Metabolism

فريق طوفان الأقصى

Modified N: 9

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Metabolism of lipids V:

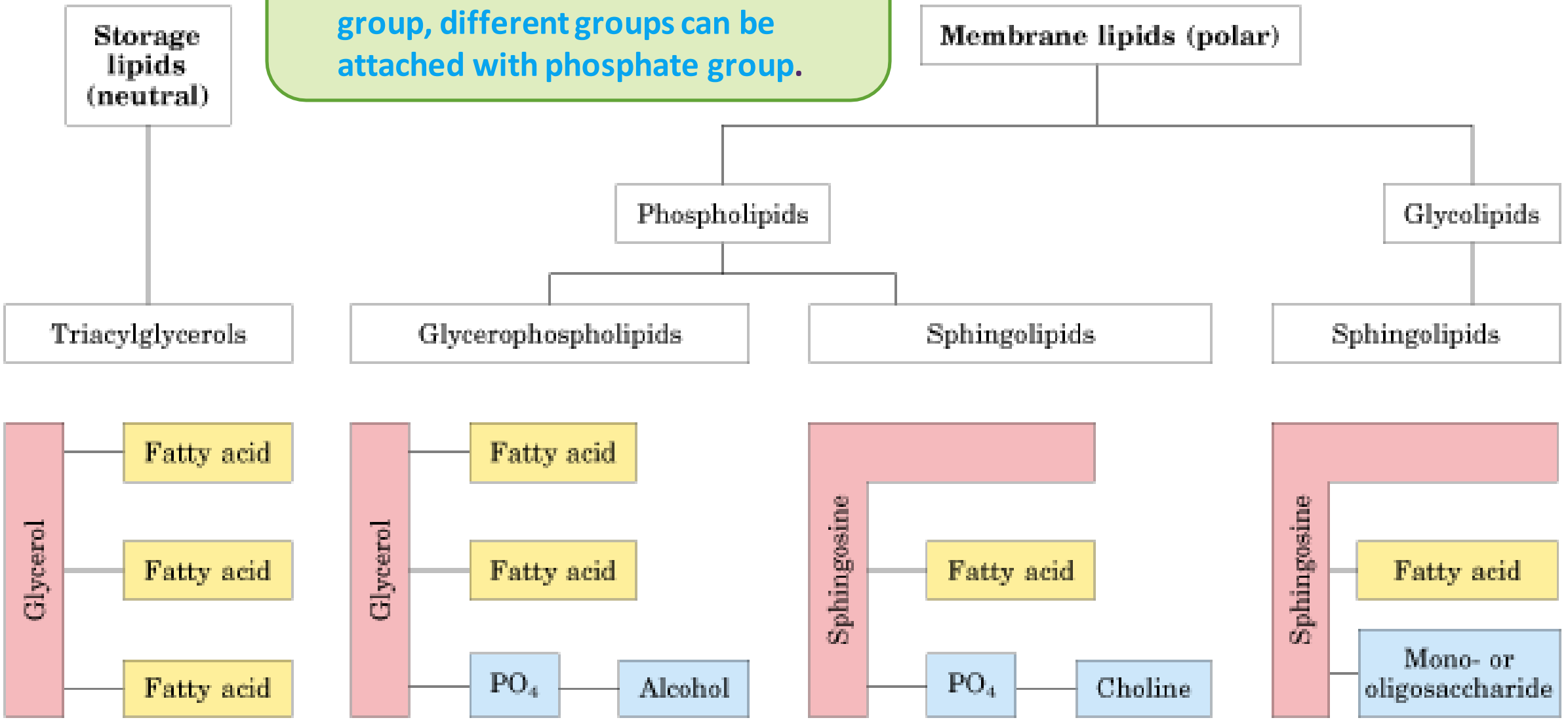
Glycerophospholipids

Prof. Mamoun Ahram

Resources

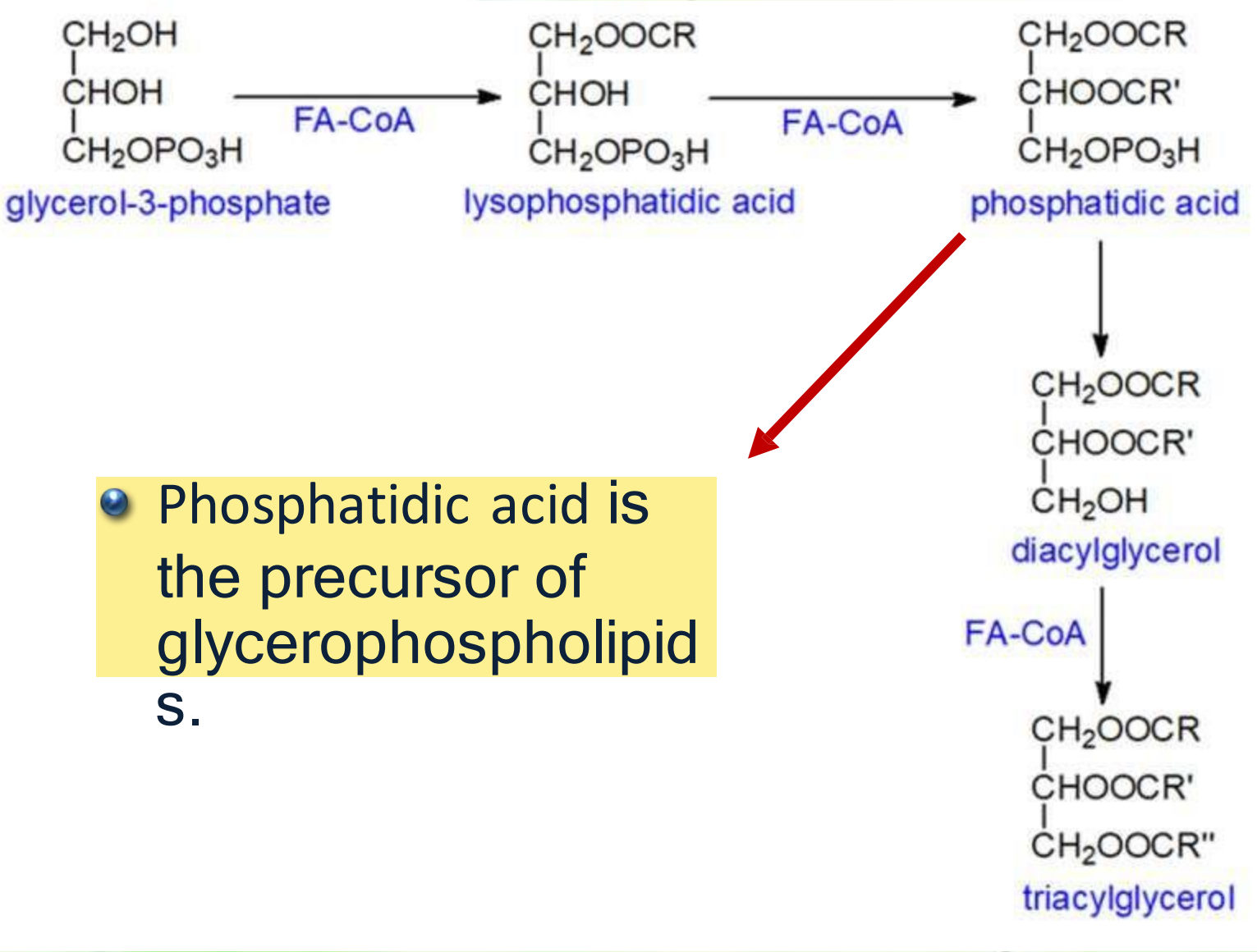
- This lecture
- Lippincott's Biochemistry, Ch. 17

NOTE: The backbone of glycerophospholipids is glycerol that has 2 FAs and phosphate group, different groups can be attached with phosphate group.



Phosphatidic acid

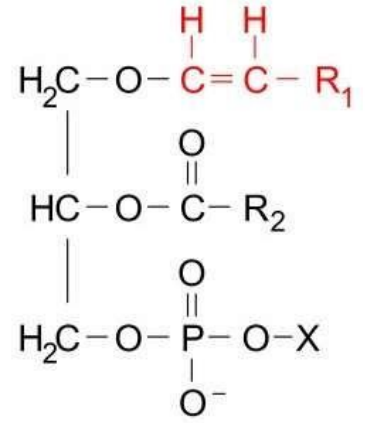
- **NOTE:** We studied that pathway in the previous lecture. Just note that phosphatidic acid is the precursor for glycerophospholipids

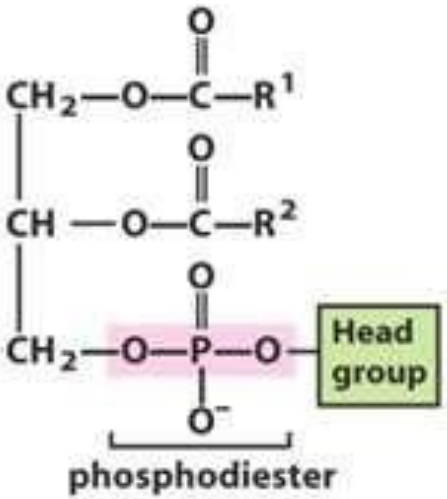


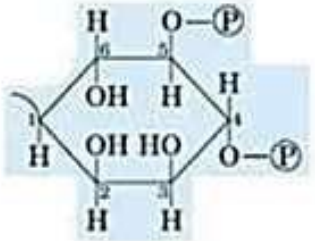
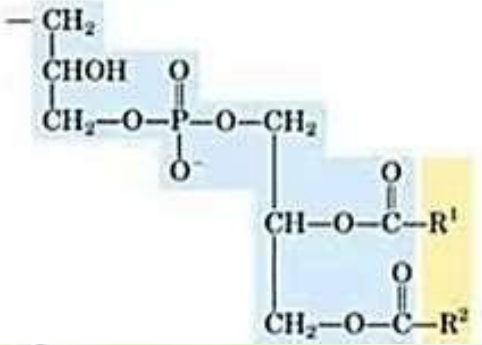
- Phosphatidic acid is the precursor of glycerophospholipids.

Classification of Glycerophospholipids

- Phosphatidic acids
- Phosphatidylcholine (lecithin)
- Phosphatidylethanolamine
- Phosphatidylserine
- Phosphatidylinositol
- Cardiolipin
- Plasmalogens



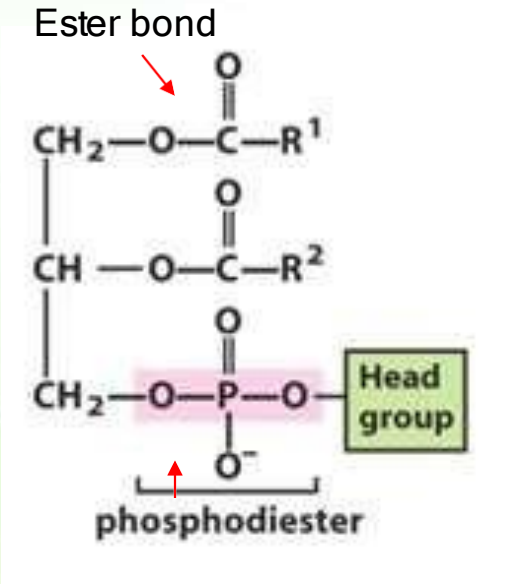


Phosphatidic acid	—	—H
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	$-CH_2-\underset{COO^-}{CH}-\overset{+}{N}H_3$
Phosphatidylglycerol	Glycerol	$-CH_2-\underset{OH}{CH}-CH_2-OH$
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate	
Cardiolipin	Phosphatidyl-glycerol	

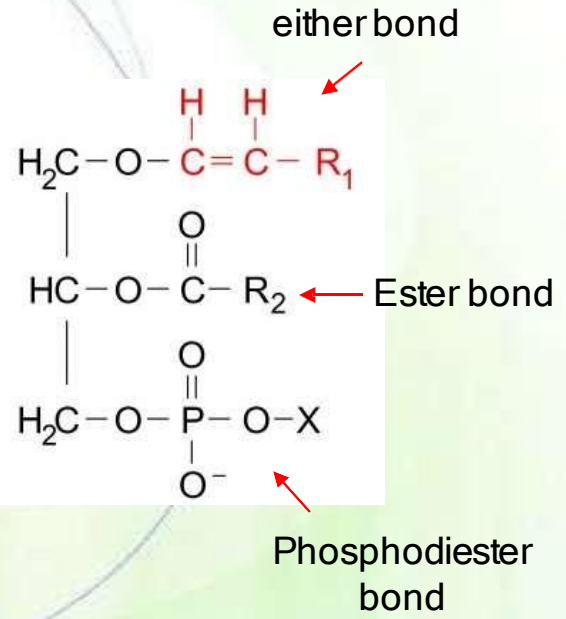
- **The complement in this slide:**

- Phosphatidic acids: the basic glycerophospholipid, the precursor to all glycerophospholipids
- After getting phosphatidic acid, we add a head group to the phosphate group to make a different glycerophospholipids. (EX: when we add ethanolamine, it become phosphatidylethanolamine). ((memorize them from the previous slide))

- All of them (except Plasmalogens) have the 2 fatty acid linked by ester bond and the phosphate group linked by phosphodiester bond.



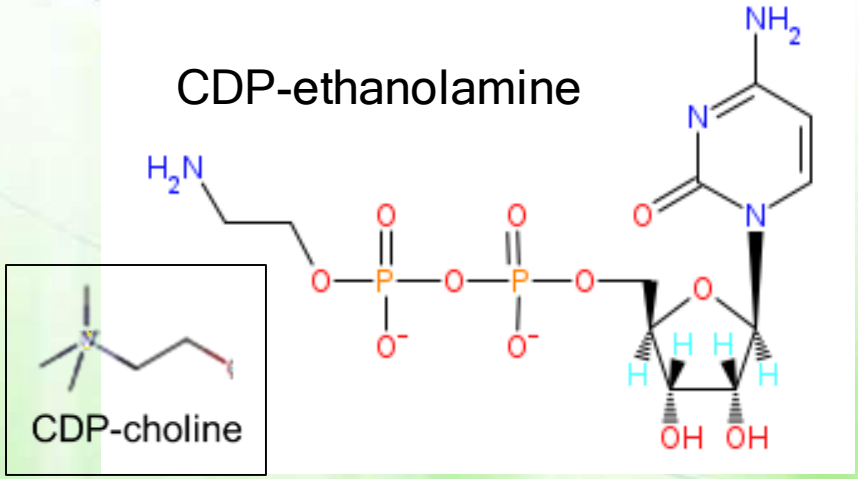
- Plasmalogens is the same as phosphatidic acid, but the difference is the bond that link the first fatty acid is (either bond).
- Either bond may contain alkene group (double bond) .

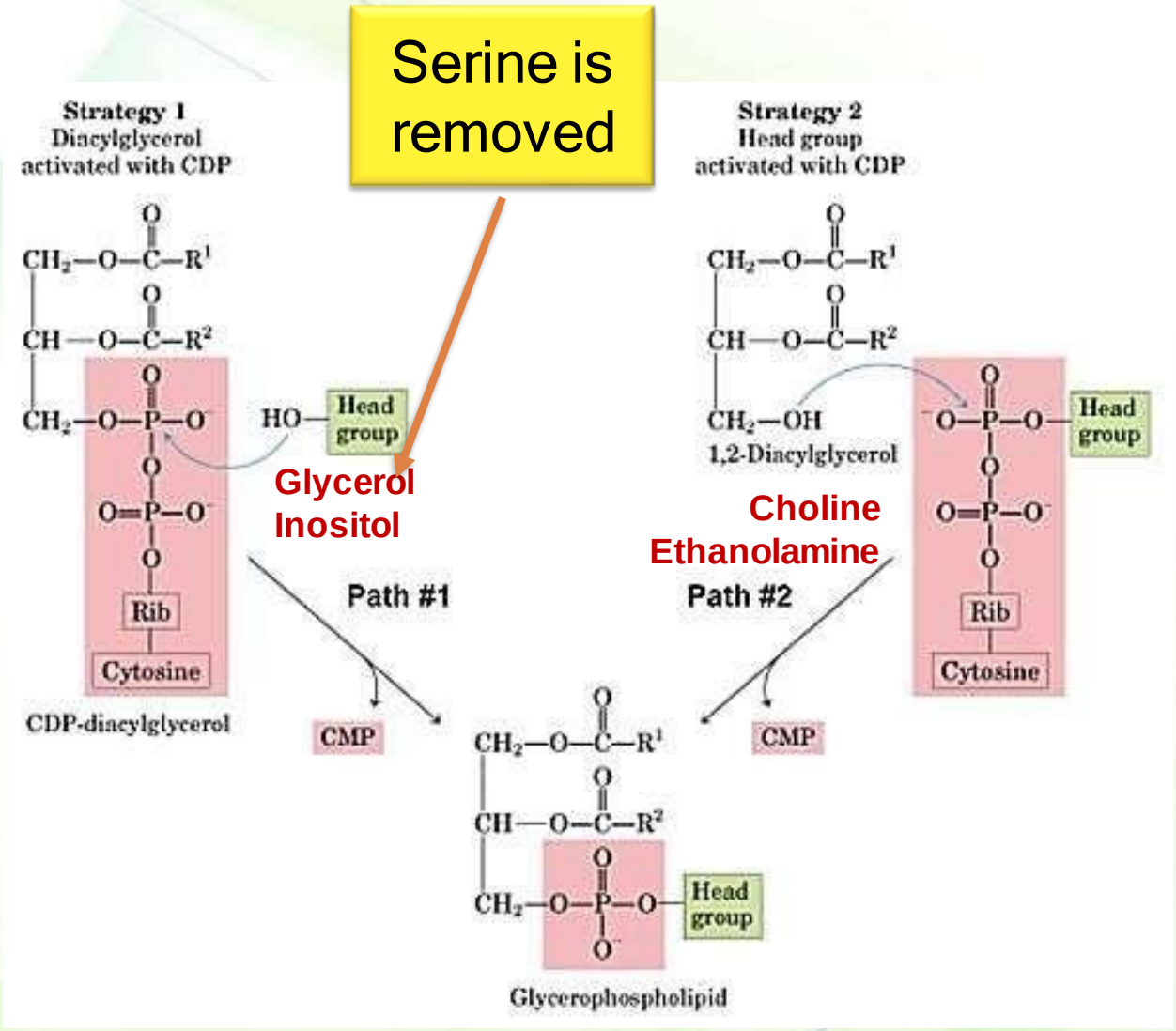


Synthesis

- Location: smooth ER
  - Except for ether lipids
- Activation by CDP is necessary.

  Either:
  - CDP-DAG (glycerol, inositol, serine)
  - CDP-alcohol (choline, ethanolamine)





- The complement in this slide:

- To Synthesize glycerophospholipids, you must activate it using high energy molecule, in lipids it is CDP. You can activate two part of the glycerophospholipids:

  1) the backbone (the Diacylglycerol)
  CDP-Diacylglycerol + glycerol → phosphatidylglycerol + CMP
  CDP-Diacylglycerol + inositol → phosphatidylinositol + CMP

  2) the head group
  CDP-choline + Diacylglycerol → phosphatidylcholine + CMP
  CDP-ethanolamine + Diacylglycerol → phosphatidylethanolamine + CMP

- HIGH ENERGY MOLECULES: Main: ATP, CoA, Carbs: UDP, Lipids: CDP, Proteins: GDP. (the doctor mentions them).

Sources of choline and ethanolamine

- Choline and ethanolamine are
  - obtained from diet,
  - synthesized, or
  - re-cycled from the turnover of pre-existing phospholipids
- Diet is still essential since demand > supply

To make sure you have enough

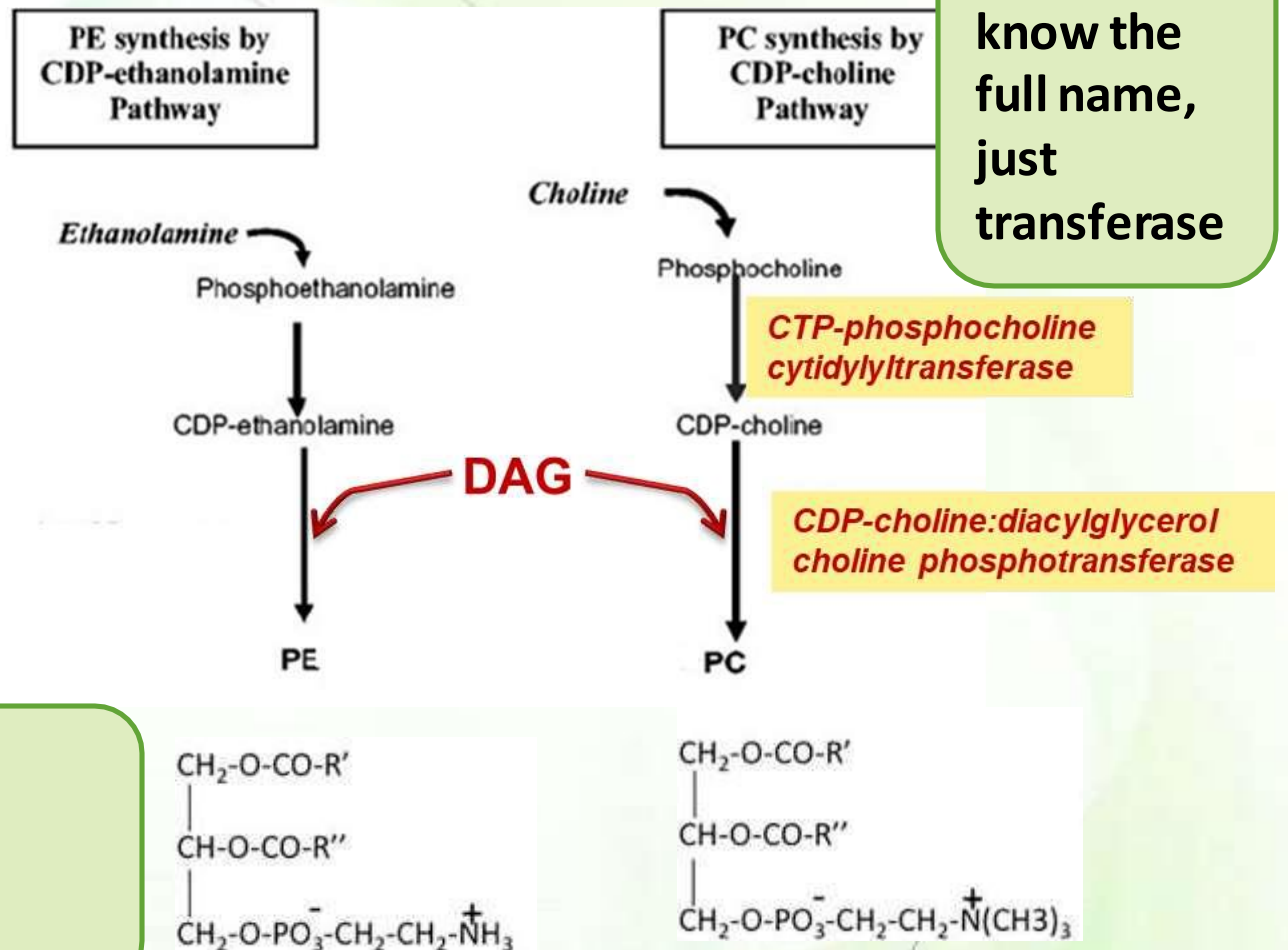
Synthesis of *ph*-choline and *ph*-ethanolamine

- Choline or ethanolamine are phosphorylated by *kinases*, then activated by *transferases* to form, CDP-choline or CDP-ethanolamine.
- Choline phosphate or ethanolamine phosphate is transferred from the nucleotide (releasing CMP) to DAG

NOTE:

kinase transferase transferase +DAG

Choline → phosphocholine → CDP-choline → PC

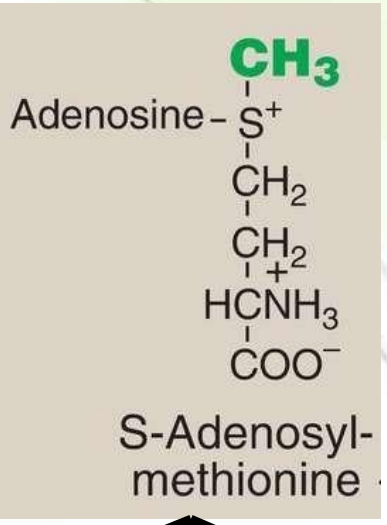


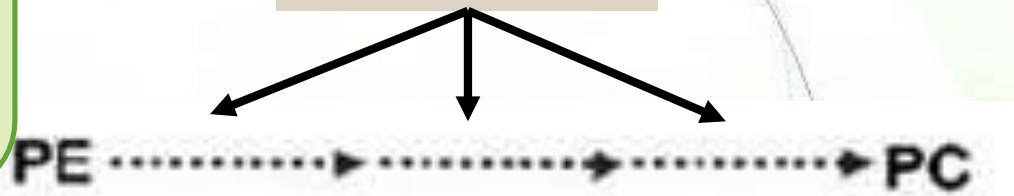
NOTE: you don't need to know the full name, just transferase

Synthesis of *ph*-choline from *ph*-ethanolamine

- Methyl groups are donated by S-adenosylmethionine to convert PE to PC by PE methyltransferase.

- **NOTE:** to convert Ph-ethanolamine to Ph-choline, you need to add 3 methyl groups to the amine group in 3 reactions, we get the methyl groups from S-adenosylmethionine (methyl doner).
- Those reactions are catalyzed by methyltransferase (PEMT).





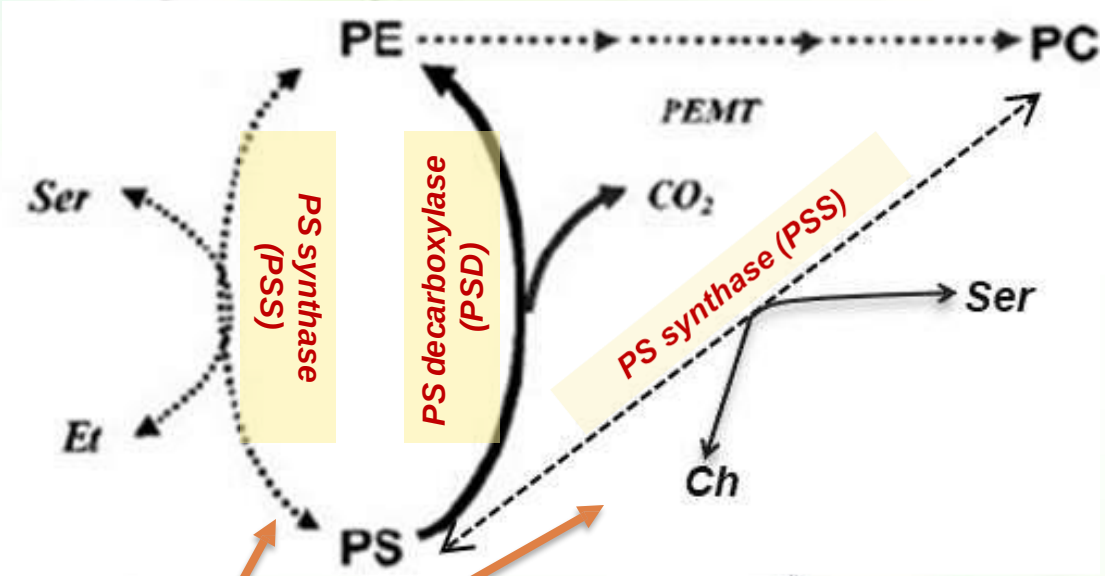
Phosphatidylethanolamine N –methyltransferase (PEMT)

Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$

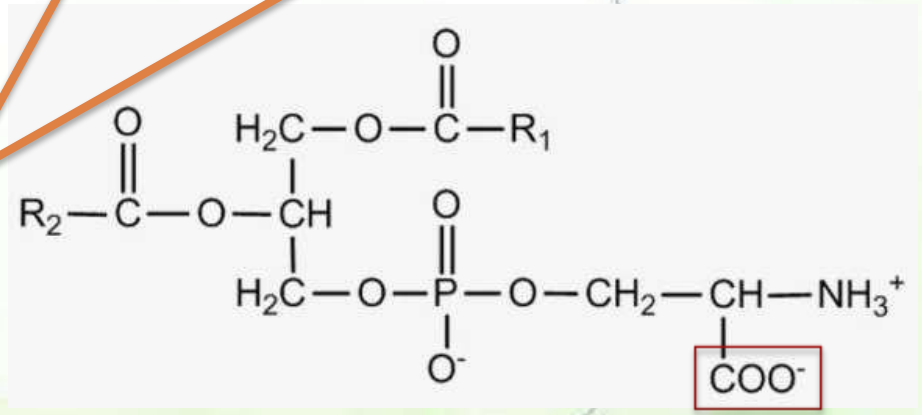
3 methyl groups

Synthetic pathways for and from ph-serine

- The liver requires another mechanism to produce PC because it uses it to make bile and other plasma lipoproteins.
- PS is decarboxylated to PE by PS decarboxylase (PSD) or exchanged from PE or PC by PS synthases (PSS).



Synthase not decarboxylase

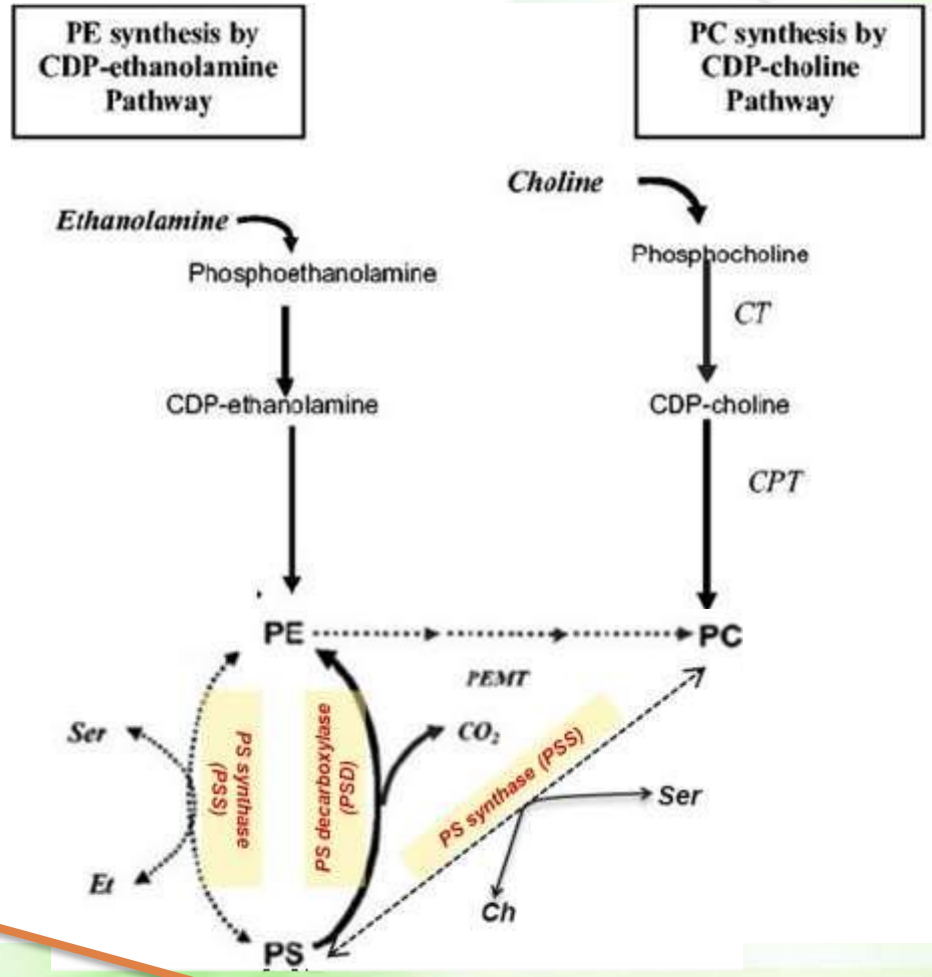


phosphatidylserine

- **The complement in this slide:**
- **PS structure is the same as PE but with a carboxyl group.**
- **PS reactions:**
  (PS → PE) using synthase, or decarboxylase.
  (PS → PC) using synthase.
- **PE reactions:**
  (PE → PC) using PEMT.
  (PE → PS) using synthase, but you can't use carboxylase.
- **PC reactions:**
  (PC → PS) using synthase.

- **The complement in this slide:**
- **PE:** *ph*-ethanolamine
- **PC:** *ph*-choline
- **PS:** ph-serine

Summary of synthesis pf PE, PC, and PS



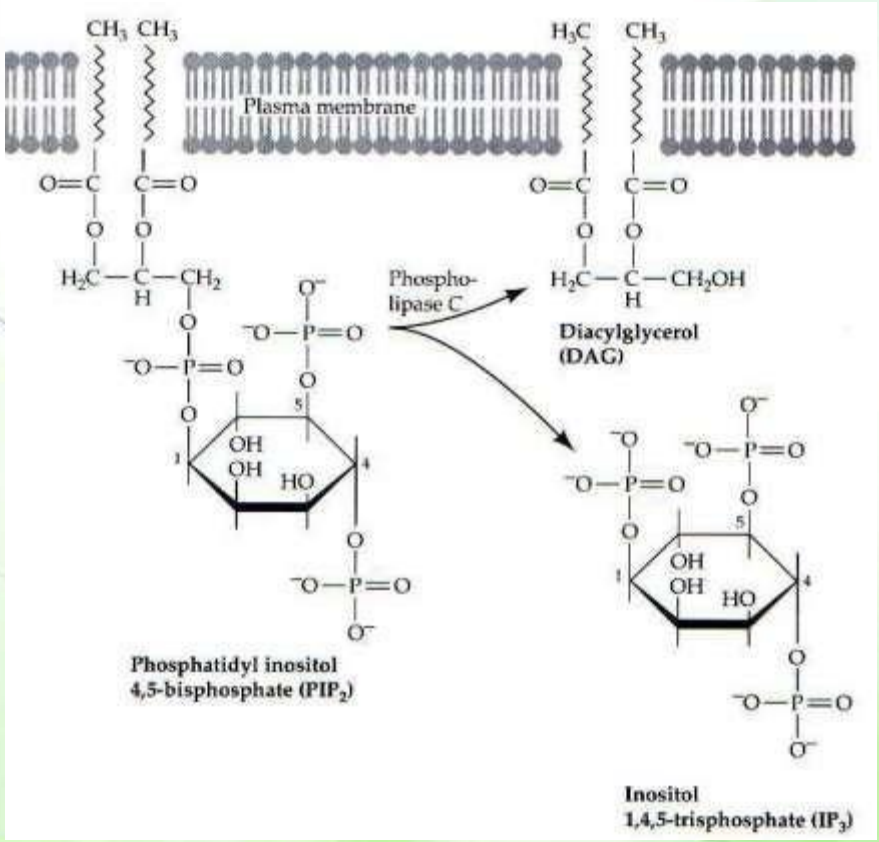
The bottom part is removed

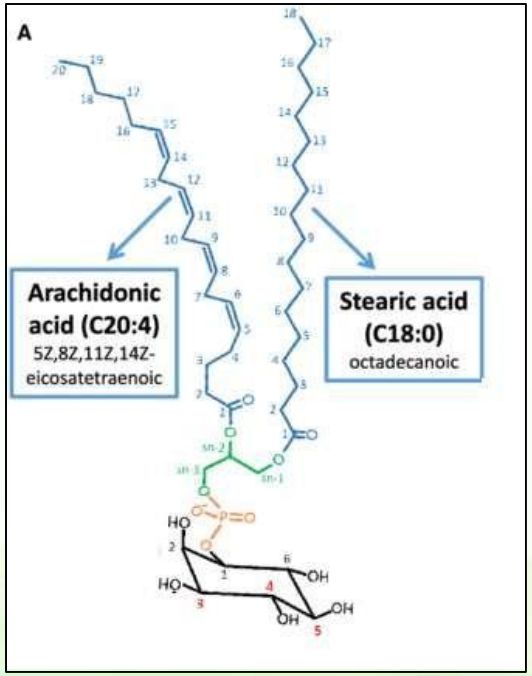
Synthesis of ph-inositol

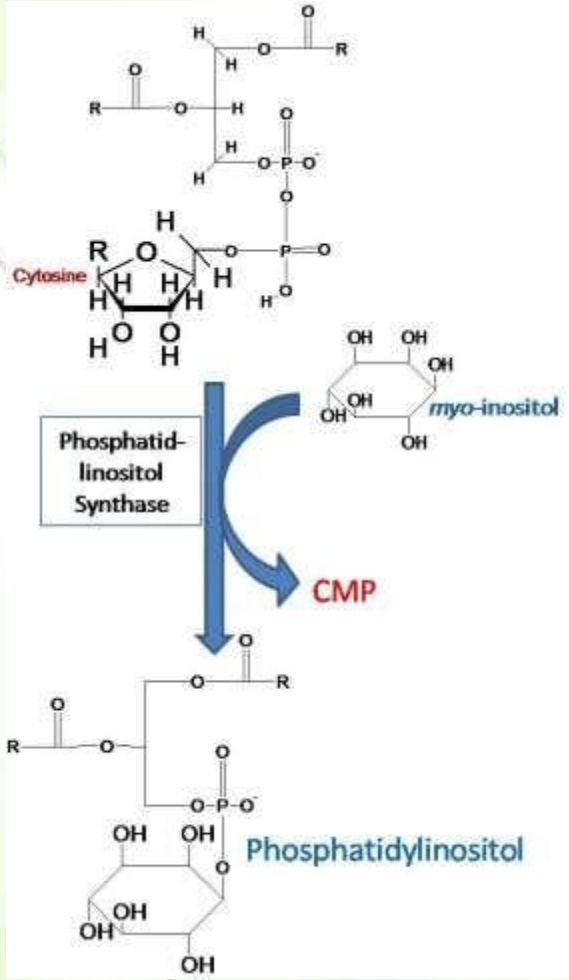
This was not clear

Note the synthasis

- Inositol is combined with CDP-DAG by PI synthase to produce phosphatidylinositol.
- It is a reservoir of arachidonate.
- It also produces signaling molecules when cleaved by phospholipase C.

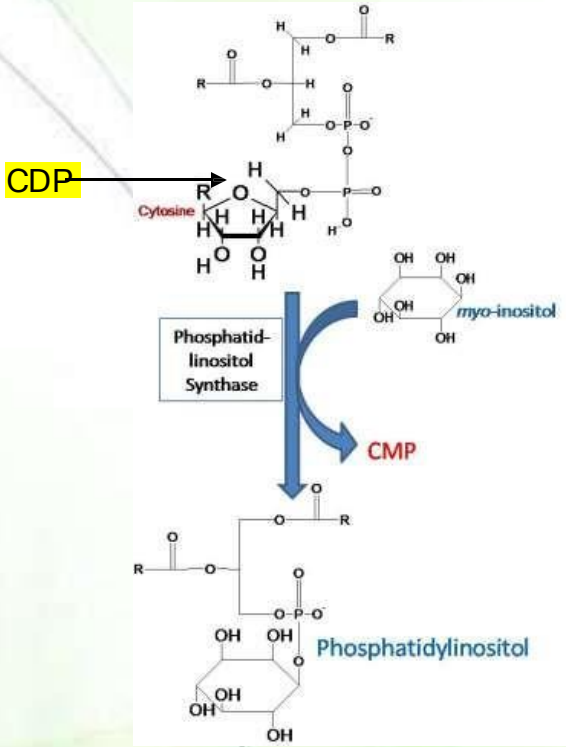




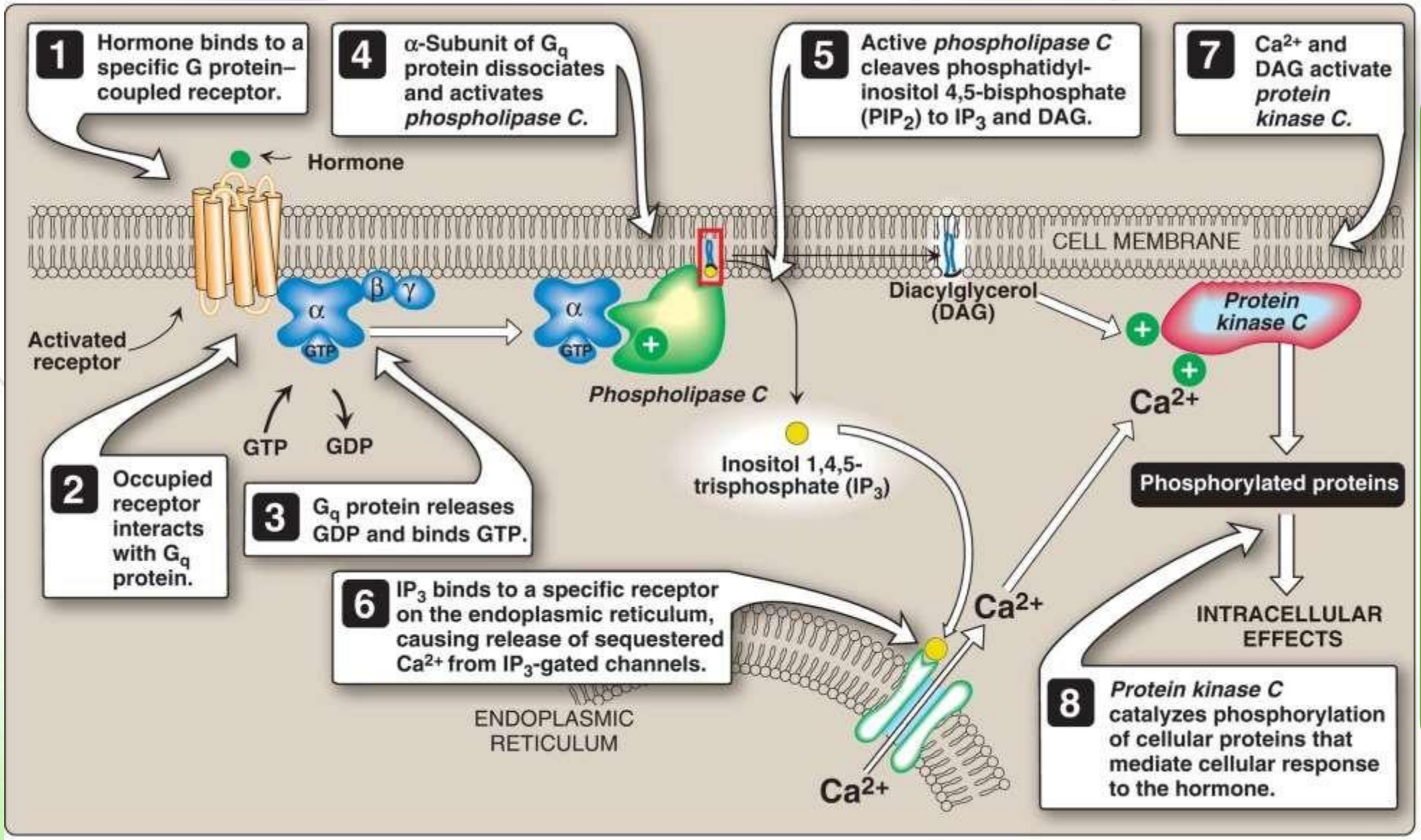


- **The complement in this slide:** synthesis of phosphatidylinositol inositol (PI); basically, we need the glycerol to be activated by CDP, we add (inositol), CMP gets released to form phosphatidylinositol inositol

- **Importance of** phosphatidylinositol inositol (PI):
- **1.reservoir of arachidonate**: on carbon 2, we have unsaturated FA, specifically arachidonic acid. It is the precursor of eicosanoids (inflammatory lipids)
- **2. signaling**: Phospholipase C cleaves PI → DAG & IP3. Both are signaling molecules.
- **3.Production of Plasma membrane proteins !:** PI has 2 FA on carbon 1 and 2 which are integrated in plasma membrane, the phosphatidylinositol on the 3rd carbon can be modified by adding a chain of sugars & then adding proteins on the sugars → protein plasma membrane.



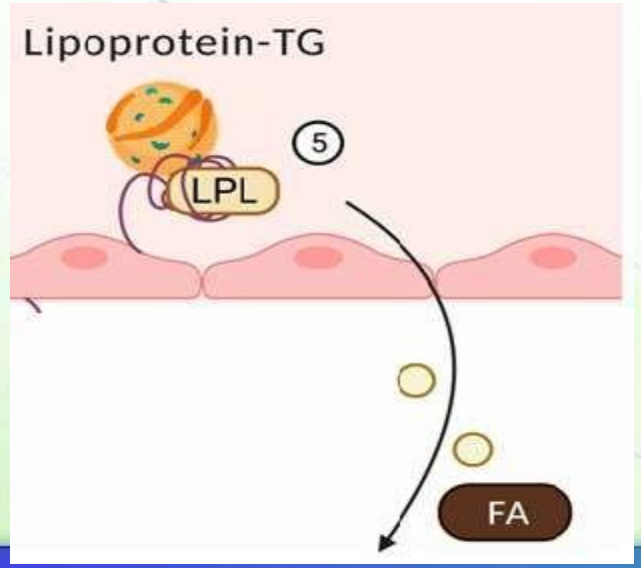
Signaling by PIP2 products

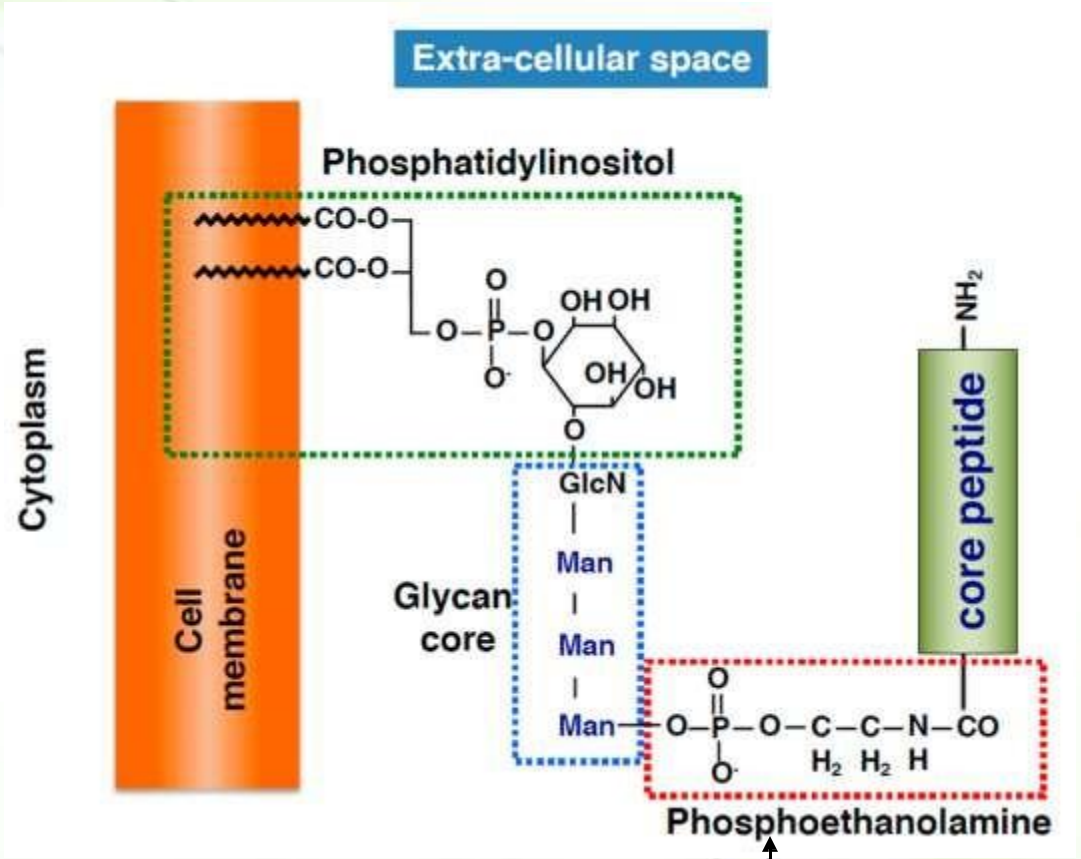


- **NOTE: READ THE Figure!! NB(mark well) :**
- **-IP3 causes Ca+2 release from ER**
- **-DAG is bound to membrane, while IP3 is motile in cytoplasm.**
- **-DAG & Ca+2 activate PKC**

GPI for membrane attachment

- Glycosyl phosphatidylinositol (GPI) attaches proteins to the plasma membrane.
- Advantage: lateral mobility
  - Example: lipoprotein lipase is attached to capillary endothelial cells by a (GPI) anchor.

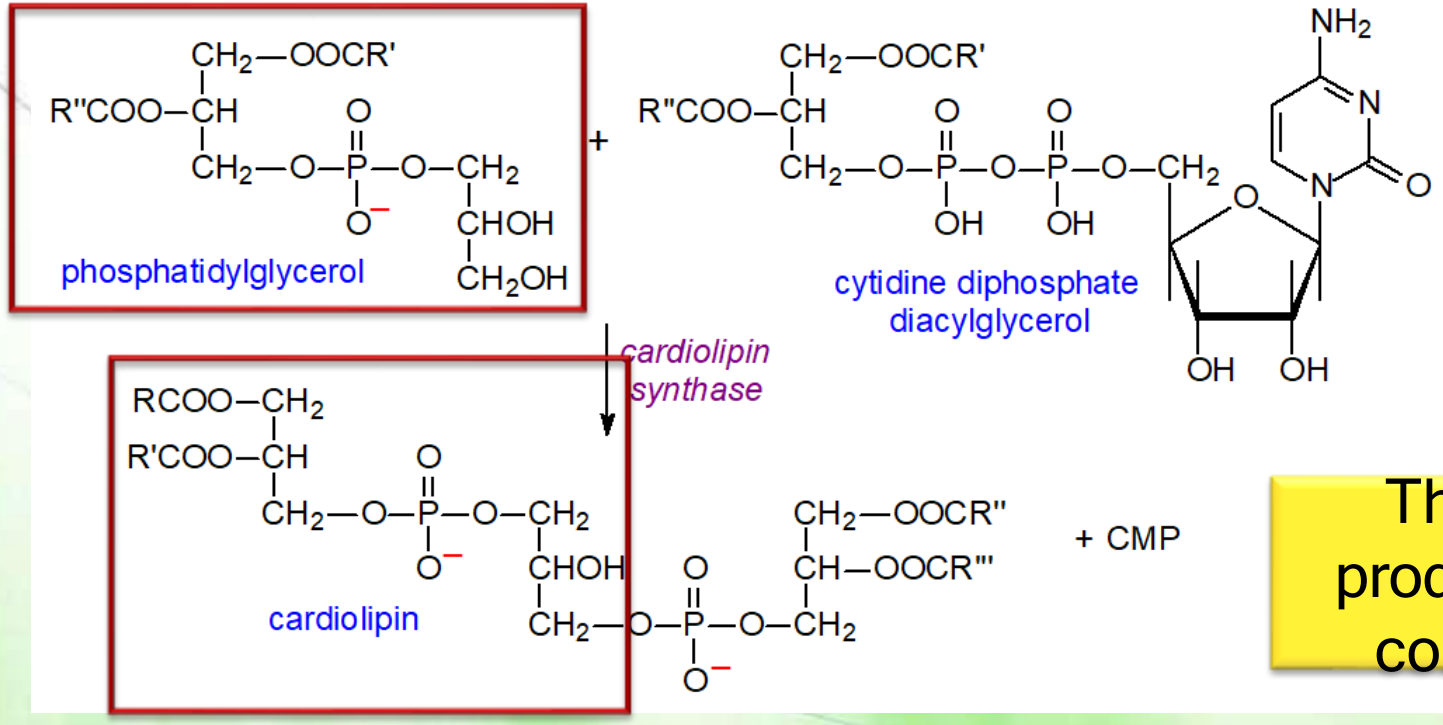




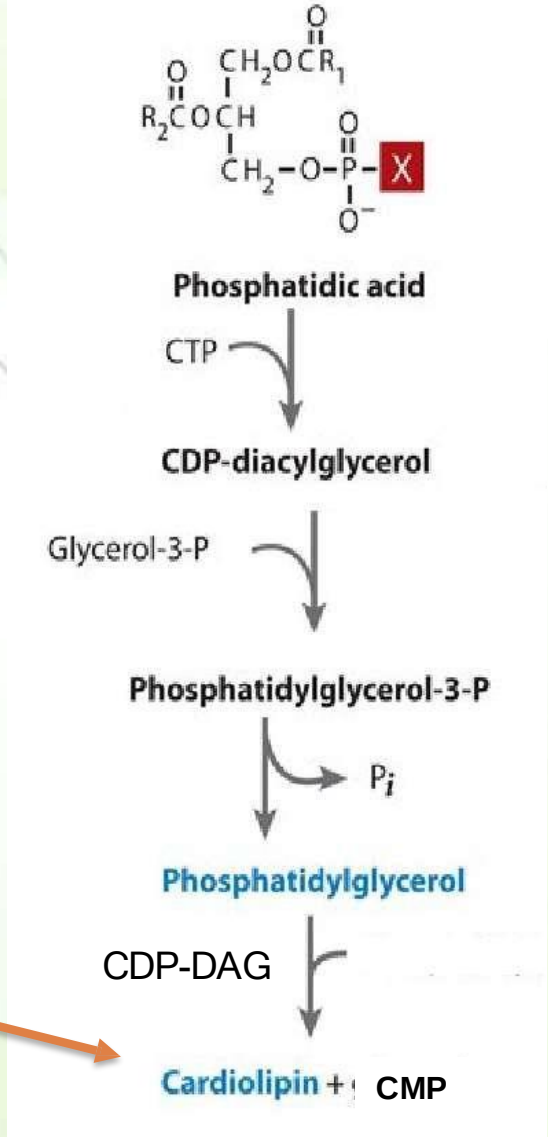
■ **NOTE: Structure not required** 😁

Phosphatidylglycerol and cardiolipin

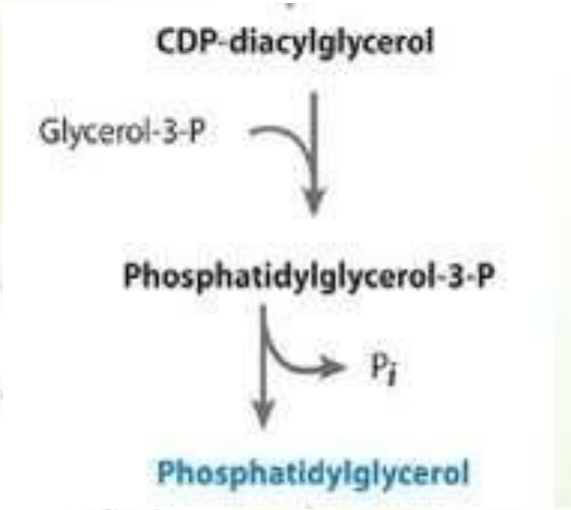
- Phosphatidylglycerol is synthesized from CDP-DAG and glycerol 3-phosphate.
- Cardiolipin is synthesized by the transfer of DAG from CDP-DAG to a pre-existing molecule of phosphatidylglycerol.



The final products are corrected



- **The complement in this slide**: in phosphatidylglycerol, both substrates need to be activated; phosphatidic acid is activated by adding CTP forming CDP-DAG, and glycerol is phosphorylated to G3P.



- Cardiolipin is synthesized from phosphatidylglycerol;
- Phosphatidylglycerol + CDP-DAG → cardiolipin
- Found in cardiac tissue and the only phospholipid localized exclusively to the mitochondria of mammalian cells
- It has 3 glycerol molecules (structure not required)

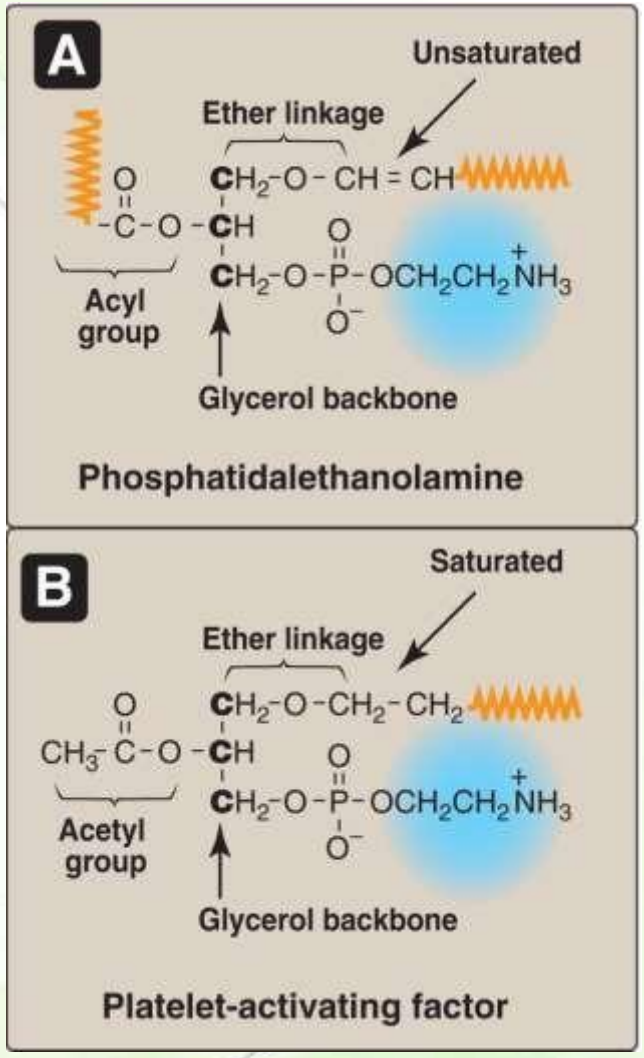
Ether glycerophospholipids

The FA at carbon 1 is replaced by an unsaturated alkyl group attached by an ether linkage.

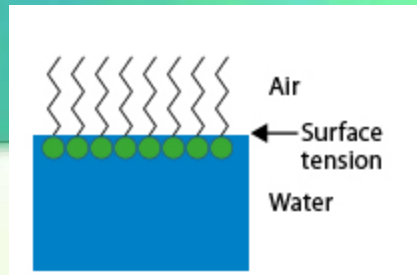
- Plasmalogens: PhosphatidAlethanolamine (abundant in nerve tissue, is similar in structure to phosphatidylethanolamine.
  - Phosphatidalcholine (abundant in heart muscle) is another significant ether lipid in mammals.

NOTE: don't worry about details ! ☝

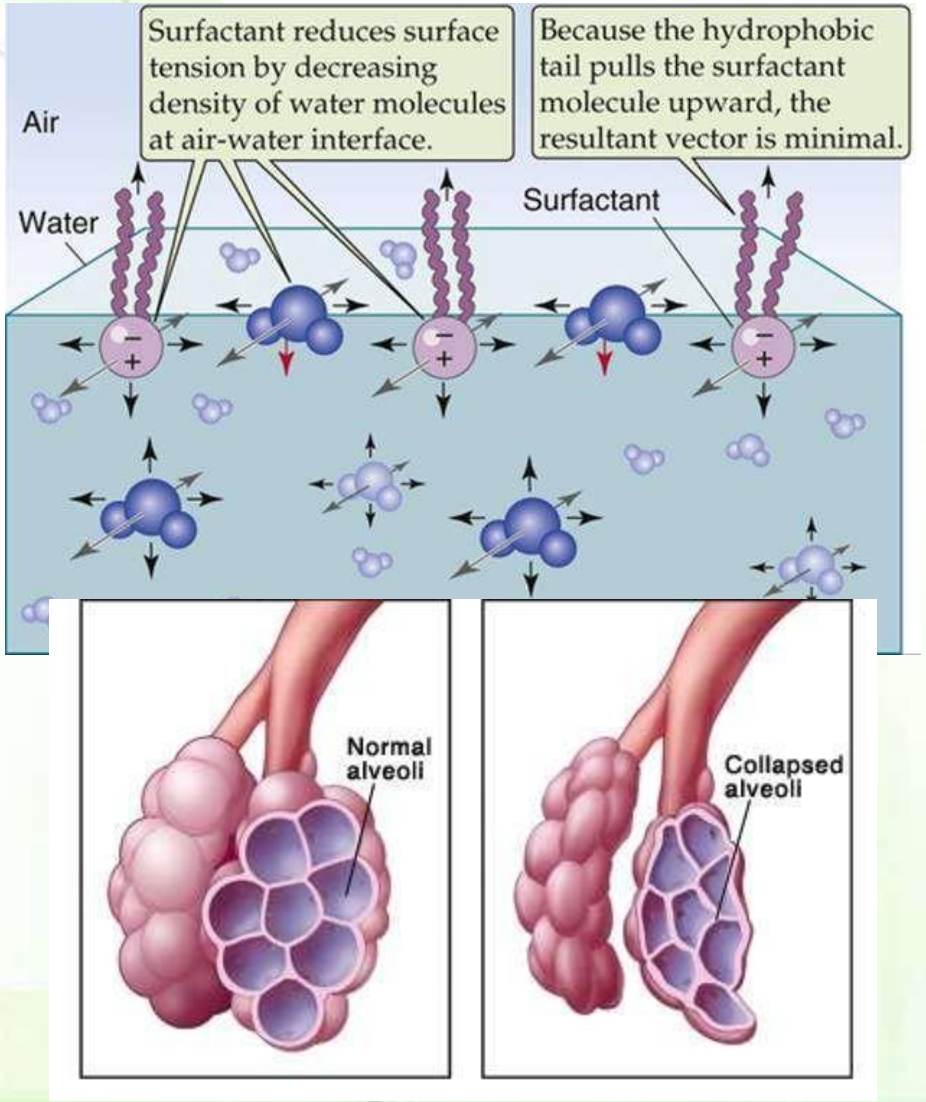
- Platelet-activating factor has a saturated alkyl group in an ether link to carbon 1 and an acetyl residue at carbon 2 of the glycerol backbone.
  - Prothrombotic and inflammatory factor



Surfactants



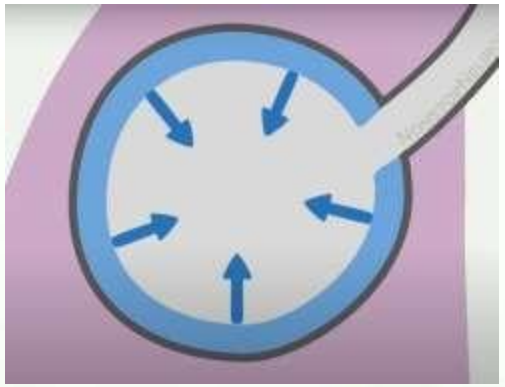
- Surfactants are a complex mixture of lipids (90%) and proteins (10%) that make the extracellular fluid layer lining the alveoli and are secreted by type II pneumocytes in the lungs.
- Dipalmitoylphosphatidylcholine (DPPC) is the major lipid in surfactants.
- Surfactants serve to decrease the surface tension of the fluid layer allowing reinflation of alveoli and preventing alveolar collapse (atelectasis).

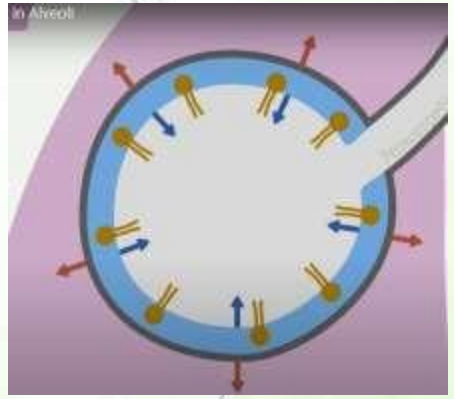


- Respiratory distress syndrome (RDS) in preterm infants is associated with insufficient surfactant production and/or secretion.
- Prenatal administration of glucocorticoids shortly before delivery to induce expression of specific genes.

- **The complement in this slide:** Surfactants found on the surface of the epithelial cell of alveoli. Without them we won't breathe properly, because the surface tension of the fluids tends to collapse the alveoli. Our cell surface are hydrophilic, so when air enters alveoli, air makes the alveoli clumps or collapses. Therefore, surfactants are secreted to make the environment more hydrophobic. It will lead to good air transfer.
- The more the surface tension, the harder it is to expand the alveoli. Surfactants decrease surface tension and decreases tendency of alveoli to collapse. Thus, in presence of surfactants it becomes easy to expand the alveoli or in fancy words, the compliance of lungs increases.

- Dipalmitoyl-phosphatidylcholine= 2 FA (Palmitate) + phosphatidylcholine
- **Importance**: preterm infants (babies born alive before 9 months of pregnancy), are kept in nurseries; because they can't breathe well, they don't have surfactant.
- So, administration of glucocorticoids are given to induce expression of surfactant genes.





- **Additional information:** Functions of Surfactants in Alveoli (youtube.com) - (0:00 - 1:30)

Degradation of Phospholipids

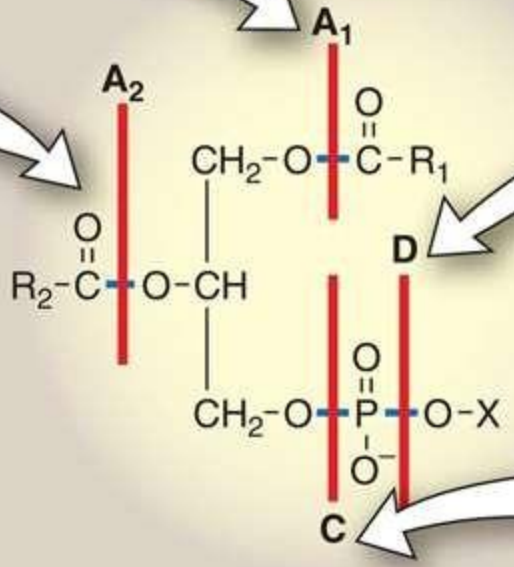
This is different than what's in the textbook

PHOSPHOLIPASE A_2

- *Phospholipase* A_2 is present in many mammalian tissues and pancreatic juice. It is also present in snake and bee venoms.
- 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, acting on phosphatidyl-inositol, releases arachidonic acid (the precursor of the eicosanoids).
- *Phospholipase* A_2 is inhibited by glucocorticoids (for example, cortisol).

PHOSPHOLIPASE A_1

- *Phospholipase* A_1 is present in many mammalian tissues.



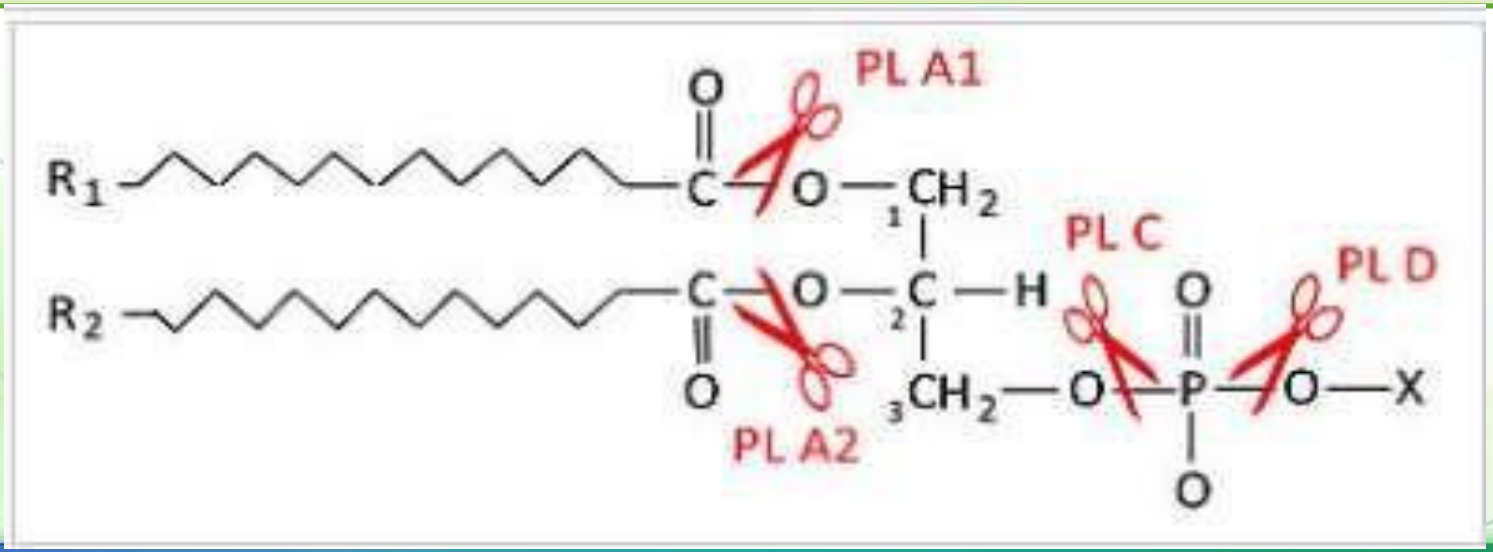
PHOSPHOLIPASE D

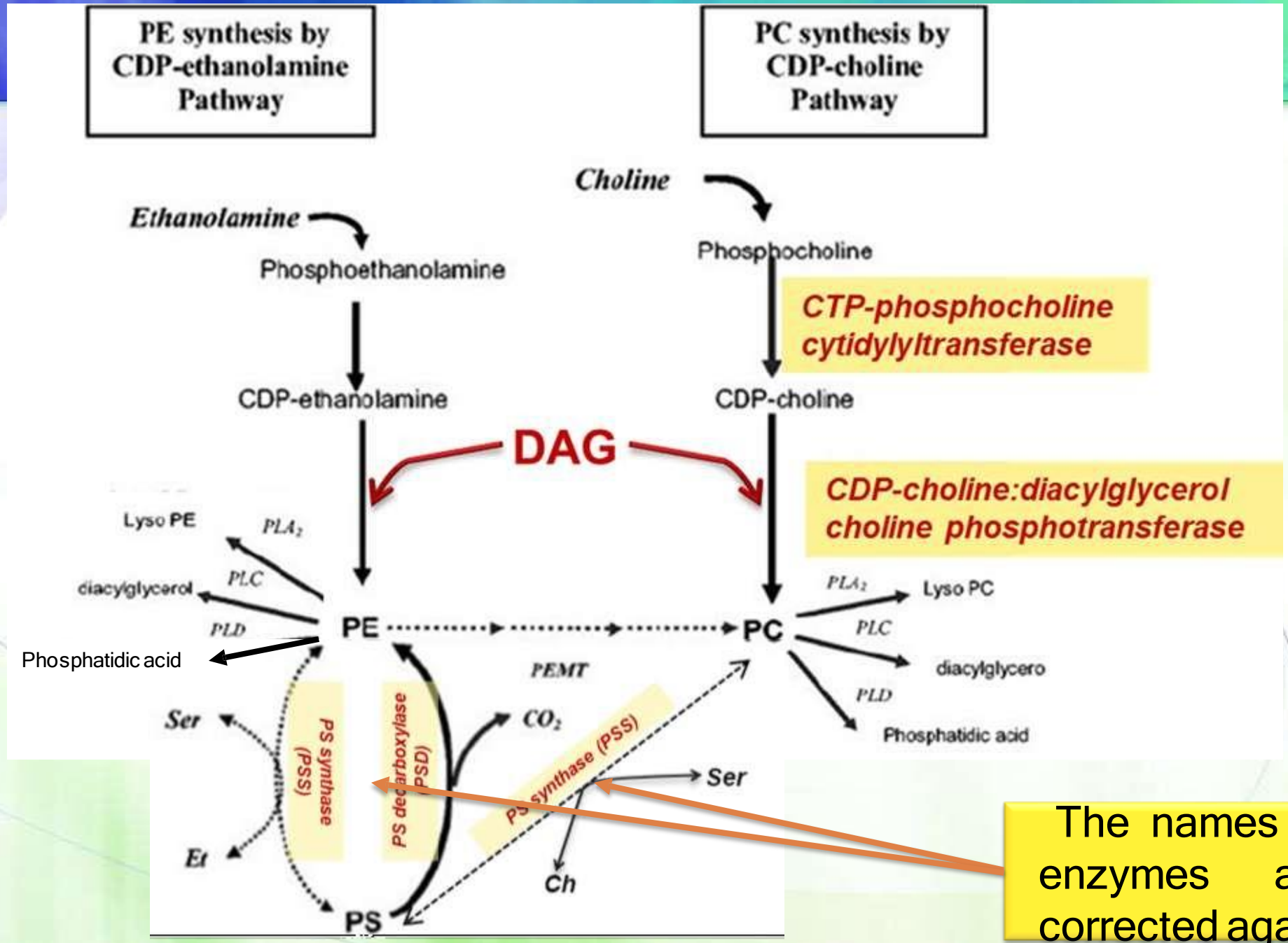
- *Phospholipase D* cleaves the head group generating PA, followed by the action of *a* phosphohydrolase that generates DAG, which is a signaling molecule.

PHOSPHOLIPASE C

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

- **The complement in this slide:**
- **Phospholipase A_1** is responsible for releasing the FA attached to carbon no.1
- **Phospholipase A_2** is responsible for releasing the 2nd FA attached to carbon no.2 and responsible for releasing the arachidonic acid from the phosphatidyl inositol PI (in signaling)+ Cortisol inhibit A2 (anti-inflammatory)
- **Phospholipase C**: cleavage between phosphate group & glycerol; producing DAG + Phospho-head group (used in signaling)
- **Phospholipase D**: cleavage of the ester bond between phosphate & head. Then, another enzyme phosphohydrolase that generates DAG, cleaves between phosphate &glycerol.





The names of enzymes are corrected again

V1: **CAMP**

V2: **CMP**

Slide 17