

steve when its immature

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

Synthesis of PE and PC

Choline, ethanolamine are the most abundant PL classes. Head group has no net charge

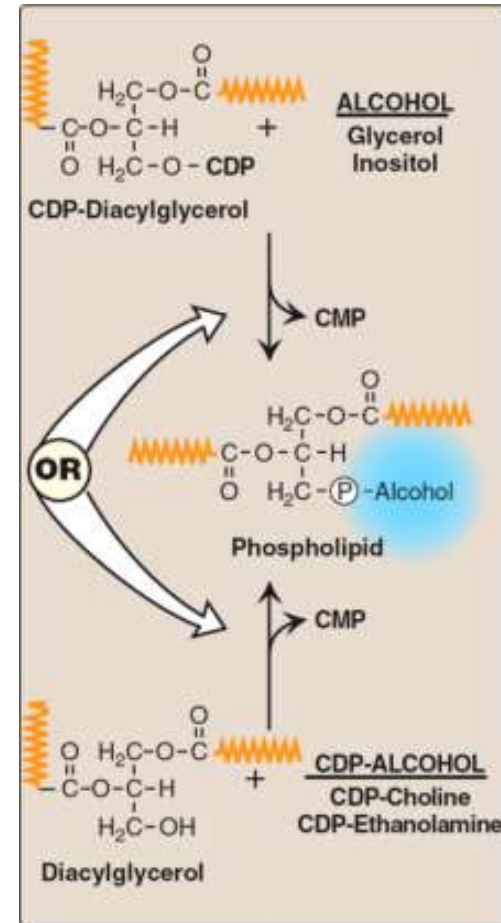
➤ PC and PE are the most abundant phospholipids in most eukaryotic cells. Choline and ethanolamine are obtained either from the diet or from the turnover of the body's phospholipids.

➤ **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. إعادة الاستخدام من العضو

➤ 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.

In lungs



synthesis of PE and PC

1- phosphorylation by Kinases

2- Activation by CDP

3- transfer from CMP to diacylglycerol (DAG)

سؤال
بالامتحان sugar activation UDP

phospholipid activation CDP

amino acids activation transfer RNA

fatty acids activation CoA

How are PE and PC synthesized?

Step 1: Phosphorylation

Choline or ethanolamine is phosphorylated by kinases.

- Choline $\rightarrow$ Phosphocholine
- Ethanolamine $\rightarrow$ Phosphoethanolamine

Step 2: Activation

They are activated by binding to CDP.

- Phosphocholine $\rightarrow$ CDP-choline
- Phosphoethanolamine $\rightarrow$ CDP-ethanolamine

Think:

CDP = activated form ready for membrane synthesis.

Step 3: Transfer to diacylglycerol (DAG)

Activated groups are transferred to diacylglycerol (DAG).

- CDP-choline + DAG $\rightarrow$ Phosphatidylcholine (PC)
- CDP-ethanolamine + DAG $\rightarrow$ Phosphatidylethanolamine (PE)

Which of the following doesn't match :

Galactose: UDP

Amino acid :tRNA

Ethanolamino :CDP

Inositol:CDP (الجواب)

The phospholipid that acts as lung surfactant is:

1. ☐ Cardiolipin
2. ☐ Plasmalogen
3. ☒ Dipalmitoylphosphatidylcholine
4. ☐ Phosphatidyl inositol
5. ☐ Platelet activating factor

Synthesis of PE, PC and PS



serine

- Reaction
- PE + Serine → PS + Ethanolamine

3 enzymes

- glycogen phosphorylase
- aminotransferase
- PS decarboxylase

The diagram illustrates the synthesis of Phosphatidylcholine (PC) from Phosphatidylserine (PS). It shows the following steps:

- Phosphatidylserine** is converted to **Phosphatidylethanolamine** by the enzyme **Phosphatidylserine decarboxylase**, releasing CO_2 .
- Phosphatidylethanolamine** is converted to **Phosphatidylcholine** by the enzyme **N-Methyltransferases**, using **S-Adenosylmethionine** as a methyl donor. This process involves three successive methylations of the ethanolamine head group.
- S-Adenosylmethionine** is converted to **S-Adenosylhomocysteine** during the methylation process.
- The final product is **Phosphatidylcholine**, which has a choline head group.

Chemical structures shown include the head groups of Phosphatidylserine, Phosphatidylethanolamine, and Phosphatidylcholine, as well as the S-Adenosylmethionine and S-Adenosylhomocysteine intermediates.

Synthesis of PI **phosphatidylinositol**

second messenger

- 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.

- steric acid C₁

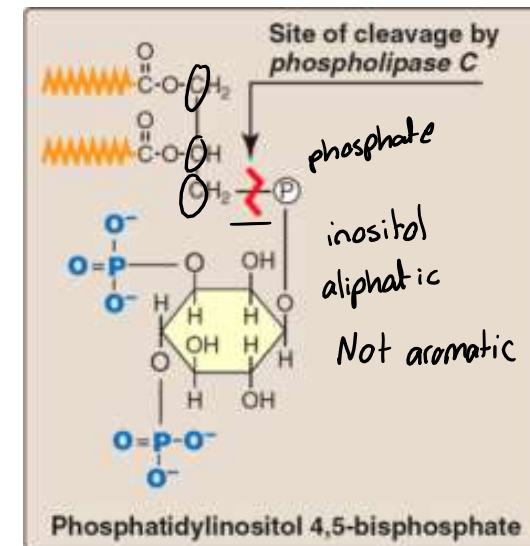
- arachidonic acid C₂

خلعيا بالاد ع.ع

phospholipase A₂ يكسر

inhibitor وال

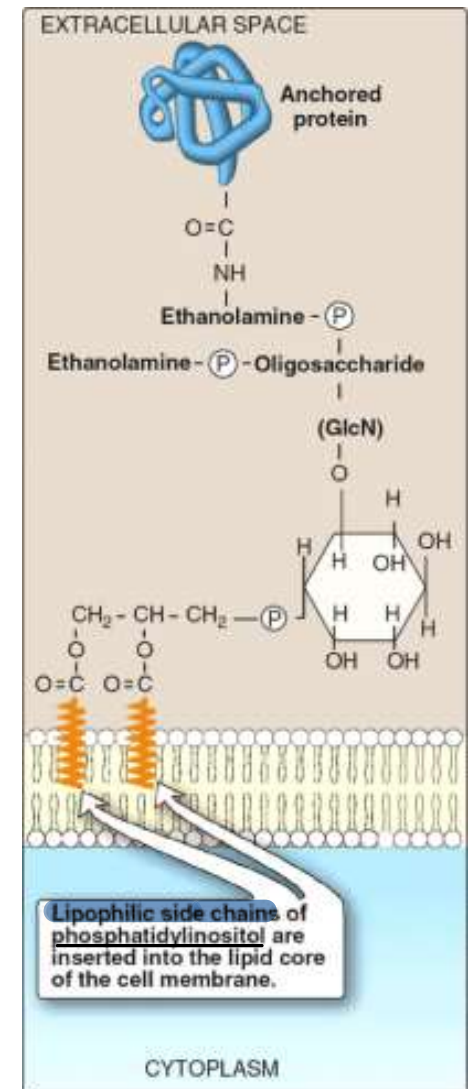
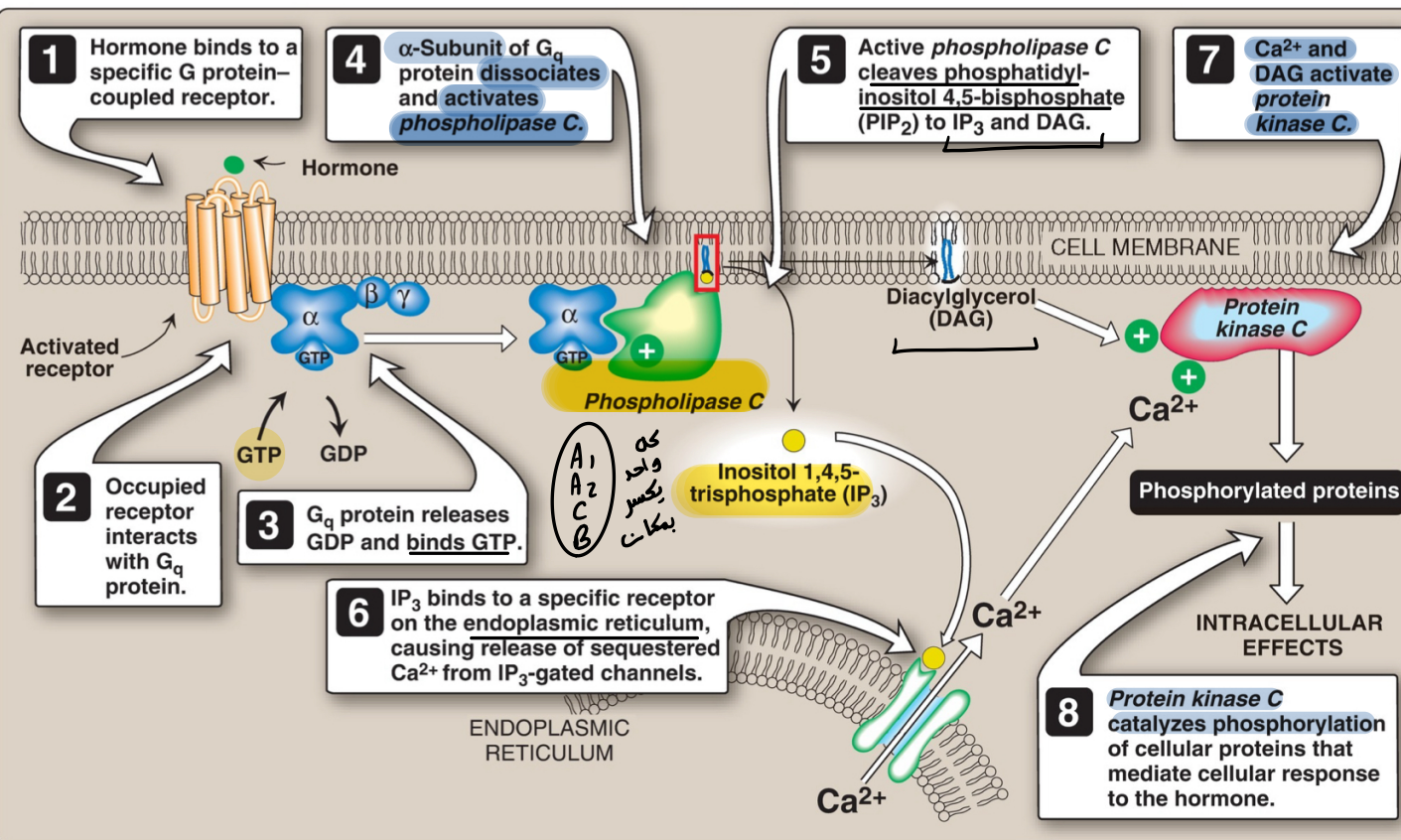
glucocorticoids (cortisol)



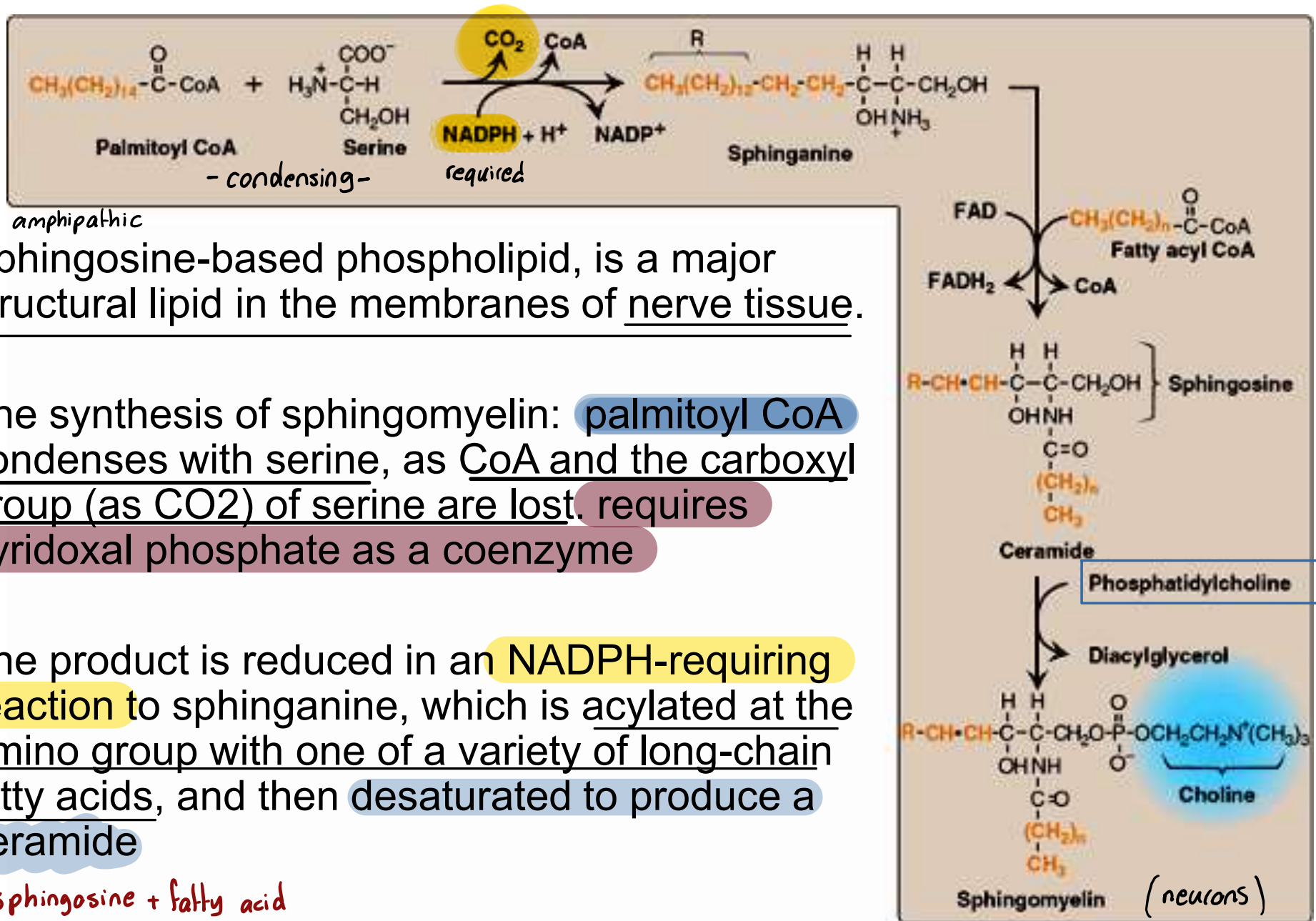
Role of PI

➤ PI in **signal transmission** across membranes

➤ PI in membrane **protein anchoring**



Synthesis of sphingomyelin



Which phospholipid acts as the primary donor of the polar head group during the conversion of a ceramide into sphingomyelin?

A. Phosphatidylcholine

B. Phosphatidylethanolamine

C. Phosphatidylinositol

D. CDP-choline

A

Degradation of phosphoglycerides

phospholipase C break DAG from inositol

- 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.
- Phospholipases release molecules that can serve as messengers (DAG and IP₃), or that are the substrates for synthesis of messengers (arachidonic acid).
C₁ ↙ ↘ break C₂ release 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

PHOSPHOLIPASE A_2

- Phospholipase A_2 is present in many mammalian tissues and pancreatic juice. It is also present in snake and bee venoms.
- Phospholipase A_2 , acting on phosphatidylinositol, releases arachidonic acid (the precursor of the prostaglandins). ✓
- Pancreatic secretions are especially rich in the phospholipase A_2 proenzyme, which is activated by trypsin and requires bile salts for activity.
- Phospholipase A_2 is inhibited by glucocorticoids (for example, cortisol).

PHOSPHOLIPASE A_1

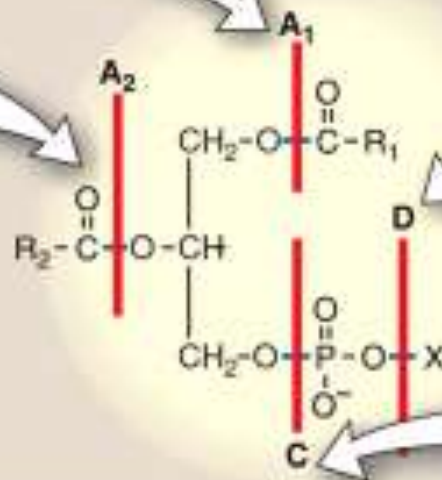
- Phospholipase A_1 is present in many mammalian tissues.

PHOSPHOLIPASE D

- Phospholipase D is found primarily in plant tissue.

PHOSPHOLIPASE C

- Phospholipase C is found in liver lysosomes and the α -toxin of clostridia and other bacilli.
- Membrane-bound phospholipase C is activated by the PIP_2 system and, thus, plays a role in producing second messengers.



QUESTION 22 / 20

Which of the following phospholipases does not match:

1. ☐ Phospholipase A1: break fatty acid at C1 ✓
2. ☐ Phospholipase A2: can be inhibited by glucocorticoid ✓
3. ☒ ~~Phospholipase C~~_{A₂}: Present in snakes and bees ✗
4. ☐ Phospholipase C: breaks the second messenger PIP2 ✓
5. ☐ Phospholipase D: break the base from the phospholipid ✓

3

Next

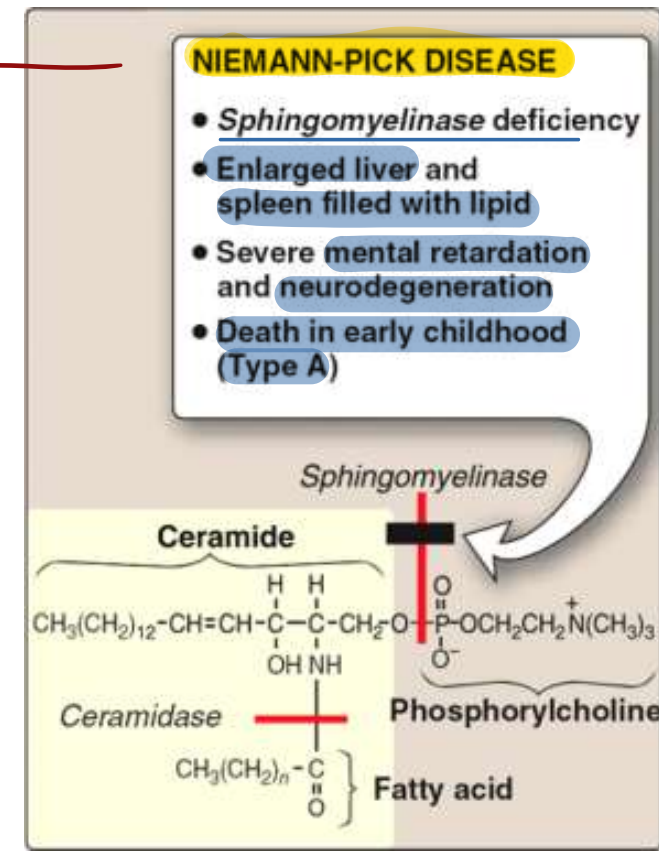
Degradation of sphingomyelin

- Sphingomyelin is degraded by the lysosomal sphingomyelinase.

niemann-pick disease *نيمان-بيك*

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

*sphingomyelin
accumulation*



Synthesis of PGH_2

- The first step in the synthesis of prostaglandins is the oxidative cyclization of free arachidonic acid to yield PGH_2 by prostaglandin endoperoxide synthase (PGH synthase).
- This enzyme is an endoplasmic reticulum membrane-bound protein that has two catalytic activities:
 - fatty acid cyclooxygenase (COX), which requires two molecules of O_2 , and
 - peroxidase, which is dependent on reduced glutathione
- PGH_2 is converted to a variety of prostaglandins and thromboxanes, by cell-specific synthases.

7. Arachidonic Acid Pathway
(Extremely High Yield)

COX Pathway

Arachidonic acid

→ PGH_2

→ Prostaglandins + Thromboxanes

Enzyme:

- PGH synthase (Cyclooxygenase, COX)

Isozymes of PGH synthase

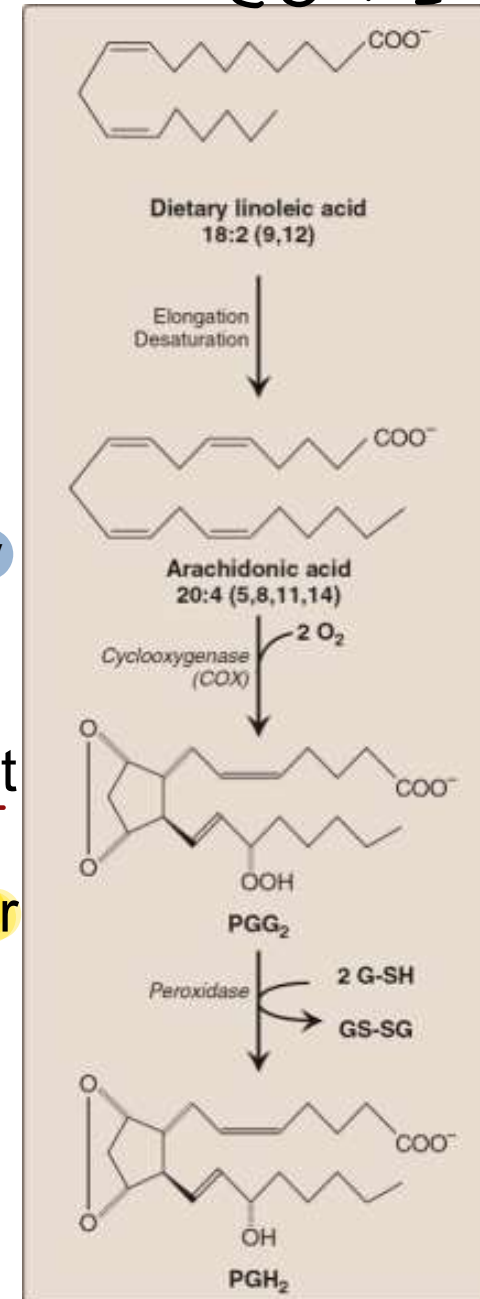
COX-1
COX-2

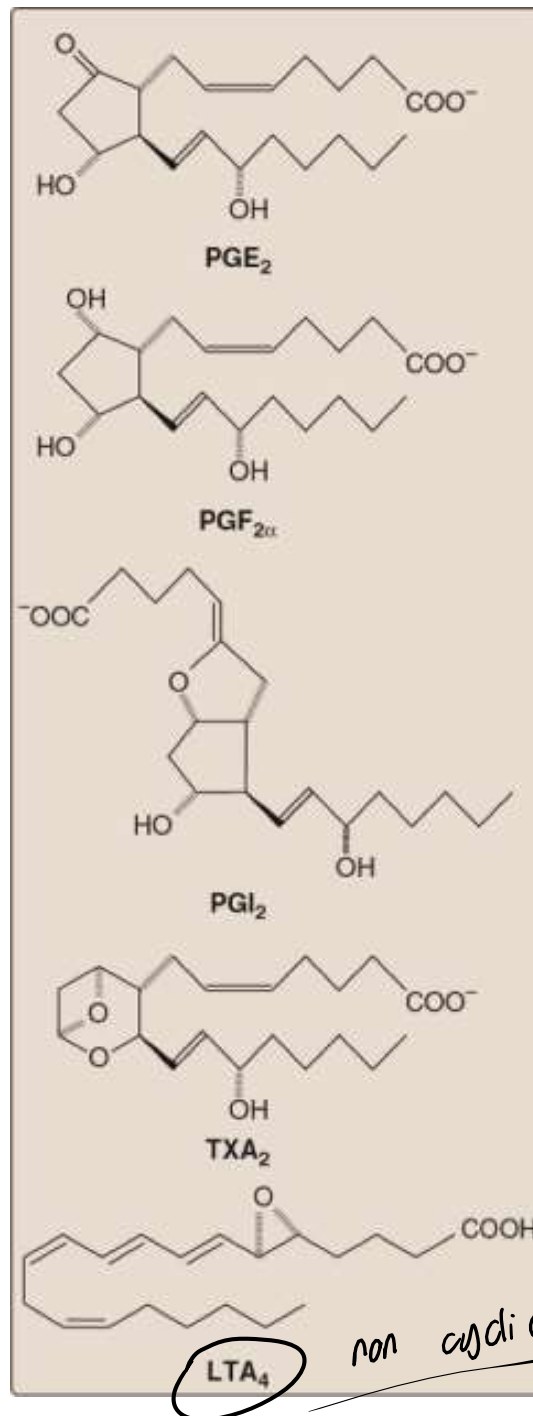
- Two isozymes of the synthase are known.
 - COX-1 is made constitutively in most tissues, and is required for maintenance of healthy gastric tissue, renal homeostasis, and platelet aggregation.

inflammation related ➤ 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.

COX-2 makes prostaglandins, which cause inflammation (pain, heat, redness, swelling) and fever.





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. (indirect)
arachidonic acid
- 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. *the goal to only inhibit it.*
- 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 functions of COX-1 (*has good functions*)

on empty stomach can causes ulcer
NSAID-RELATED ULCERS: (Due to inhibition of COX-1, prostaglandin-endoperoxide synthase).

Question 15 / 56

Aspirin inhibits:

1. ☐ Cyclooxygenase-1 (COX-1) ✓
2. ☐ Cyclooxygenase-2 (COX-2) ✓
3. ☐ Lipooxygenase enzyme ✗
4. ☐ Phospholipase A2 ✗ cortisol inhibit it
5. ☒ Two of the choices

Which is correct about prostaglandins (PG):

1. ☐ They mediate pain, redness, swelling, inflammation and fever of infection
2. ☐ They are synthesized in all cells from arachidonic acid
3. ☐ Nonselective inhibition of PG synthesis may cause gastric ulcer
4. ☐ They are required for the maintenance of platelet aggregation
5. ☒ All of the above

Next

إضافة ملاحظة

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DELL

Question 4 / 56

A person who was on a fat-free diet for several weeks may suffer severe deficiency in the ability to synthesize:

1. ☐ Triacylglycerol
2. ☐ Phospholipids
3. ☒ Cholesterol
4. ☐ Acetone
5. ☐ Prostaglandins

no fat No essential fat No linoleic acid No arachidonic acid

No prostaglandins synthesis

Next

إضافة ملاحظة

سألت عن cortisol
وجابت سؤال بعدها ايش الخطأ

NSAIDS]) inhibit both COX-1 and COX-2

Aspirin's inhibition of COX-1 only



NSAIDS]) prevent the synthesis of the parent prostaglandin, PGH₂

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.
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- 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

Leukotrienes

- Asthma -
The precise mechanism remains unknown, but it is presumed that aspirin inhibits the cyclooxygenase pathway of arachidonic acid metabolism without affecting the lipoxygenase route, thereby shifting the balance of production toward Leukotrienes that cause bronchial spasm and vasoconstriction.
Leukotrienes = vasoconstriction

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

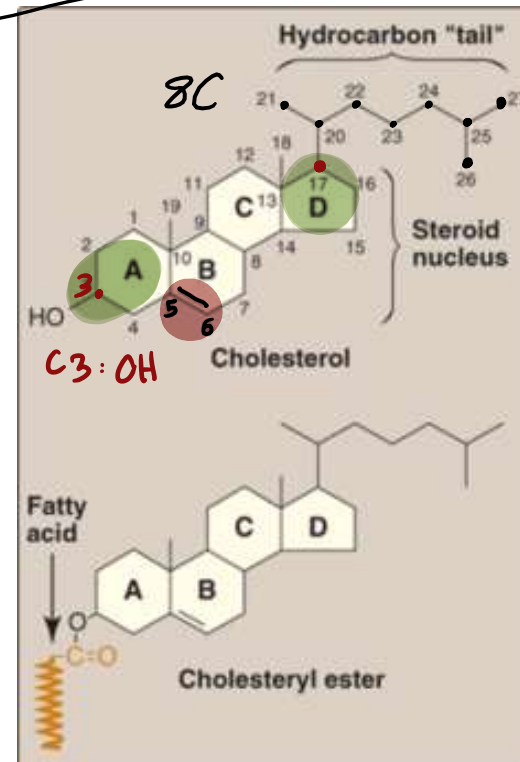
patho

- Lipoxygenases are not affected by NSAIDs. Leukotrienes are mediators of allergic response and inflammation.
- Inhibitors of 5-lipoxygenase and leukotriene receptor antagonists are used in the treatment of asthma.

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

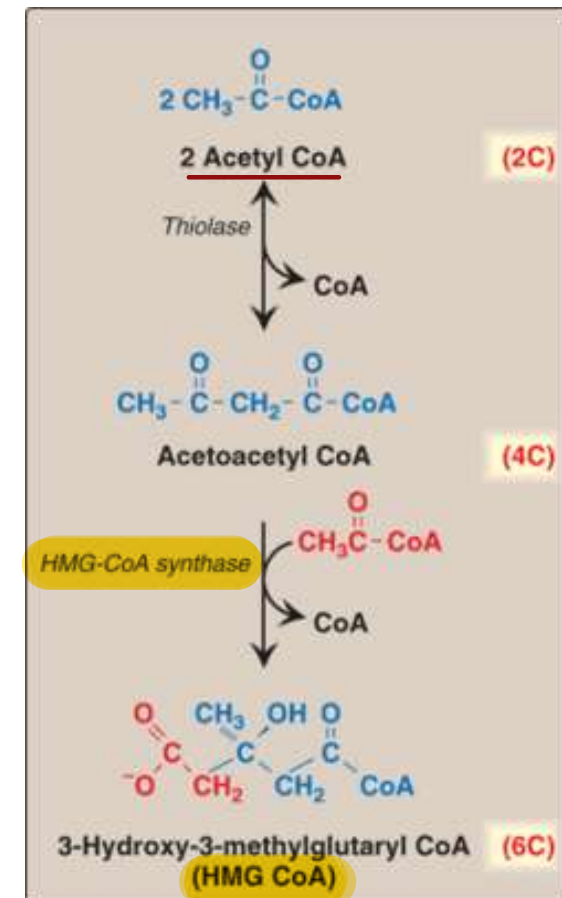
(جی اسلک)



Cholesterol synthesis

Cytoplasm

- 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



lyase enzyme *Only liver*

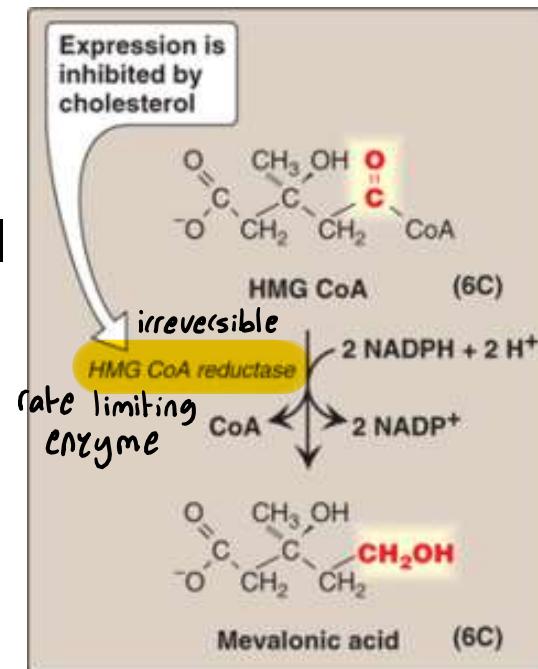
HMG-reductase
other tissues

Cholesterol synthesis

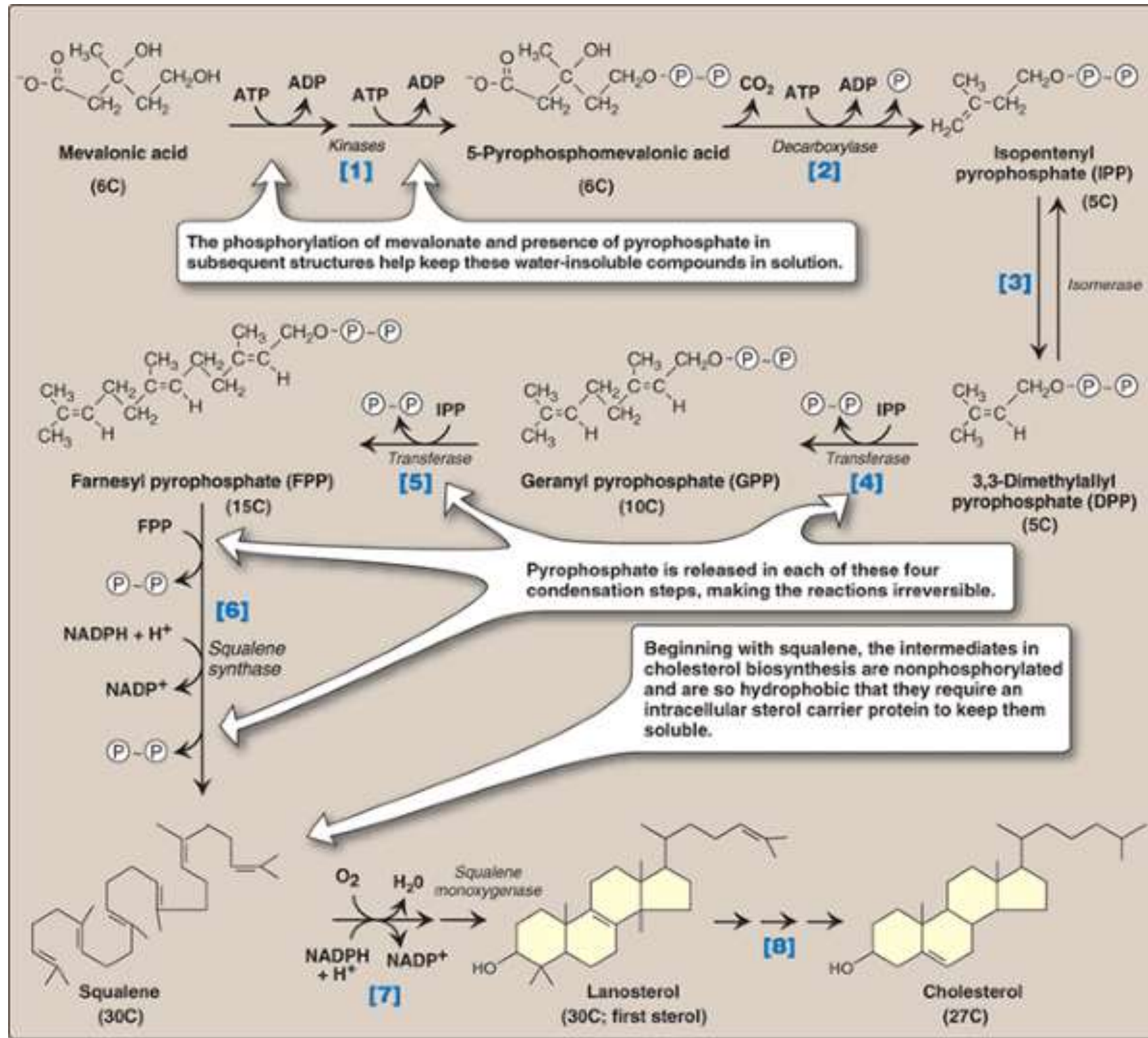
- The next step, the reduction of HMG CoA to mevalonic acid, is catalyzed by HMG CoA reductase, and is the rate-limiting and key regulated step in cholesterol synthesis. *HMG-CoA → mevalonate*

- 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



need
ATP
(fed state)
+
NADPH



Regulation of cholesterol synthesis

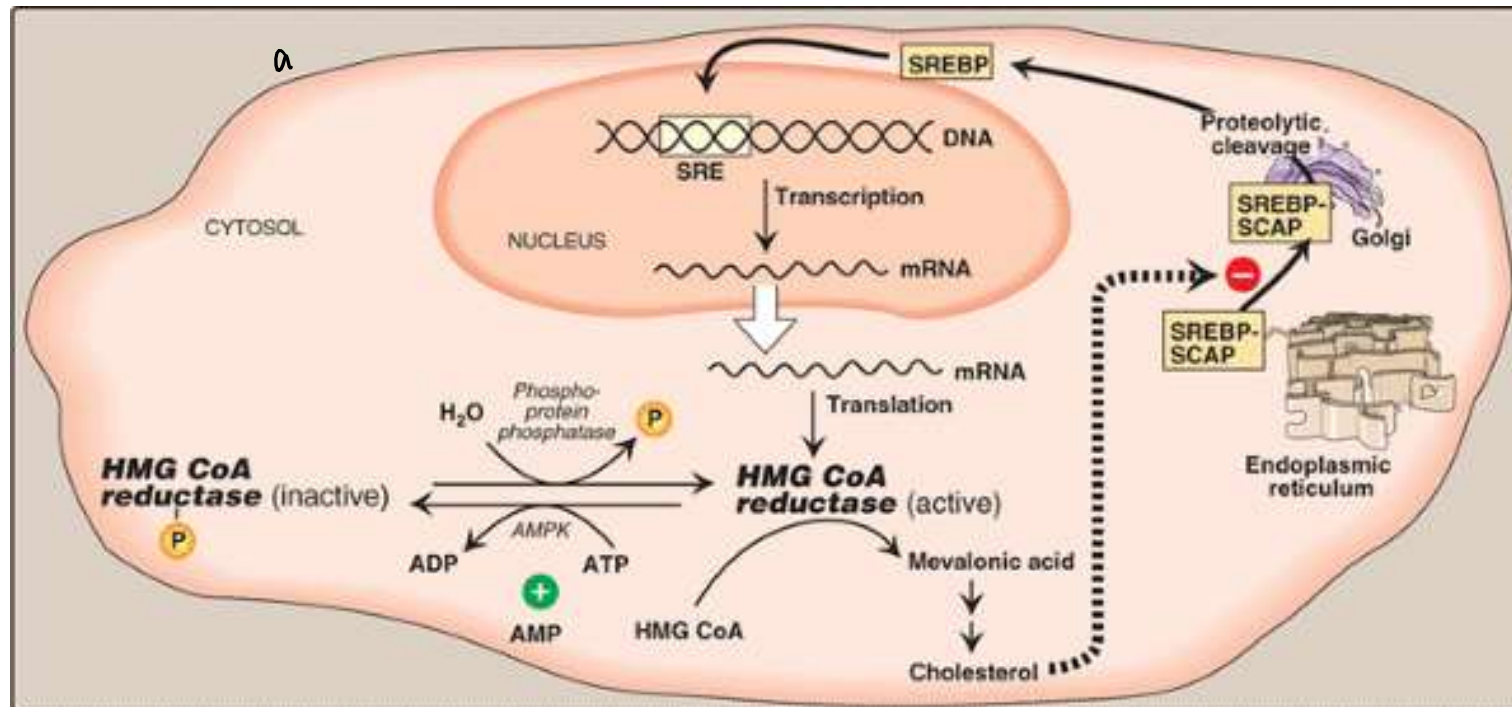
- Fed state ↗
- Activated By -insulin
- low cholesterol levels
- inhibition : ~~phosphorylation~~
+ AMPK phosphorylation (inactive)
- HMG CoA reductase, the rate-limiting enzyme, and is subject to different metabolic control.
 - **Sterol-dependent regulation of gene expression:** Expression of the HMG 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 associated with a **second ER membrane protein SCAP** (SREBP cleavage-activating protein).
 - 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.
 - **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.

ubiquitination
labeling & destruction
for proteins that
need to be degraded

Sterol level	What happens?	Effect on cholesterol synthesis
Low sterol	SREBP-SCAP moves ER → Golgi → Nucleus	↑ Cholesterol synthesis
High sterol	SREBP-SCAP retained in ER	↓ Cholesterol synthesis
High sterol	HMG-CoA reductase binds Insig → degradation	↓ Cholesterol synthesis

Regulation of cholesterol synthesis

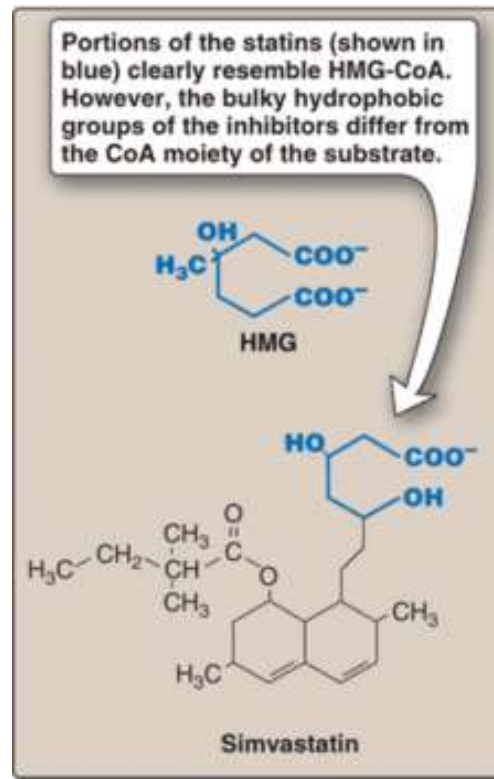
- **Sterol-independent phosphorylation/dephosphorylation:** HMG CoA reductase activity is controlled covalently through the actions of **AMP-activated protein kinase (AMPK)**, and a **phosphoprotein phosphatase**. The phosphorylated form of the enzyme is inactive, so cholesterol synthesis, is decreased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

logic



this
competitive

Which is incorrect about de novo synthesis of cholesterol:

1. ☒ HMG coA reductase enzyme is inhibited by high ATP
2. ☐ Enzymes responsible for its synthesis are present in the cytosol and the membrane of endoplasmic reticulum
3. ☒ The precursor for cholesterol synthesis is acetyl coA
4. ☐ The rate limiting step is catalyzed by HMG coA reductase enzyme that is activated by low levels of cholesterol
5. ☐ Atorvastatin inhibits cholesterol synthesis and so used to treat hypercholesterolemia

Next

إضافة ملاحظة



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.
 - coprostanol
 - cholestanol

Which does not produce CO_2 and water as end products during its metabolism:

1. ☐ Glucose $\text{CO}_2 + \text{ATP} + \text{H}_2\text{O}$
2. ☐ Fatty acids $\text{CO}_2 + \text{ATP} + \text{CO}_2$
3. ☐ Amino acids $\text{CO}_2 + \text{H}_2\text{O} + \text{urea}$
4. ☒ Bile acids x
5. ☒ Two of the choices

Next

إضافة ملاحظة

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DELL

secondary bile acids:

- deoxycholic acid (DCA)
- ursodeoxycholic acid (UDCA)

liver

down regulation

primary bile acids:
- cholic acid
- chenodeoxycholic acid

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

8-3
= 5C

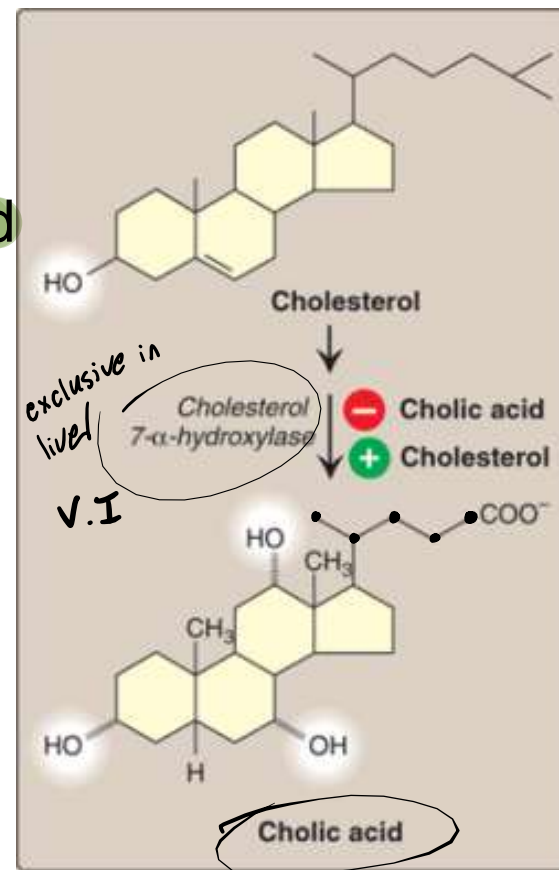
- The most common resulting compounds, **cholic acid** (a triol) and **chenodeoxycholic acid** (a diol), are called "primary" bile acids.

- 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**

✱

cholesterol $\rightarrow$ cholic acid

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



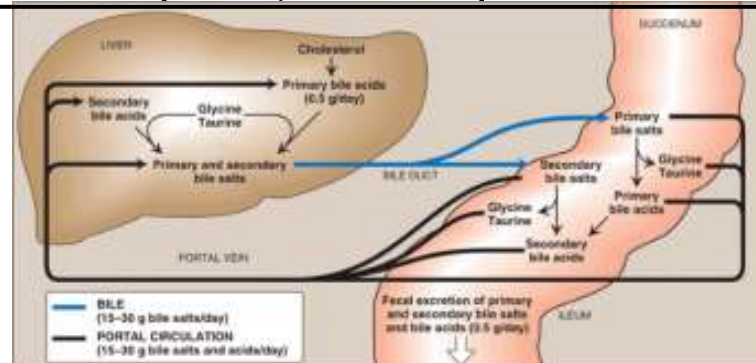
Enterohepatic circulation of bile salts

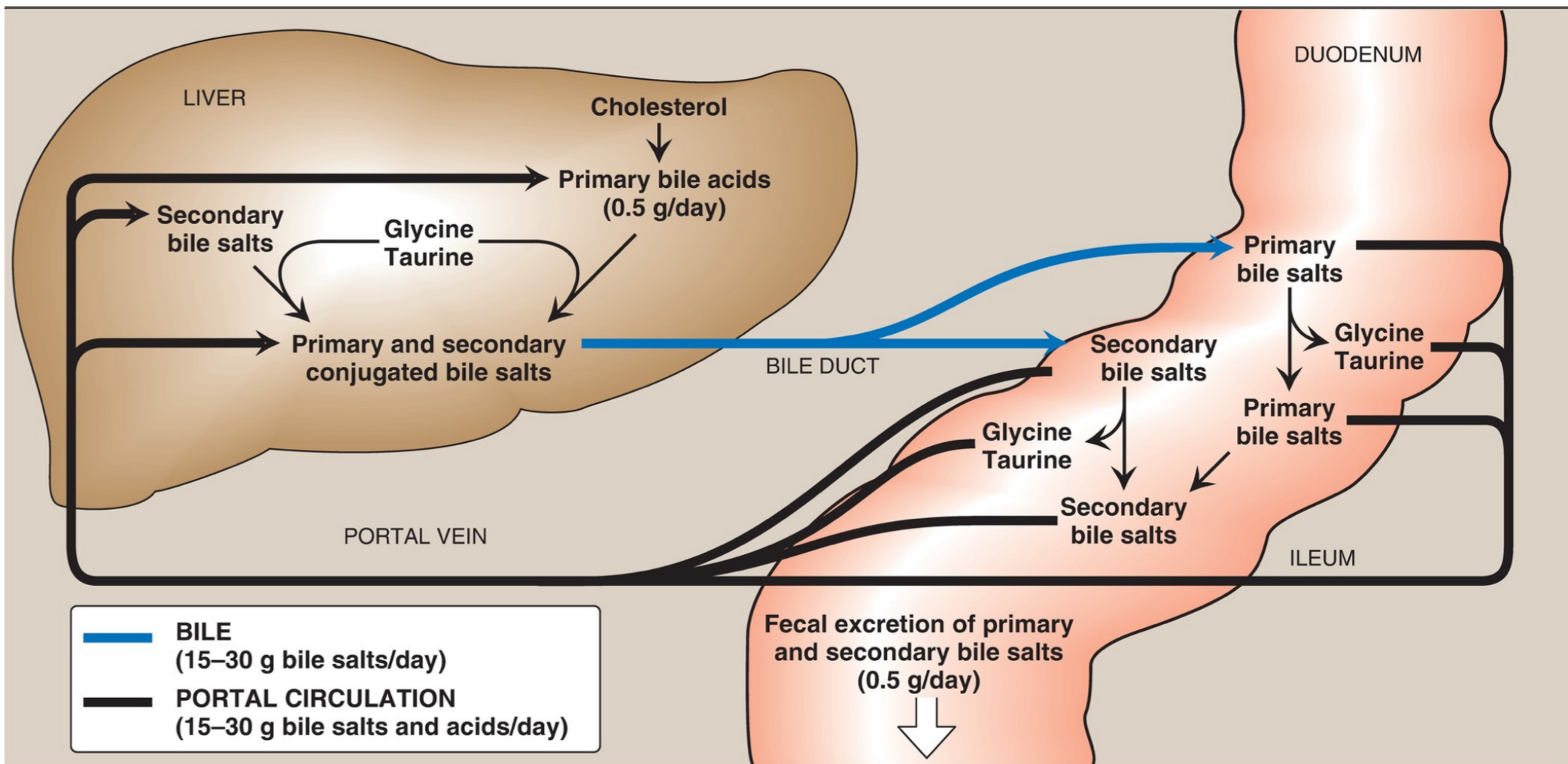
- Bile salts secreted into the intestine are efficiently reabsorbed (greater than 95%) and reused. The mixture of primary and secondary bile acids and bile salts is absorbed primarily in the ileum. They are actively transported from the intestinal mucosal cells into the portal blood, and are efficiently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

مواد عازلة

drug

- Bind bile salts
- prevent absorption
- increase excretion





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

Function & responsible for the cytochrome enzymes of oxidative phosphorylation

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

ether PL

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

➤ **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

Carbon 1 → saturated alkyl group
Carbon 2 → acetyl group

Exam point:

Cardiolipin is required for normal mitochondrial oxidative phosphorylation

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

- **dipalmitoylphosphatidylcholine (DPPC)** made and secreted by **Type II pneumocytes**, is **the major lipid component of lung surfactant**. Surfactant

a ceramide, which can also serve as a precursor of **glycolipids**

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