لجان الدفعات

BIOCHEMISTRY

MORPHINE ACADEMY

By Maryam Alhasan

Metabolism of phospholipids and cholesterol

- ذكرناهم سابقًا وشرحنا كيف عملية الmetabolism او عملية digestion الهم , بس انه كيف بكسرهم بجسمي ما حكينا

- قلنا الdigestion كيف بصير الهم ؟ لما باكل اشياء فيها phospholipids كيف بكسره ؟ بكسر pancreatic phospholipase A2بال بكسر الfatty acid التاني ، بعدين lysophospholipase بكسر الاول

Phospholipids

- Are polar, ionic compounds composed of an alcohol that is attached by a phosphodiester bridge to either diacylglycerol or sphingosine (amphipathic)

موجودين في cell membrane بكميات كتير كبيرة

- 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**.

اشبك protein مع cell membrane والinositol هو اللي بعمل anchoring

- 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**

عندهم 5 functions:

1. Component of cell membrane
2. Reservoir for intracellular massengers
3. Anchor protein to cell membrane
4. Component of lung surfactant
5. Component of bile aid in solubilization of cholesterol

حكينا لما بلشنا بالglycolysis وقلنا عندي G protein coupled receptor 2 ، mechanisms ، وحكينا عن mechanism تبع Adenylyl cyclase اذا متذكرين ، بعد هيك قلنا في mechanism تانية تاع protein kinase c منحكي عنها لما نروح على lipid metabolism (اذا ناسيين ارجعو لسلايدات glycolysis)

عندي phospholipids دايبة in solution مش انها بالmembrane شابكة وهيك ، اللي همه اول اشي في ، lung surfactant بكون , palmatic acid 2 لكن رابط عليه phosphotidylcholine وهو عبارة عن dipalmitoyl phosphotidylcholine DPPC بالlung بالalveoli, في بعض الاطفال اذا نولد قبل موعده بكون مش مكتمل عنده lung surfactant فبتكون الlung زي مقفلة ، فشو بعملوا؟ بعطو الام corticosteroid خلال يومين تلات بكون اكتمل عنده lung surfactant

عندي phospholipids بتنفرز بالbile عشان تعمل solubilization of cholesterol , شو مكونات bile ؟ bile salt , cholesterol, phospholipids, bilirubin, في كتير ادوية كمان ممكن يصيرلها secretion عن طريق الbile

عنا phosphoglycerides وعنا sphingosines , الbackbone تبعها الاشي الاساسي الي بركب عليه الfatty acids مختلف

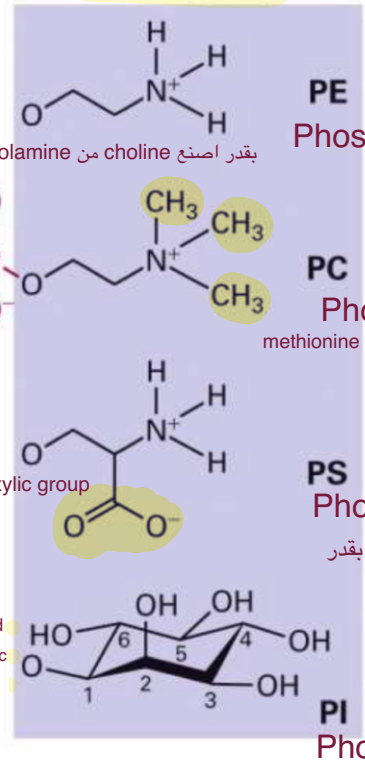
Phospholipids

(a) Phosphoglycerides

amphipathic
hydrophilic head
hydrophobic tails

Hydrophobic tail

Head group



بقدر اصنع choline من ethanolamine

من وين بجيب CH3, مين methyl doner ؟ methionine

Carboxylic group

اذا عملته decarboxylation بقدر احوله لethanolamine

6 membered
Aliphatic not aromatic
عليها OH , وفي O رابطة مع phosphate group

PE, PC → Neutral

PS, PE → net charge Negative

Phospholipids

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

هدول منحكيلهم phosphatidal مش tidyl

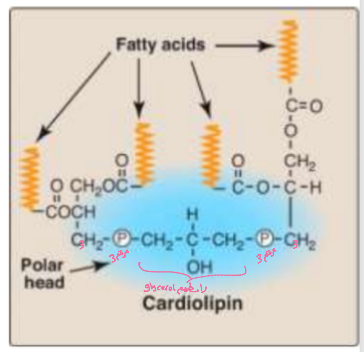
2. **Plasmalogens:** when an unsaturated alkyl group attached by an ether linkage to the core glycerol molecule, a plasmalogen is produced. phosphatidalethanolamine (abundant in nerve tissue, phosphatidalcholine (abundant in heart muscle) is the other quantitatively significant ether lipid in mammals.

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

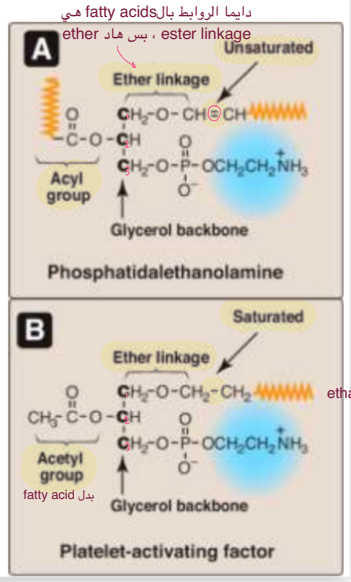
↑ aggregation
↑ inflammation
macrophages & shit

- 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

يزيد Thromboss



دايما الروابط بالfatty acids هي



عنا بعض الphospholipids الخاصين بأماكن معينة والهم functions معينة

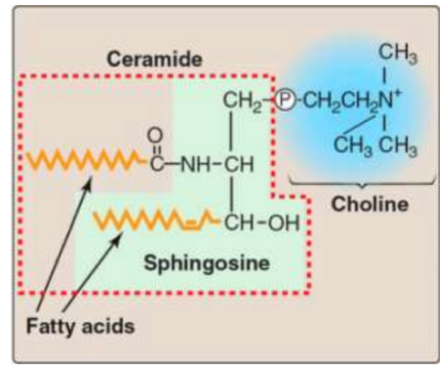
الcardiolipin حكينا مرة عن الfatty acids انه دخل وطلع وبده carnitine عشان يدخله ... قلنا وقتها عن inner membrane تاع الmitochondria انه ما بفوت اشي اصعب تى من blood brain barrier ، فشو السب ؟ مش phospholipid عادية ، عنده بالاضافة هديك الphospholipid عنده cardiolipin ، مكنها exclusive to the inner membrane of mitochondria ، الهدف منها والفكرة انه عندي بالinner membrane cytochromes للrespiration للخلية منوخدهم بآخر تشابتر فبمسكهم لcardiolipin

Sphingophospholipids sphingomyelin

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

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



ال backbone تبع sphingomyelin هو sphingosine
فال backbone اختلف مش glycerol

التركيبة تبعه :
عنا اول شي ال sphinganine بعدين بس
اركب عليه ال fatty acid ال backbone
تاعه ببدا ب serine وبصيرله
decarboxylation فالرابطة بتكون
covalent bond اول fatty acid,
تاني fatty acid برتبط عال Nitrogen
فبصير amide واسمه ceramide ،
واخر اشي لما اركب عليه
ال phosphotidylcholine بصير اسمه
sphingomyelin

موجود ب neurons

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. or ether linkage
  - Addition of hydrophilic head group through phosphodiester linkage.
  - Alteration or exchange of head group to yield final phospholipids.

مثلا بقدر اغير من ethanolamine ل choline

ما في proteins بالموضوع

وين تتم العملية؟

- 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

بما انه لازم يصيرلها secretion عسطح الخلية معناته golgi should be involved

- All cells except mature RBC can synthesize phospholipid

كل الخلايا الجسم بقدروايصنعو phospholipids ما عدا mature RBCs , عنا ال precursors لل RBC بقدر يصنع ال phospholipids ،
لكن بس يصيرلها maturation وتخسر nucleus وتخسر mitochondria وتخسر كل الاجزاء المهمة اللي فيها فبتكون ما عندها قدرة تغير
اشي بال phospholipids تاعتها او تصنع

للتذكير ، كيف بصير activation !

Glucose → UDP

Proteins, aa → Transfer RNA

Fatty acids → CoA

Phospholipids → CDP

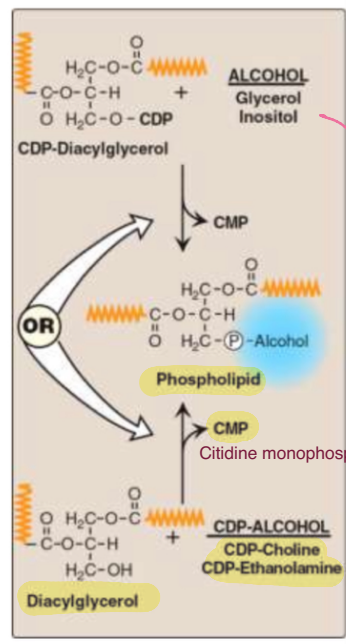
بقدر اصنعهم او اعيد تدويرهم اعيد استخدامهم

Synthesis of PE and PC

Choline Ethanolamine

ال synthesis الهم بتعتمد
عشو نوع ال base الموجود عنا

- 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.



في حالات inositol وglycerol

بتكون diacylglycerol وهو اللي
بربط مع CDP
وبعدين بركب inositol او glycerol

  - **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

حتى لو قد ما اصنع ما بقدر اكفي الجسم من ال phospholipids
فلازم اعيد تدوير اللي already كان موجود عنا

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

choline and ethanolamine اول شي
should be activated ب CDP
Citidine diphosphate

بقدر اصنعه

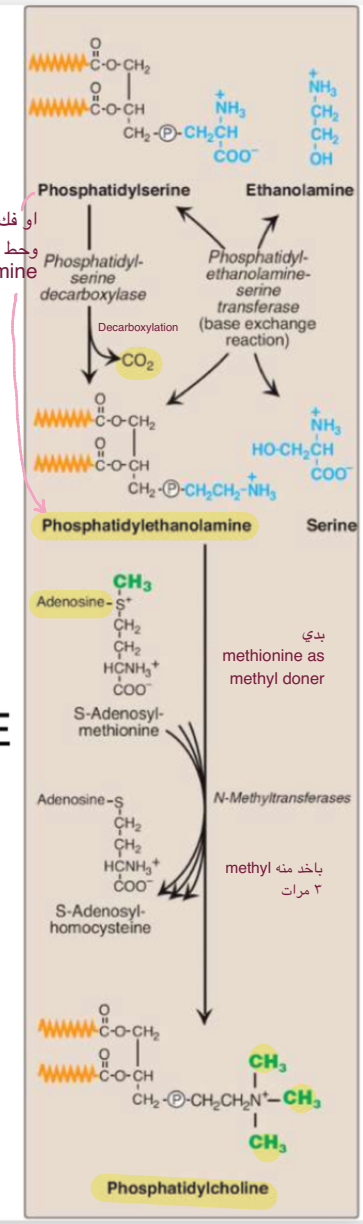
بفك ويحط
diplomatic acids

- 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.

بسرع تصنيع DPPC

ال serine بقدر اصنعه من glycine و hydroxymethyl transferase enzyme

Synthesis of PE, PC and PS



او فك serine
وحط بداله
ethanolamine

بدي
methionine as
methyl doner

باخد منه methyl
٣ مرات

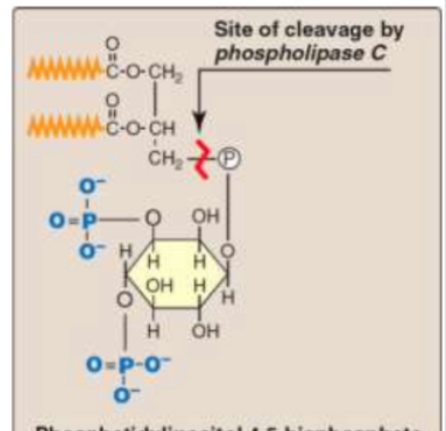
- **Synthesis of PC from PS in the liver**: To provide the needed PC (secreted in bile), PS is decarboxylated to PE by PS decarboxylase, an enzyme requiring pyridoxal phosphate as a cofactor. PE then undergoes three methylation steps to produce PC

- 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

هون الdiacylglycerol هي اللي بصيرلها activation وبحولها لCDP diacylglycerol ،
وبعدين بضيف عليها يا اما glycerol يا inositol حسب الاشي اللي بدي اصنعه

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.

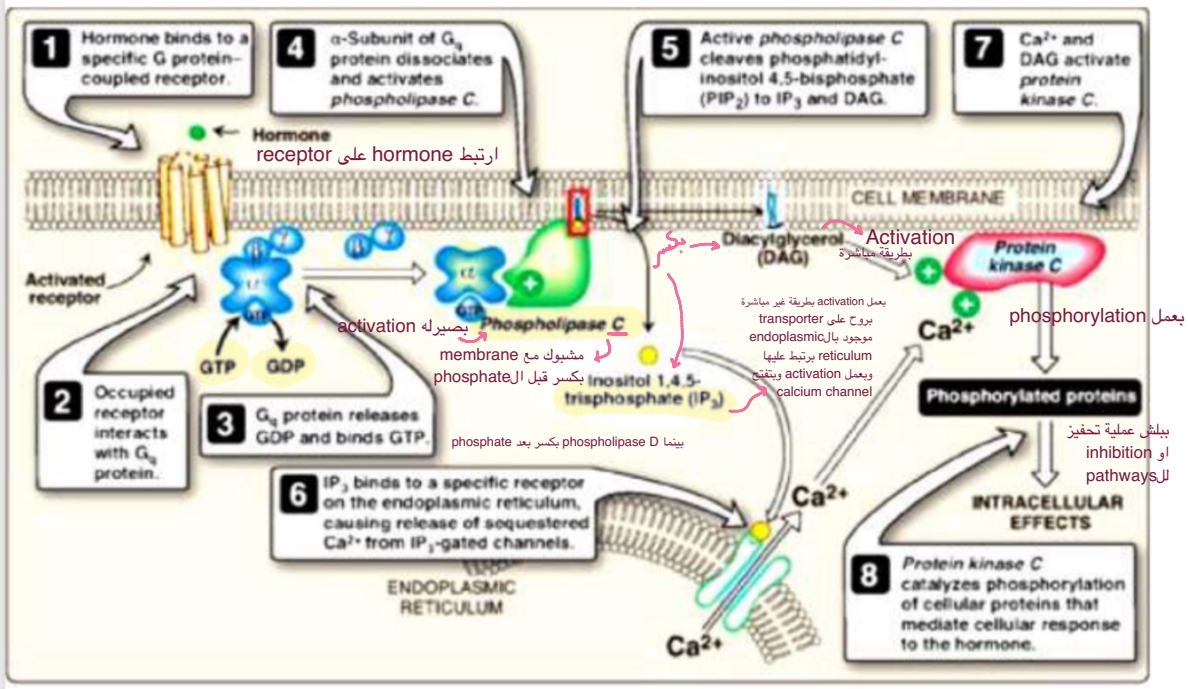


اله خصوصية لحاله لانه اله شغلتين
اول اشي انه هو مسؤول عن signaling وهو عبارة عن second messenger اللي هو inositol triphosphate منحكي عنه كمان شوي
والشغلة التانية انه هو reservoir للarachidonic acid اللي بصنع منه prostaglandins لما بدي احمي stomach وkidney ، ولما يصير عنا inflammation بأي شكل عطول الarachidonic بنفرز ، وكمان autoimmune diseases هي ضمن الاشياء اللي بتحفز arachidonic acid release من الphosphotidyl inositol

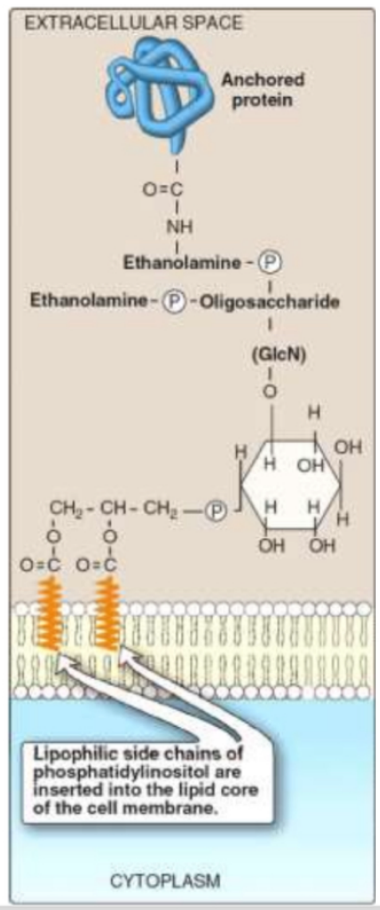
الphosphotidylinositol هو عبارة عن 3 carbons
على C1 عنا stearic acid
على C2 عنا arachidonic acid (الphospholipase A2 بكسر عرقم 2 ، يعني لما بدي اوقف عملية التكسير تبعه بوقف A2)
على C3 عنا phosphate

Role of PI

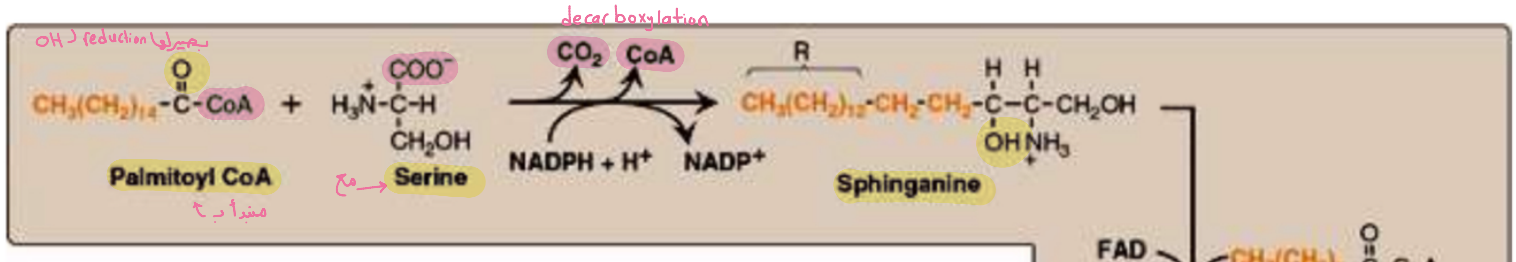
- PI in signal transmission across membranes



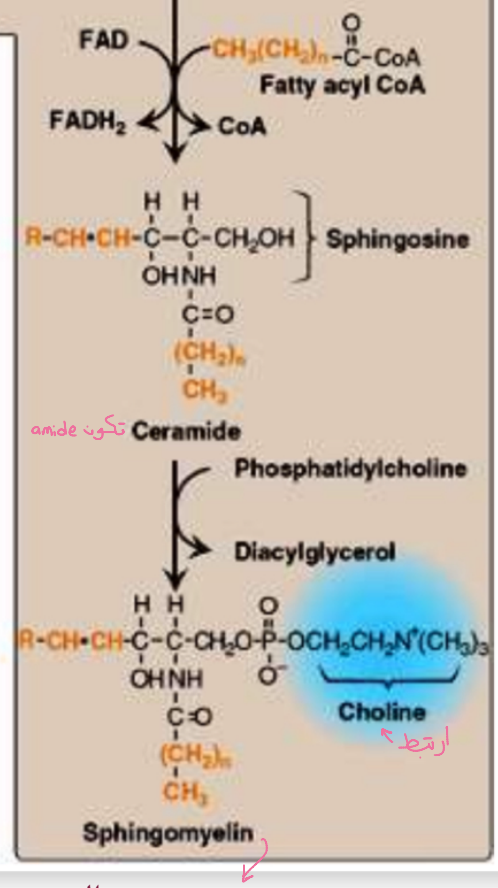
- PI in membrane protein anchoring



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



بكسر

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

ممكن افك fatty acid واركب بدالهم palmitic acid عشان اصنع lung surfactant

- 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

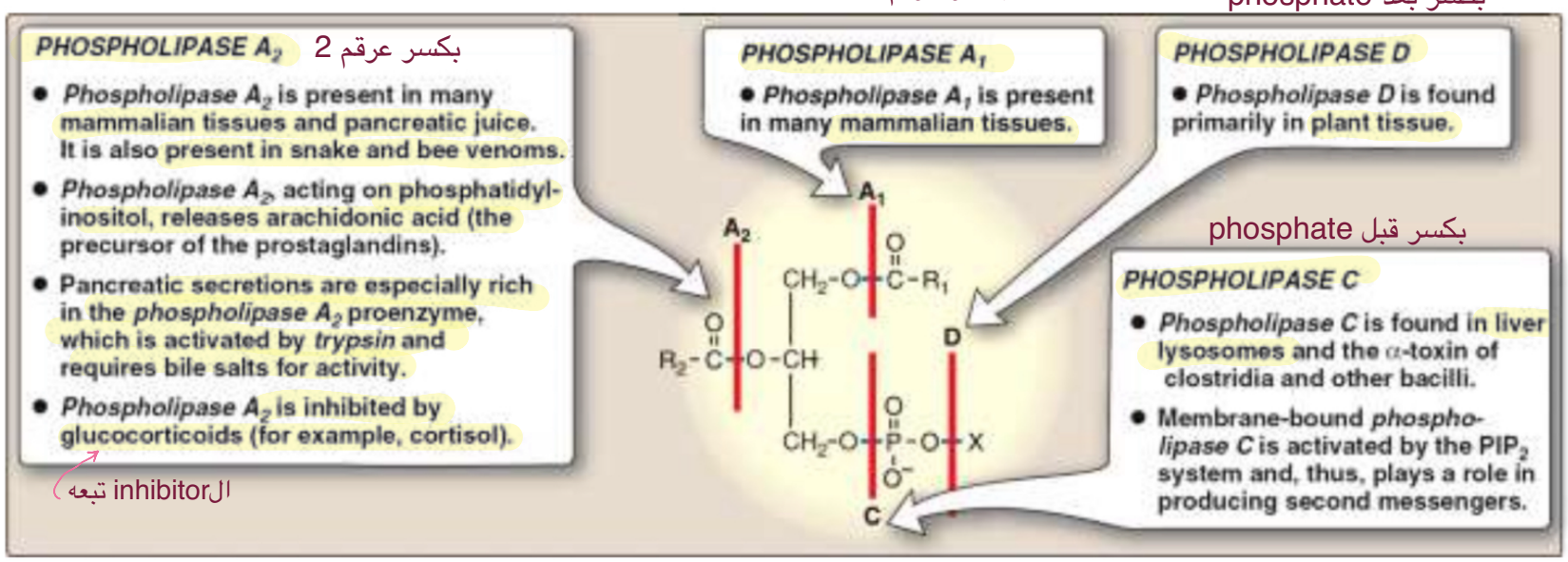
ليش الواحد بموت من سم الحية ؟ عنده بالvenom تبعه phospholipase A2 بشتغل نفسه شغله ، بكسر الarachidonic acid اللي بصنع منه prostaglandin فبحفز الinflammation بالجسم كله ، ممكن واحد يعمل عنده anaphylactic shock ينزل عنده الضغط كله ويموت

وحتى ببلش يكسر بالphospholipids بالخلايا

Degradation of phosphoglycerides

بكسر عرقم 1

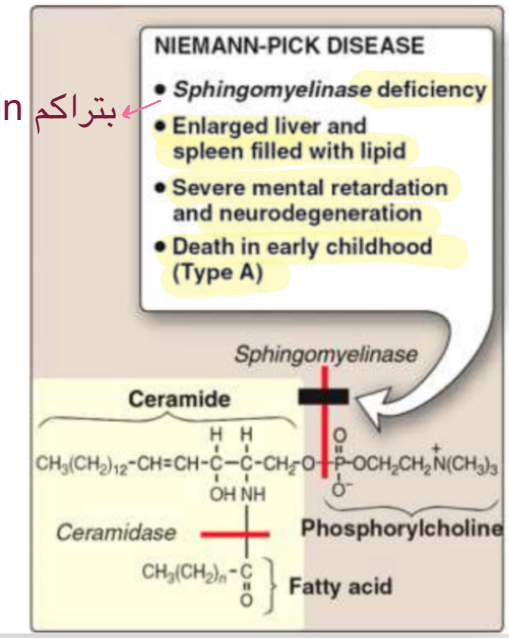
بكسر بعد phosphate



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

sphingomyelin بتراكم



Prostaglandin synthesis

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).

Prostaglandin H synthase enzyme

- 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

Hydrogen Peroxide → H_2O_2

- PGH_2 is converted to a variety of prostaglandins and thromboxanes, by cell-specific synthases.

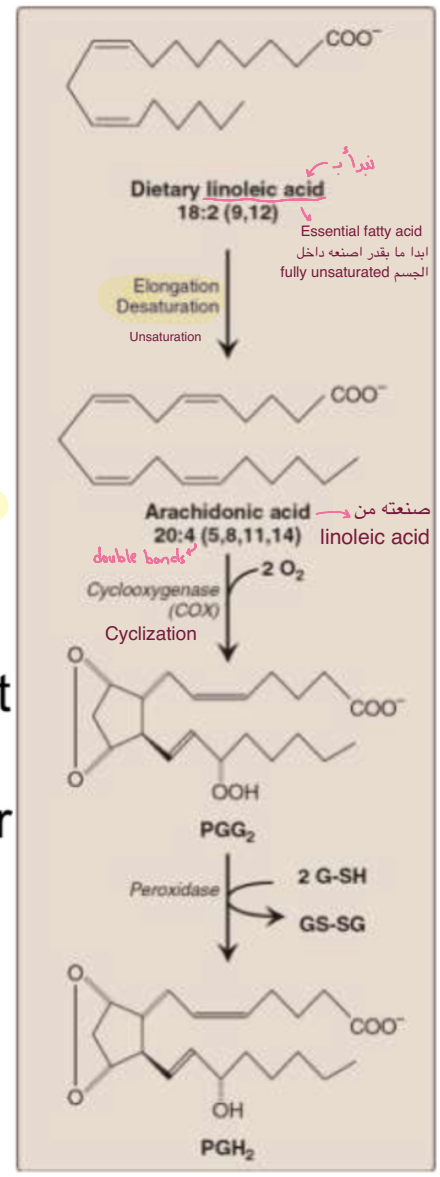
Isozymes of PGH synthase

- Two isozymes of the synthase are known.
- بدي ياه منيح ➢ 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.

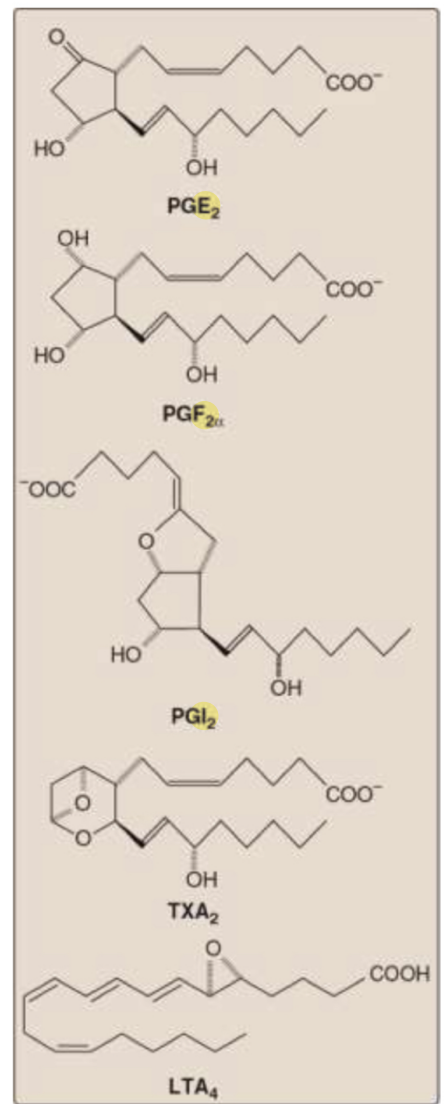
منيح بحالات الinflammation

بدي ياه بس وقت الحاجة يعني لما يكون في مثلا infection

- 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.



كمان other prostaglandins بتتصنع منه



- الNSAIDs بعمل inhibition لCOX-1 و COX-2
فالمشكلة انهم التنين inhibited , فالinflammation استفدت ، بس هداك صار خطر عالstomach والكلى

- فعملوها COX-2 specific inhibitor , يكون عندي COX-2 inhibitors بس
فعندي celecoxib و Etoricoxib هدول بشتغلوا بس على COX-2
ممكن يعمل side effect يأثر عالقلب

- احنا عنا لما منعطي NSAIDs لواحد بعمل inhibition للcycloxygenase وبراكم الarachidonic acid لواحد معه asthma ، معرض جدا يصير عنده asthma اكتر ، معناها NSAIDs هي contraindicated لمرضى asthma ،
والmechanism بروح arachidonic acid لleukotrienes synthesis وبزيد عندهم وبعملهم inflammation وتحسس اكتر

مفرود ما فيه cycle

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 A_2 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, PGH_2.

- 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

Leukotrienes

المسؤول عن عملية تصنيعه برضو من arachidonic acid هو الlipoxygenase enzyme

- 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.

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

الناس اللي عندها حساسية او asthma

كيف بعالجه؟

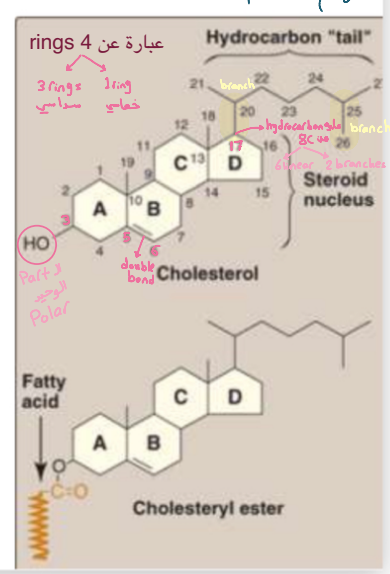
بعمل block للreceptors اللي برتبطو عليهم

- 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

مهم حفظ



مثلا adrenal gland بدها تصنع aldosterone واللي بصنعه من cholesterol

ال bile من cholesterol بال liver

ال cortisol وال sex hormones ومعناته ovary و testes كلهم بصنعو cholesterol

الكل بقدر يصنعه بس عنا tissues maily بتصنعه

Cholesterol synthesis

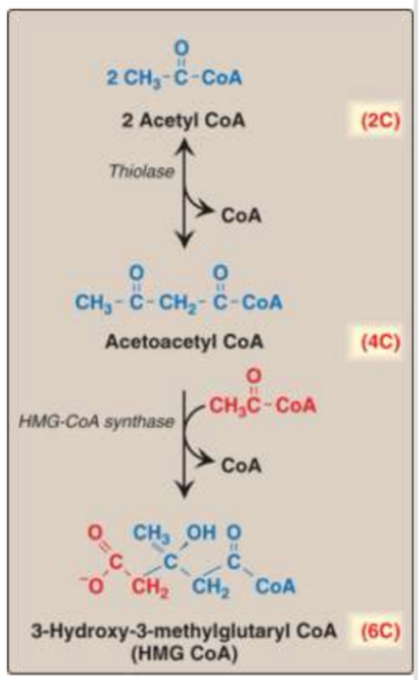
- Cholesterol is synthesized by all tissues in humans, although liver, intestine, adrenal cortex, and reproductive tissues, including ovaries, testes, and placenta, make the largest contributions to the body's cholesterol pool.

Mainly

عملية التصنيع في مش mitochondria

- 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

بداياته نفس تصنيع ketone bodies



ال lyase enzyme بس بال liver
ال reductase بال other tissues كمان

Cholesterol synthesis

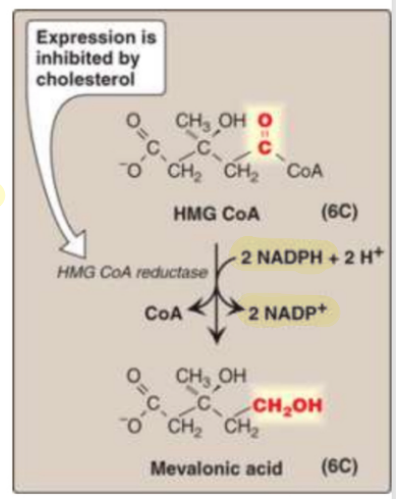
- The next step, the reduction of HMG CoA to mevalonic acid, is catalyzed by HMG CoA reductase, and is the rate-limiting and key regulated step in cholesterol synthesis.

- It occurs in the cytosol, uses two molecules of NADPH as the reducing agent, and releases CoA, making the reaction irreversible

Rate limiting step
Regulating step

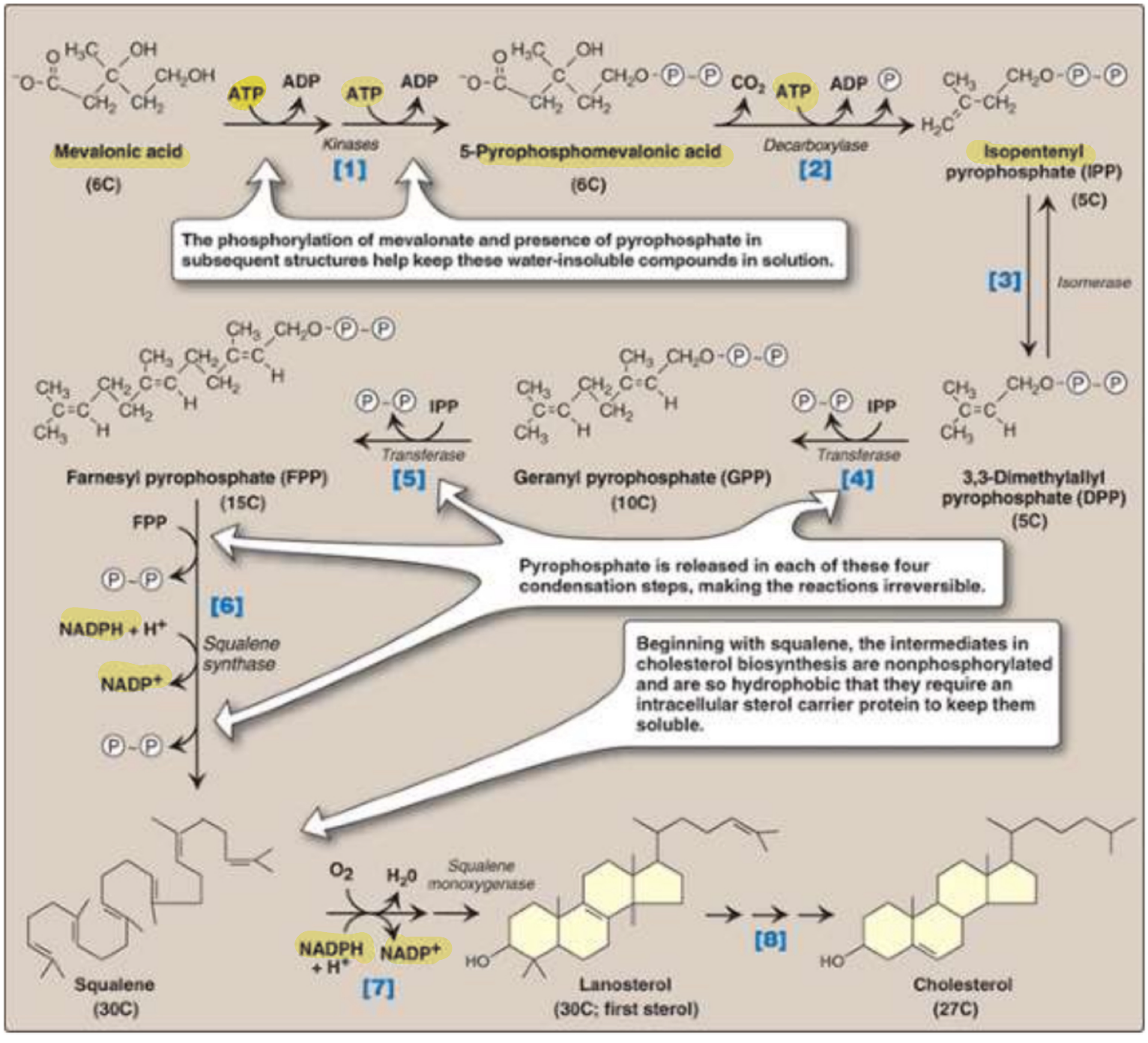
Key enzyme and rate limiting

- HMG CoA reductase is an intrinsic membrane protein of the endoplasmic reticulum (ER), with the enzyme's catalytic domain projecting into the cytosol



بحتاج NADH 2
وبحتاج ATP فلازم اكون ماكلة

الدكتورة حكت مش مطلوب كلشي
مطلوب نعرف اني بحاجة كمية ATP و NADH ، وانه اخر اشي بعمل Cyclization لأصنع cholesterol



Regulation of cholesterol synthesis

- 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 associates 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.

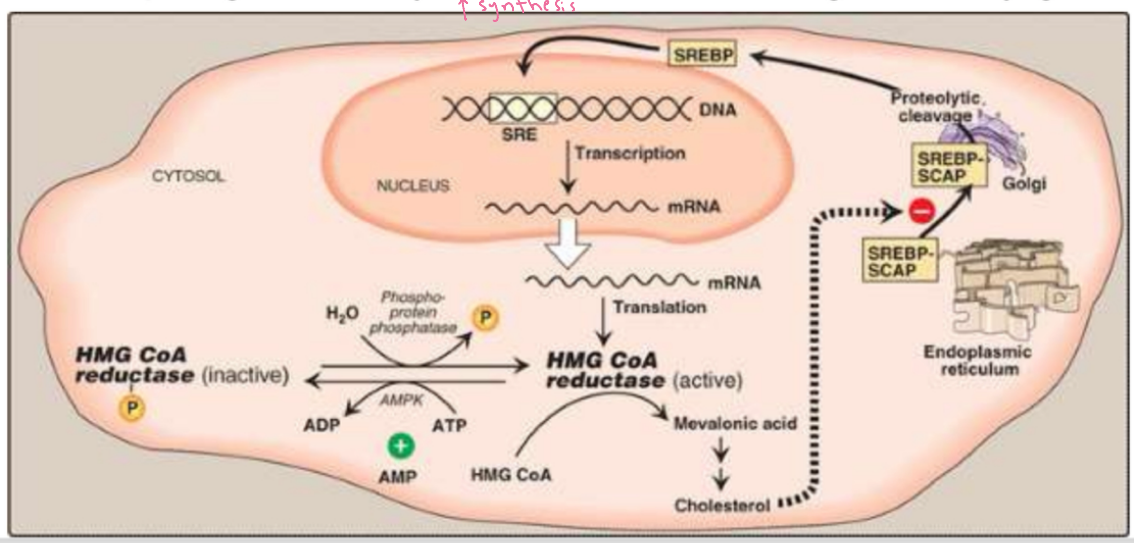
- ER فيه SREBP و SCAP
- و همه عبارة عن 2 proteins رابطين مع بعض , طالما cholesterol عندي كميته كبيرة ، لما يبلش ينقص بنسحب الinhibition وبصير SREBP وSCAP بنفصلوا عن ER وبروحو golgi
- الgolgi عنده proteolytic enzyme بكسرهم عن بعض وبطلعلي SREBP وبروح للDNA تبع HMG CoA reductase enzyme وبحفزه ، فبصنعلي messenger mRNA وبطلع ببلش عملية تصنيع HMG CoA reductase enzyme وببلش الpathway
- عملية phosphorylation وdephosphorylation , من خلال insulin and glucagon , الcholesterol متى منصنعه ؟ لما يكون عندي insulin
- الinsulin بعمل dephosphorylation بحفز proteins phosphatase enzyme و (dephosphorylated معناها active)
- بينما اذا كان عندي glucagon, بحوله لphosphorylated يعني inactive form

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.

↑ synthesis ↓ Synthesis



اذا بدي اشتغل عال as inhibitors بدي اشتغل عال key enzyme اللي هو HMG CoA reductase

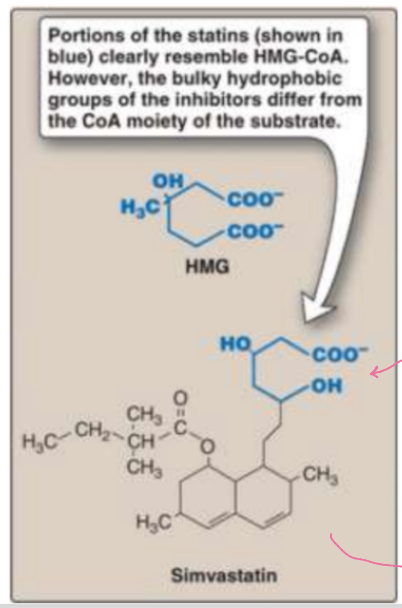
Drug Inhibitors of cholesterol synthesis

بستعملهم للناس اللي عندهم cholesterol عالي بالدم

- 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

ال statins بتشتغل عال cholesterol
فبصير , synthesis ال inhibition لل HMG CoA reductase enzyme و,عملية
ال inhibition هي reversible و competitive
هلا competitive يعني برتبط على نفس المكان اللي برتبط عليه ال substrate تبعه، مين ال substrate ؟ HMG CoA



Statins

هاد الجزء الازرق متشابه الهم

اللي ختلف الجزء اللي تحت

التغيير بال structure اللي تحت منعمله to improve physicochemical properties للمركب ، يعني بالاخر ال solubility اله ، بهمني بوصل بصيرله absorption ولا لا ، دخل جوا او لا

فالاشياء اللي بدها تتصنع بتصير توخد cholesterol من الدم وبنخفض ال cholesterol

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.

حكينا من قبل عنا phospholipids بتنفرز بالbile عشان تدوب cholesterol

فعليا هو يا اما بحوله لbile وبفرز الbile للintestine وجزء منه بروح لfeces , وحتى كميات الcholesterol اللي هناك ممكن تتأكسد في جزء منها بالبكتيريا الموجودة بالileum وبصيرلهم excretion بالfeces , large intestine

Feces ← روح ٪5 Bile فقط

Synthesis of Bile acids

منصنعه من cholesterol

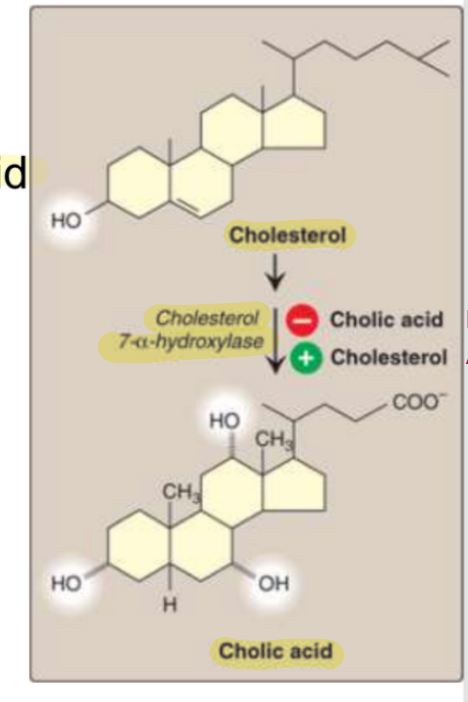
تبعه enzymeال exclusively in liver

- 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



Inhibition
Activation

Primary bile acids:
- Chenodeoxycholic
- Cholic acid

Secondary bile acids :
- Deoxycholic acid
- Ursodeoxycholic acid

- عملية تصنيع الprimary بالliver , بعدين منوديهم عالgallbladder بخزنهم هناك ومنضل نركز فيهم ، مجرد ما اكلنا بصيرلهم secretion للintestines

- بالintestine بصير عنا الmixed micelle وبصيرله penetration بروح للenterocyte للintestine وهناك بجمعه وبعمل chylomicron وبوديه

- فالbile جزء منه تم امتصاصه مع mixed micelle ، اي كمية زيادة عنا بآخر الilium عنا carriers للbile هدول برجعولي الباقي للدم ، وقلنا ما عنا غير 5% يعني 95% بصيرله reabsorption ، في جزء منهم بتحولهم بكتيريا من primary لsecondary ، ويرجع يصيرله reabsorption وuptake by liver وبعملهم release to gallbladder وبتضلها الcycle شغالة ، كل مرة بفقد بس 5% بصنع بدالهم من cholesterol

- الcolestipol و cholestyramine ، هدول عبارة عن polymers ، الfibers ، ممكن يكون من ضمن الfibers اشي nitrogenous ، هاي الاشياء اللي بكون فيها +NH3 شو بتعمل ؟
طبعا هدول من ضمن الاشياء اللي منسميهم bile acids sequestrants , يعني زي المغاناطيس بتسمكهم
- فاللي بصير انه بربط الbile ، في carboxylic group فبتربط بالamino group وبطلع بالfeces يعني صار الbile اللي بطلع اكتر من 5%
بدي اصنع بداله بجيب cholesterol المرتفع بالدم بصنع منه

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.