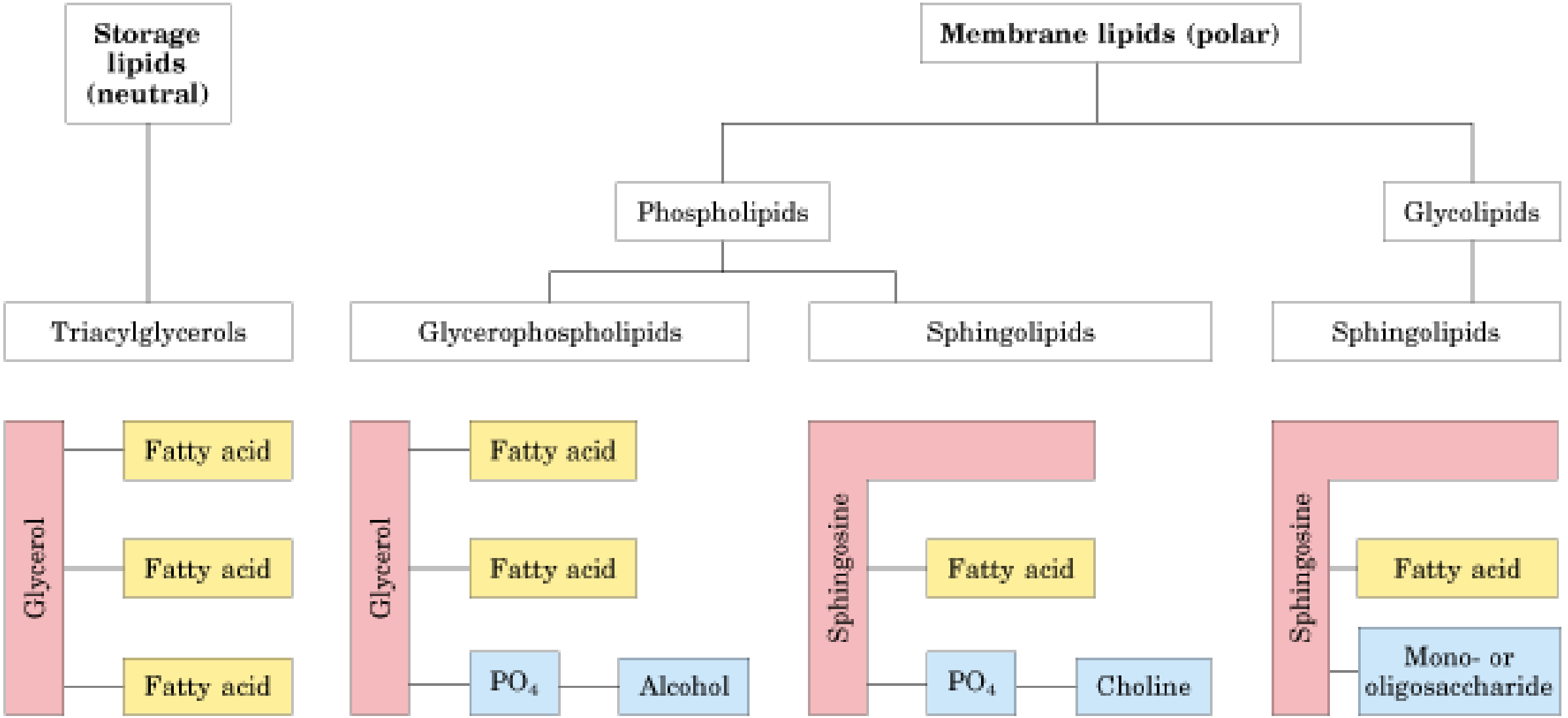
Metabolism of lipids V:
Glycerophospholipids

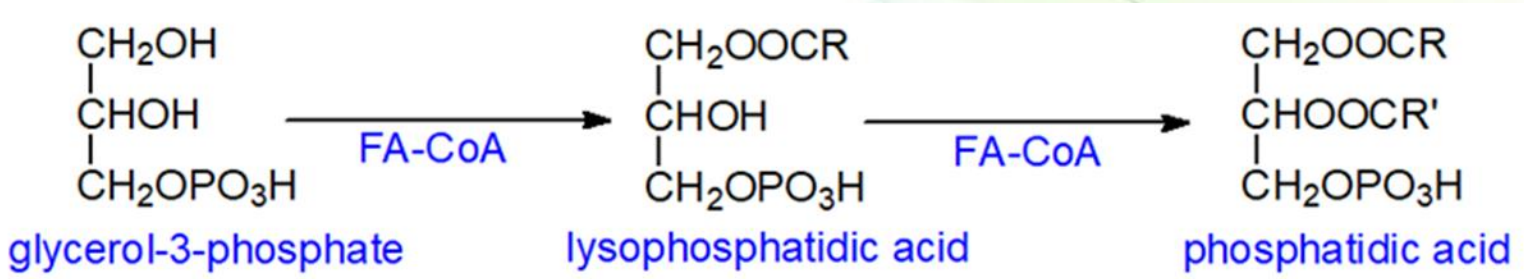
Prof. Mamoun Ahram

Resources

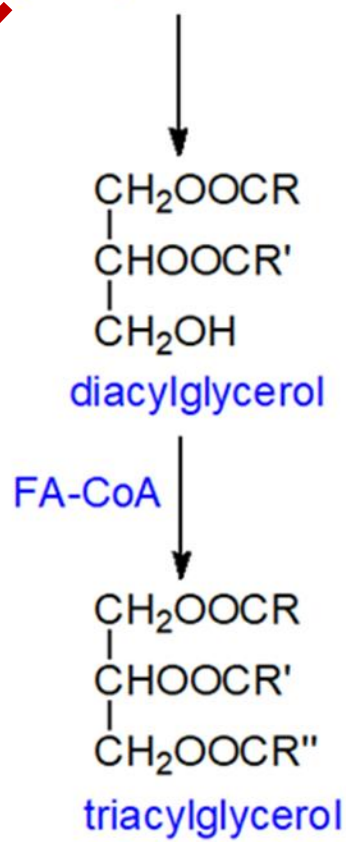
- This lecture
- Lippincott's Biochemistry, Ch. 17


Storage lipids (neutral)
Membrane lipids (polar)
Phospholipids
Glycolipids
Triacylglycerols
Glycerophospholipids
Sphingolipids
Sphingolipids
Glycerol
Fatty acid
Fatty acid
Fatty acid
Glycerol
Fatty acid
Fatty acid
PO_4
Alcohol
Sphingosine
Fatty acid
PO_4
Choline
Sphingosine
Fatty acid
Mono- or oligosaccharide

Phosphatidic acid

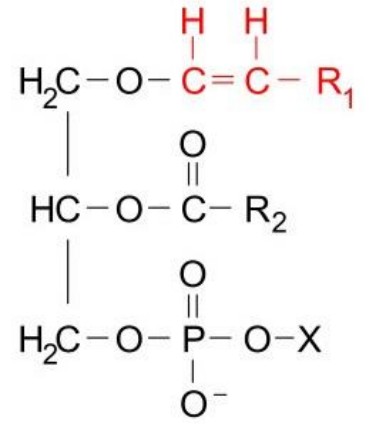


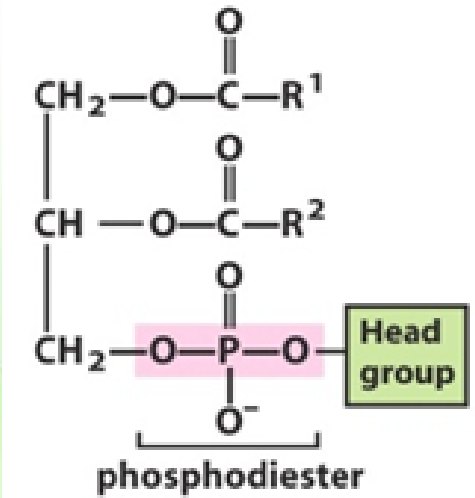
- Phosphatidic acid is the precursor of glycerophospholipids.

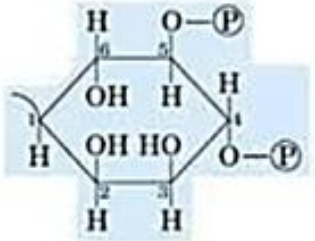
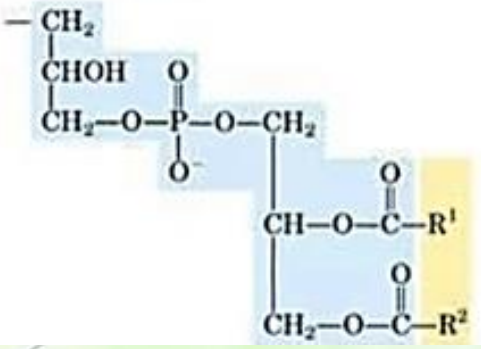


Classification of Glycerophospholipids

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

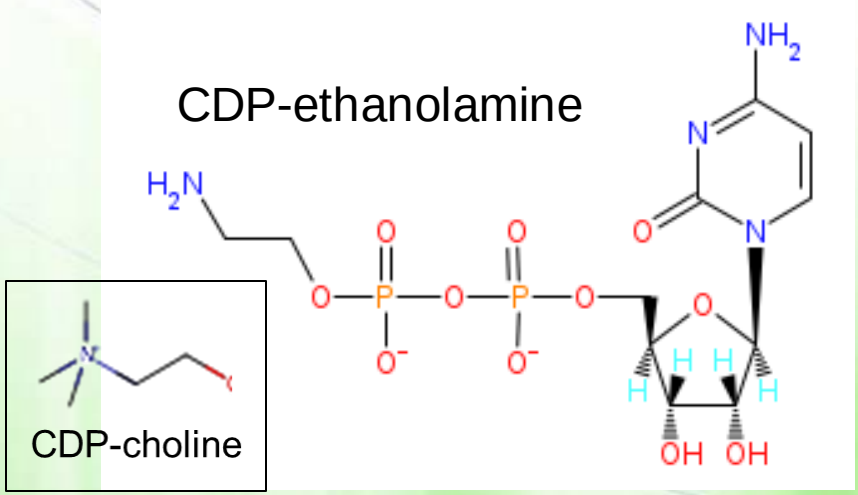


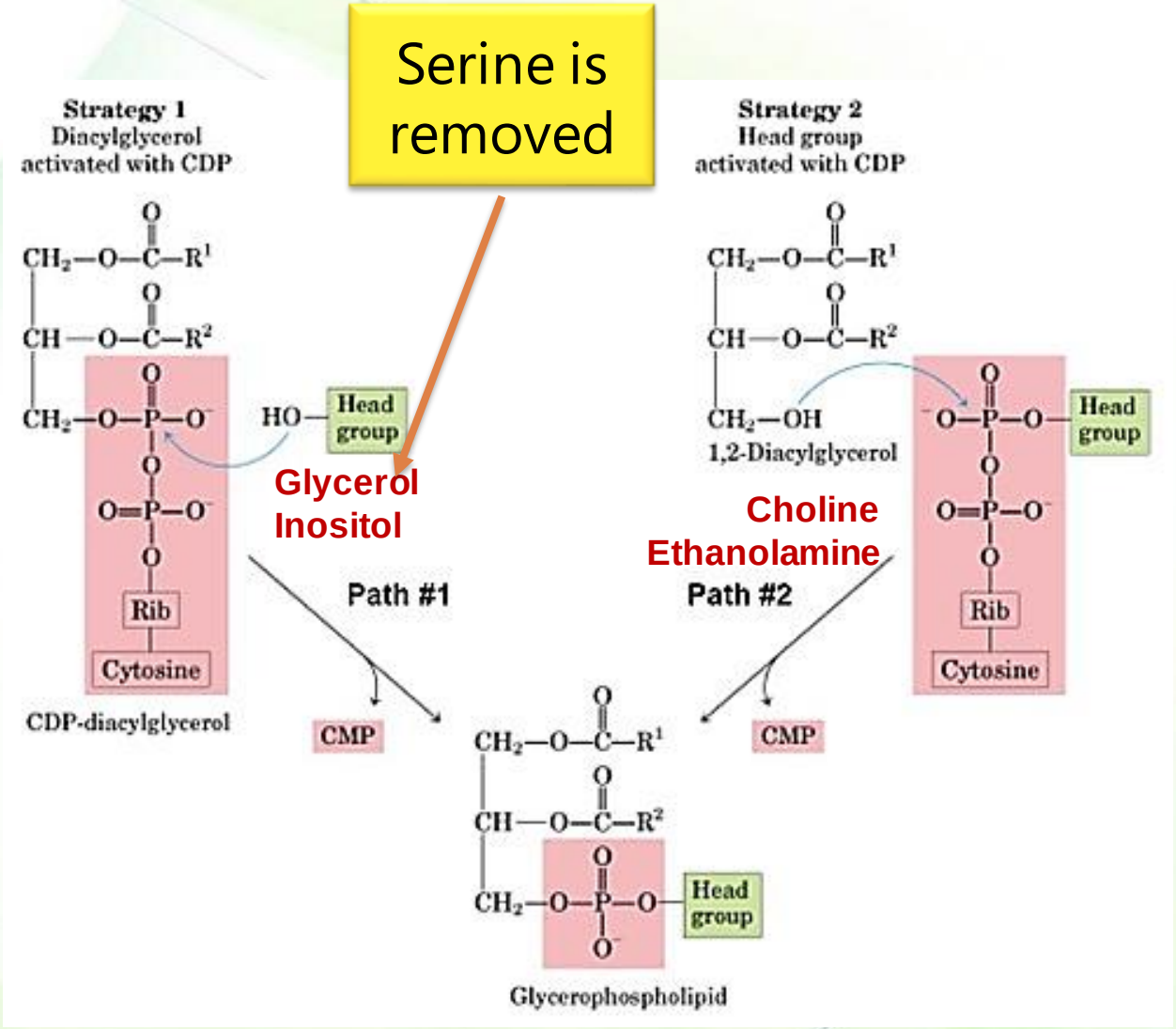


Phosphatidic acid	—	—H
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	$-CH_2-\underset{COO^-}{CH}-\overset{+}{N}H_3$
Phosphatidylglycerol	Glycerol	$-CH_2-\underset{OH}{CH}-CH_2-OH$
Phosphatidylinositol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

Synthesis

- Location: smooth ER
  - Except for ether lipids
- Activation by CDP is necessary. Either:
  - CDP-DAG (glycerol, inositol, serine)
  - CDP-alcohol (choline, ethanolamine)



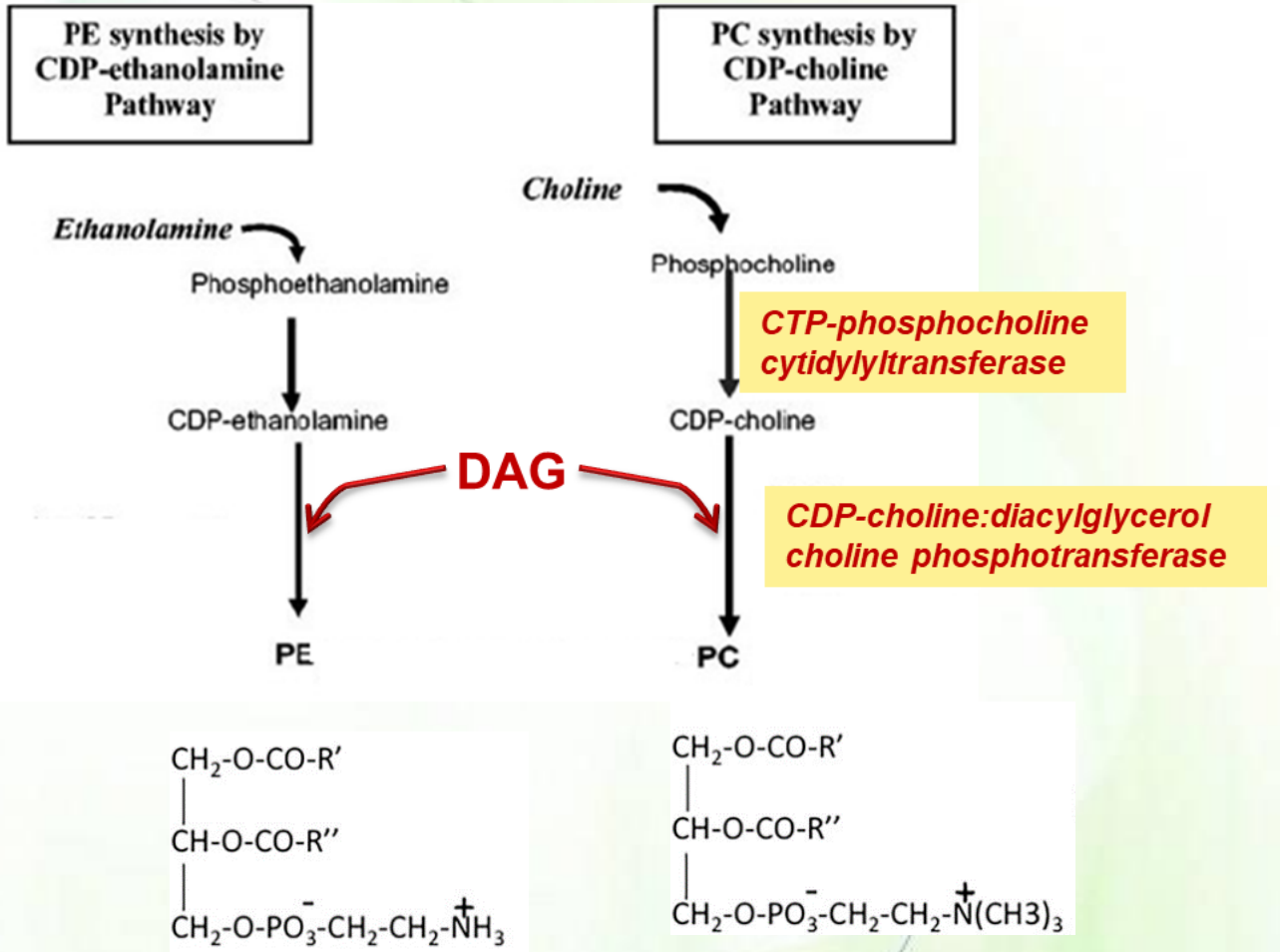


Sources of choline and ethanolamine

- 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

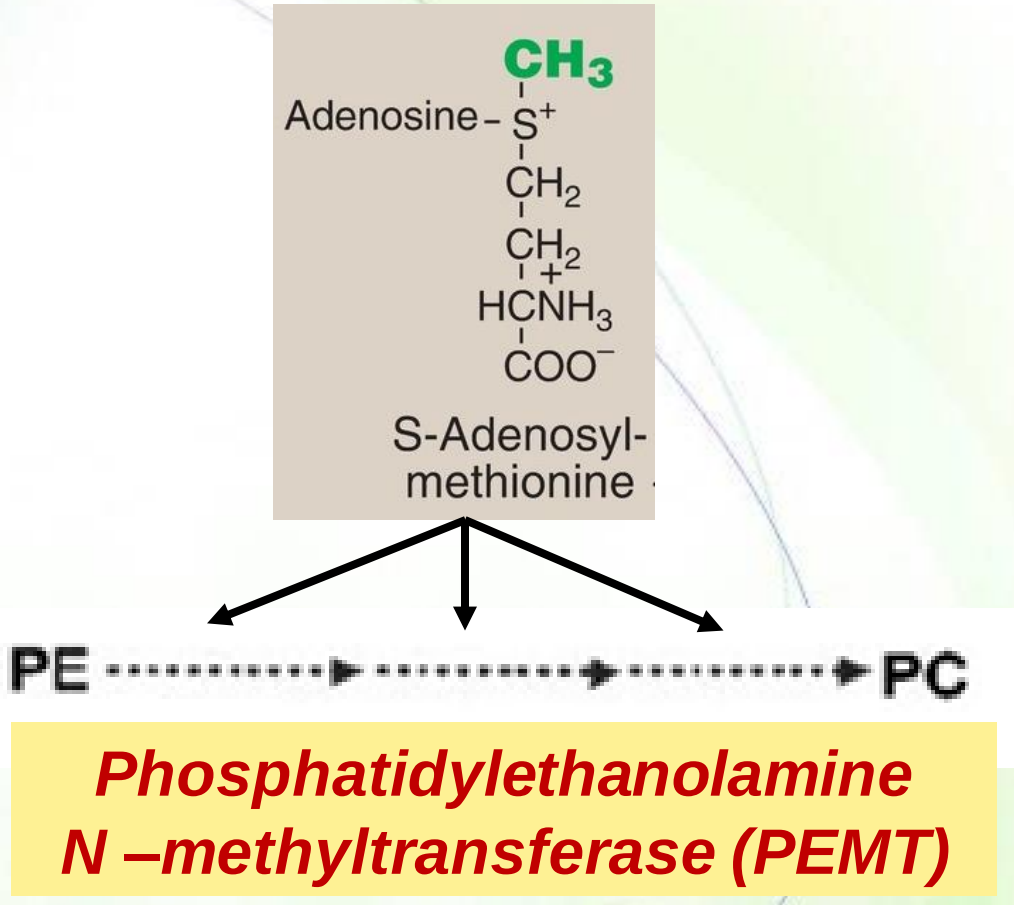
Synthesis of *ph*-choline and *ph*-ethanolamine

- 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.



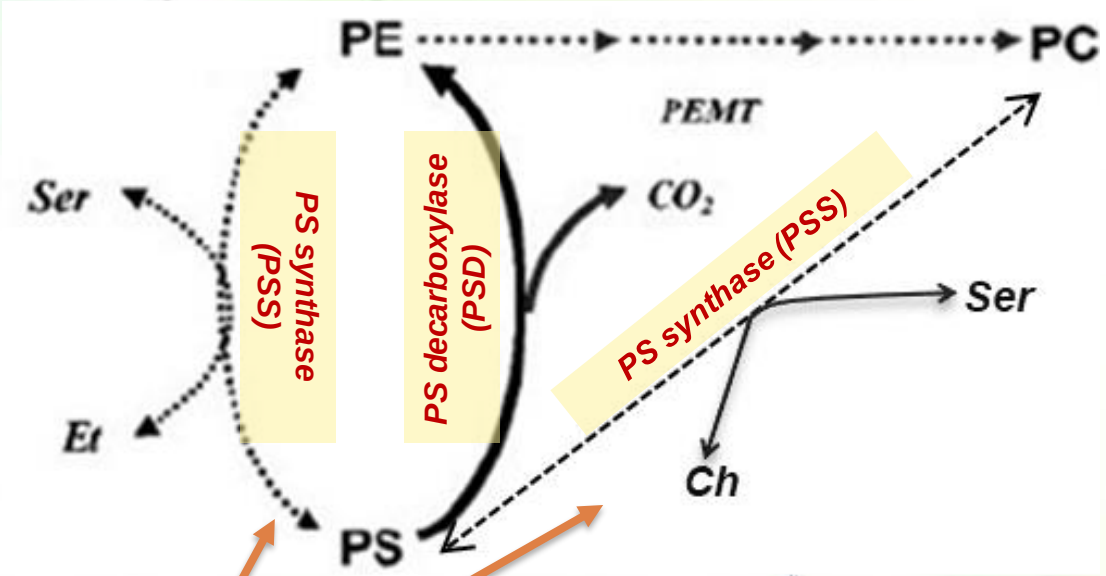
Synthesis of *ph*-choline from *ph*-ethanolamine

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

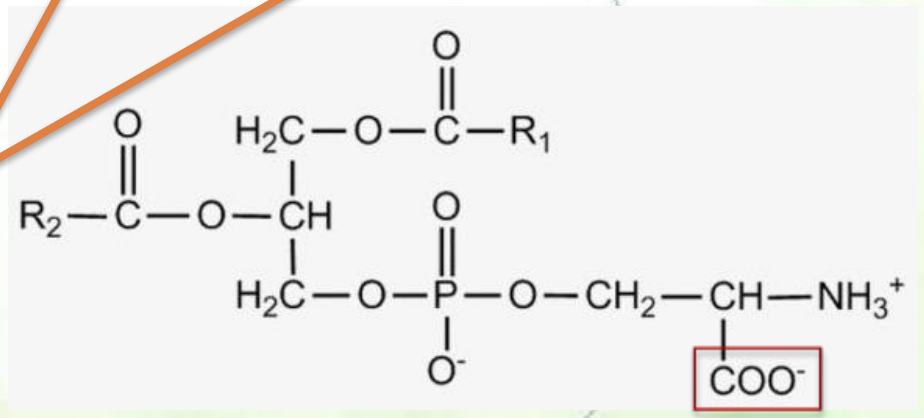


Synthetic pathways for and from ph-serine

- 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).

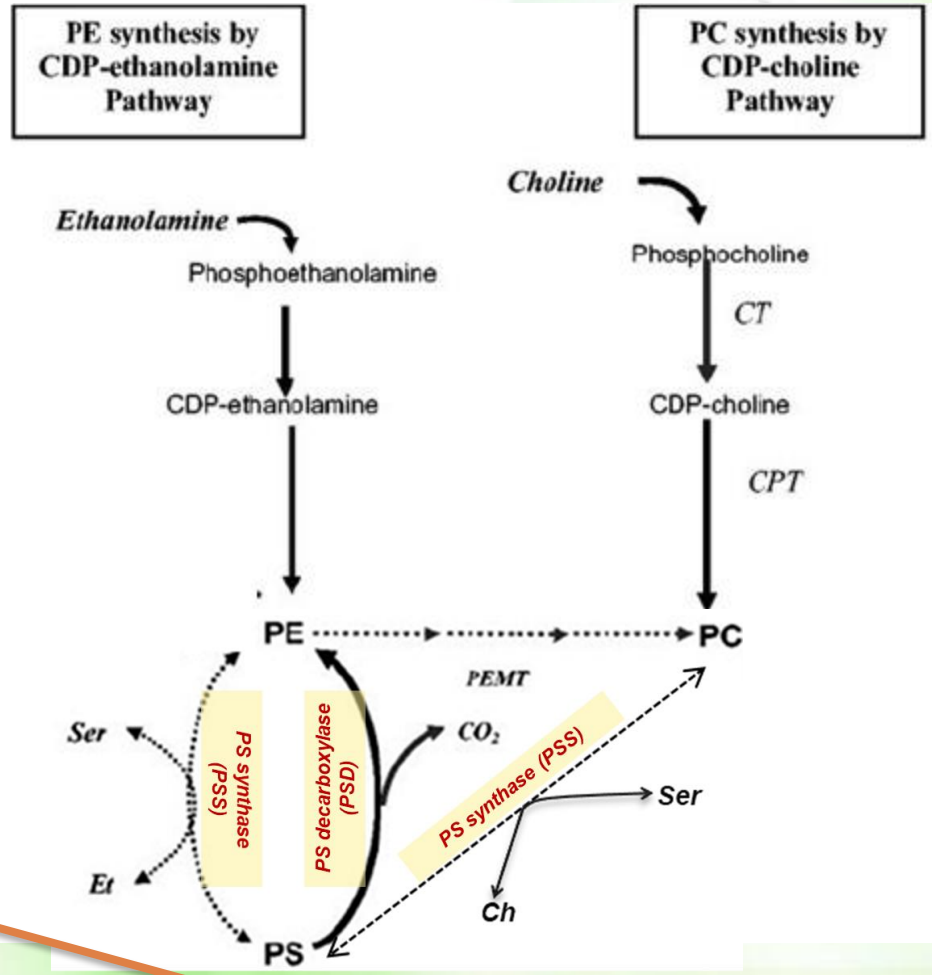


Synthase not decarboxylase



phosphatidylserine

Summary of synthesis pf PE, PC, and PS



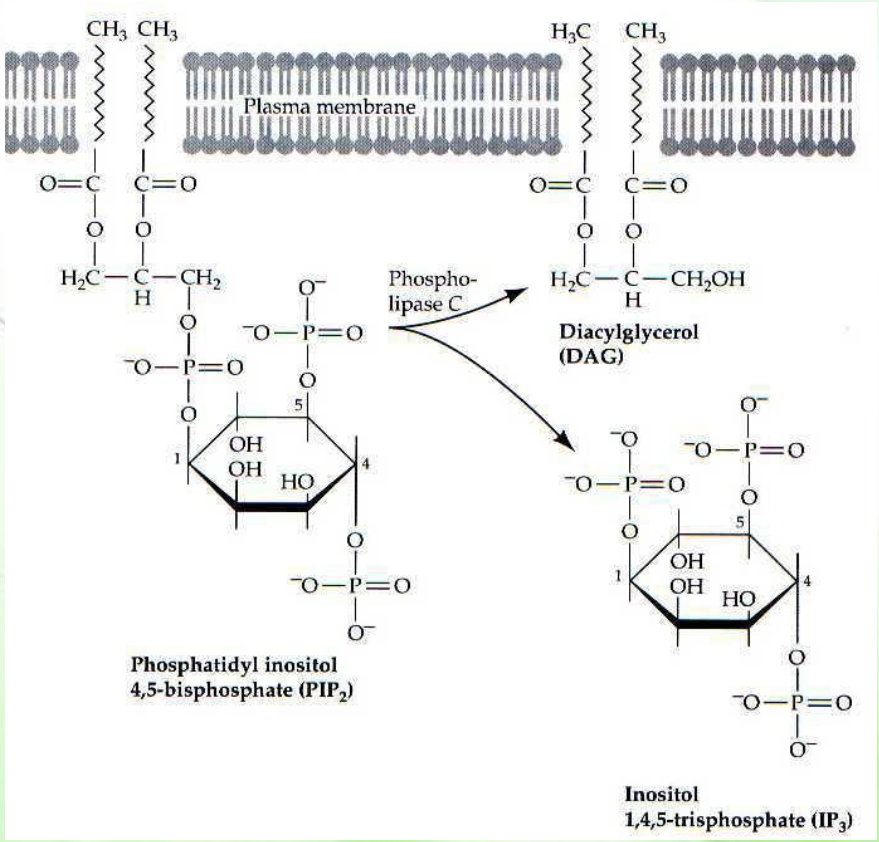
The bottom part is removed

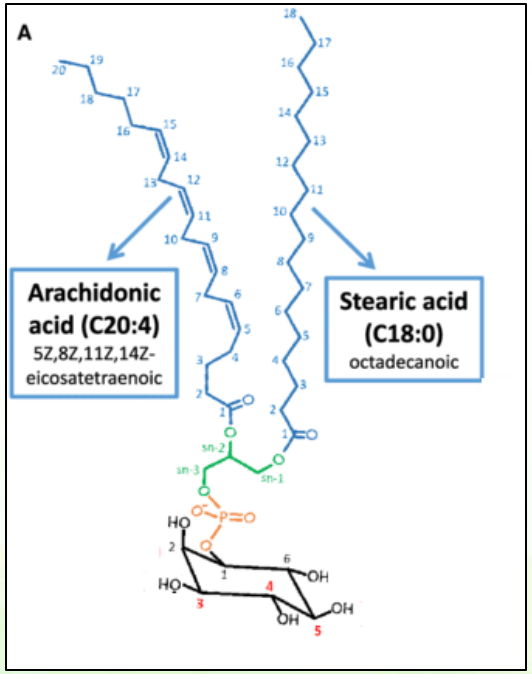
Synthesis of ph-inositol

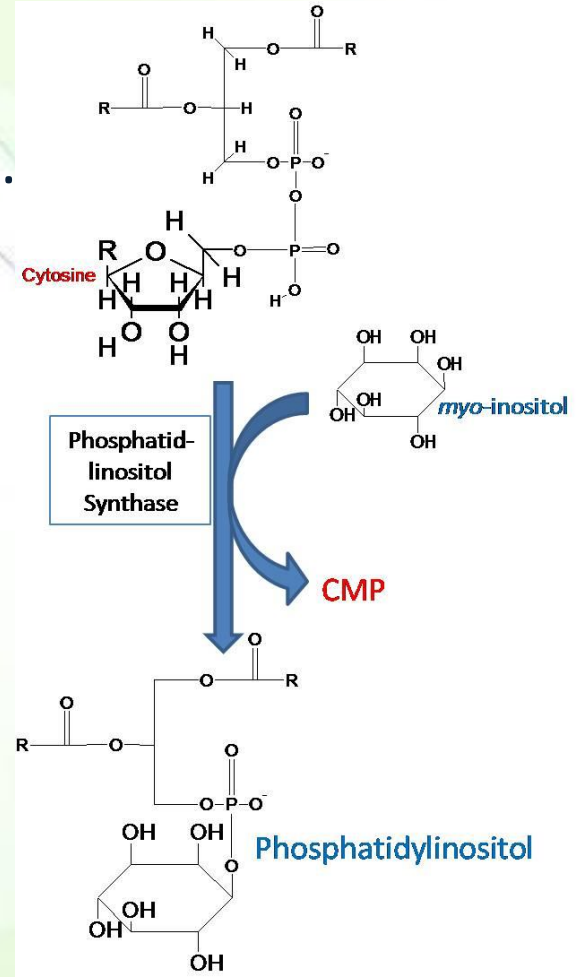
This was not clear

Note the synthasis

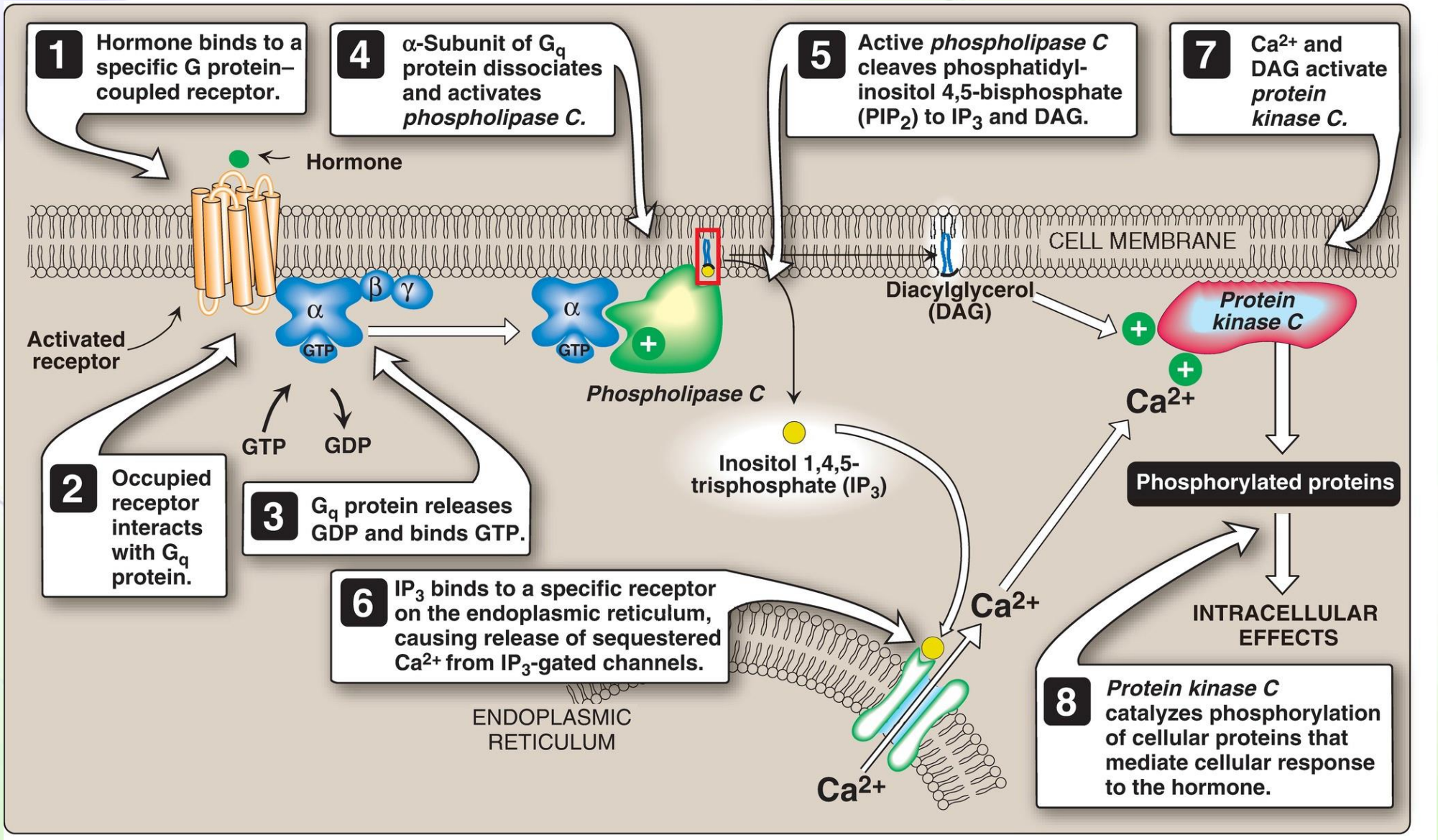
- Inositol is combined with CDP-DAG by PI synthase to produce phosphatidylinositol.
- It is a reservoir of arachidonate.
- It also produces signaling molecules when cleaved by phospholipase C.





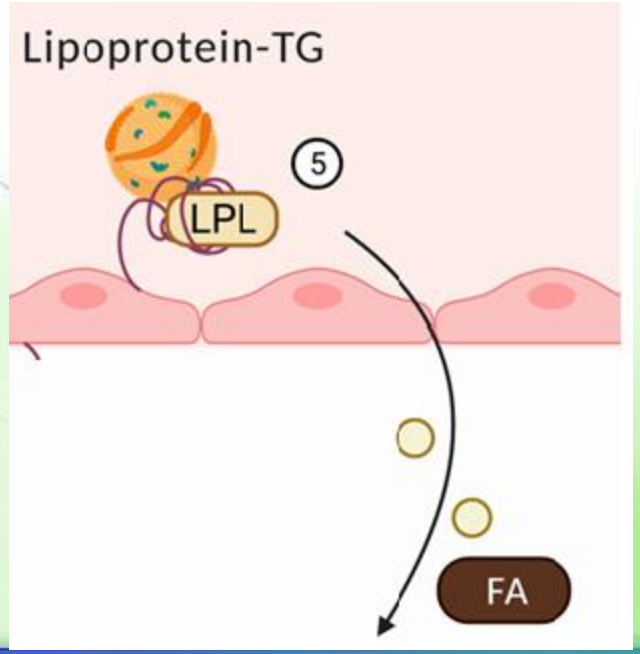


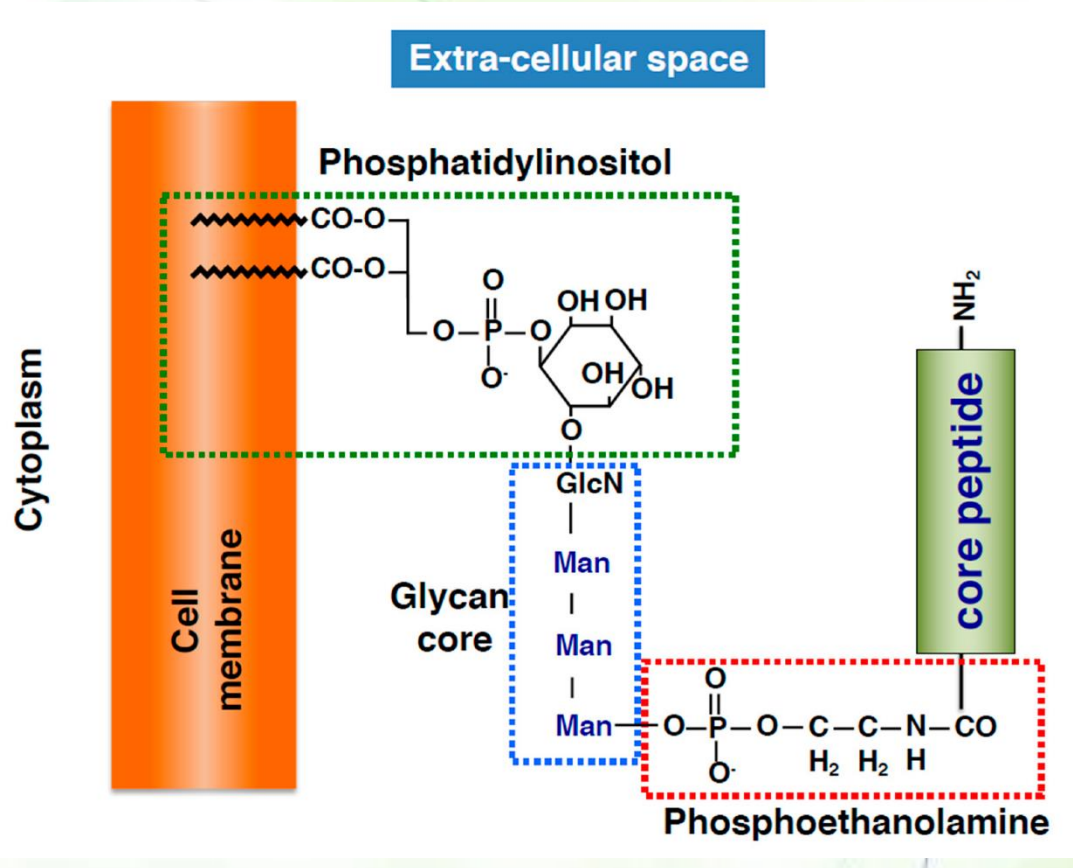
Signaling by PIP2 products



GPI for membrane attachment

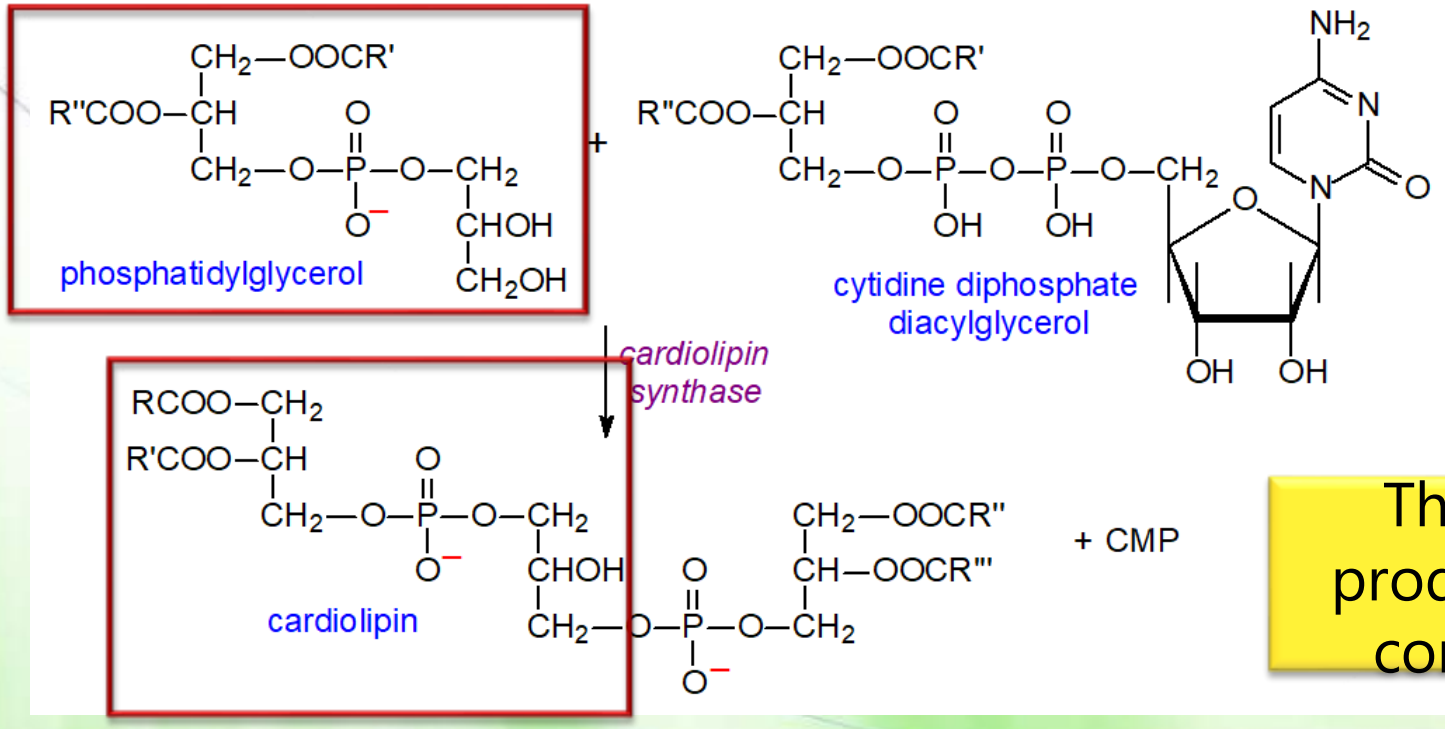
- Glycosyl phosphatidylinositol (GPI) attaches proteins to the plasma membrane.
- Advantage: lateral mobility
  - Example: lipoprotein lipase



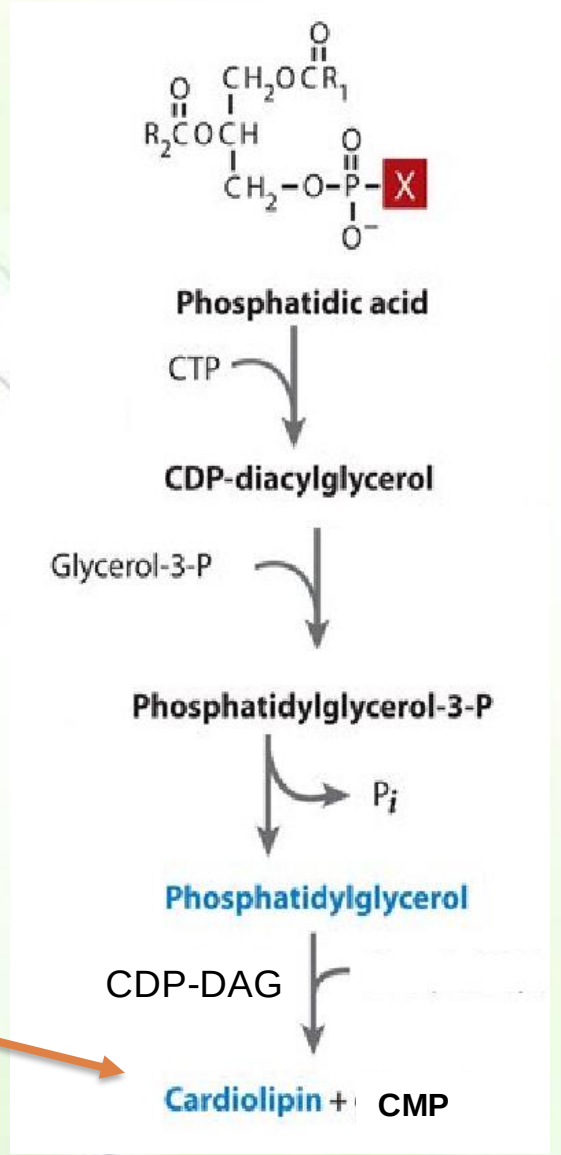


Phosphatidylglycerol and cardiolipin

- 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.



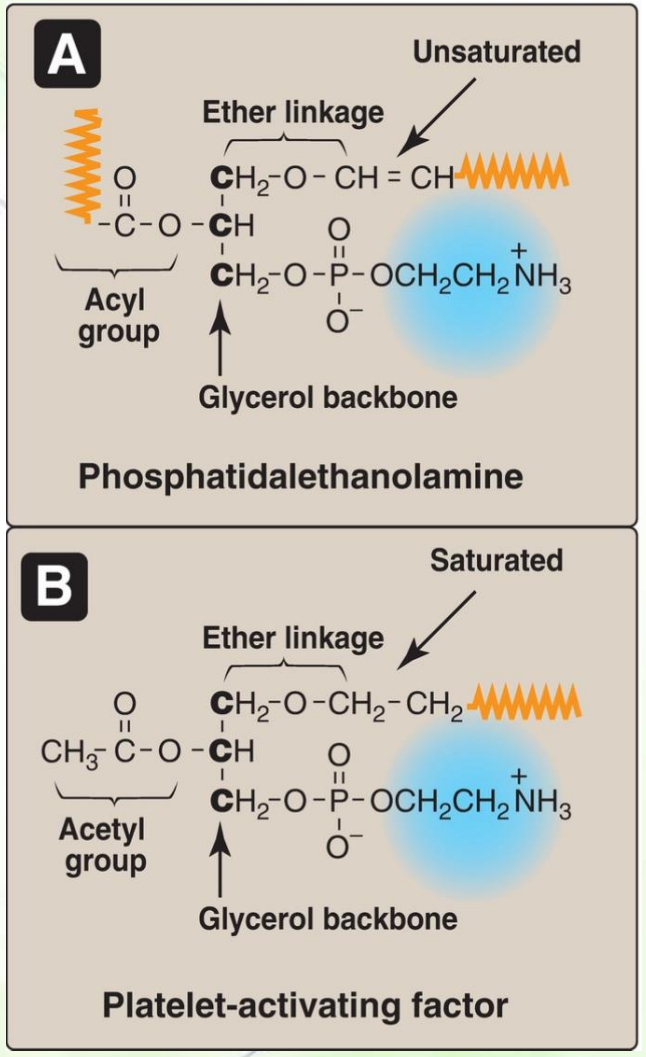
The final products are corrected



Ether glycerophospholipids

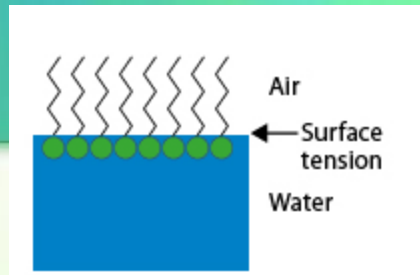
The FA at carbon 1 is replaced by an unsaturated alkyl group attached by an ether linkage.

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

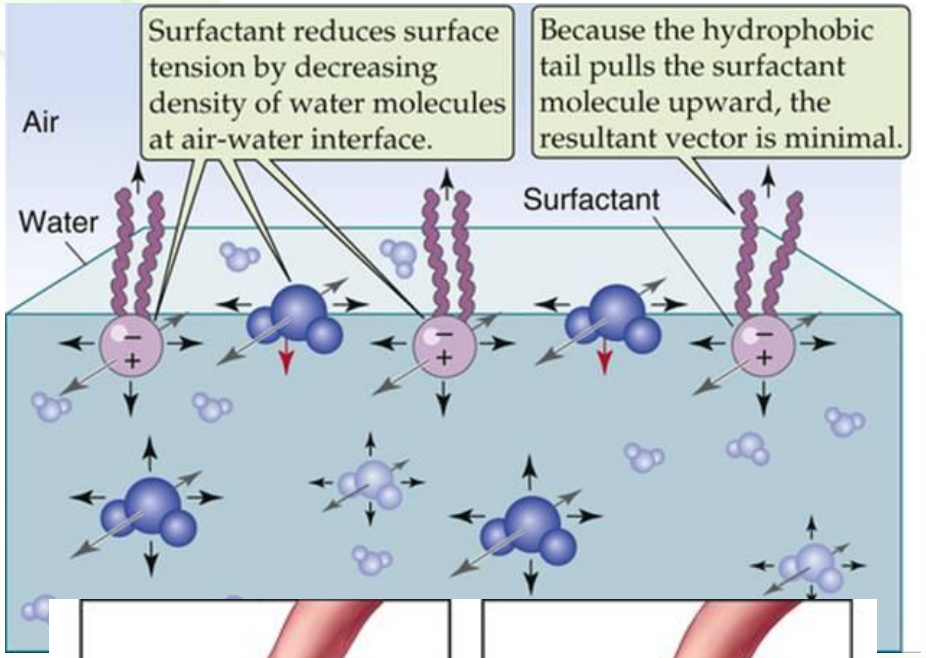


- Platelet-activating factor has a saturated alkyl group in an ether link to carbon 1 and an acetyl residue at carbon 2 of the glycerol backbone.
  - Prothrombotic and inflammatory factor

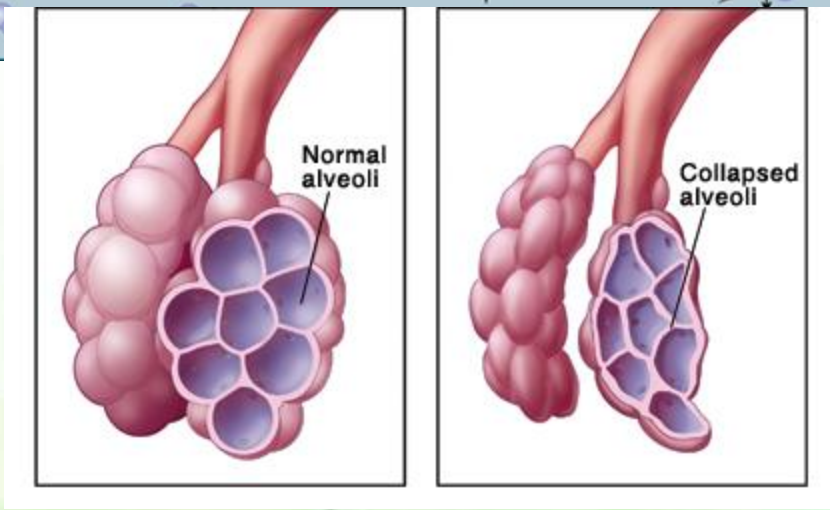
Surfactants



- 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.



Degradation of Phospholipids

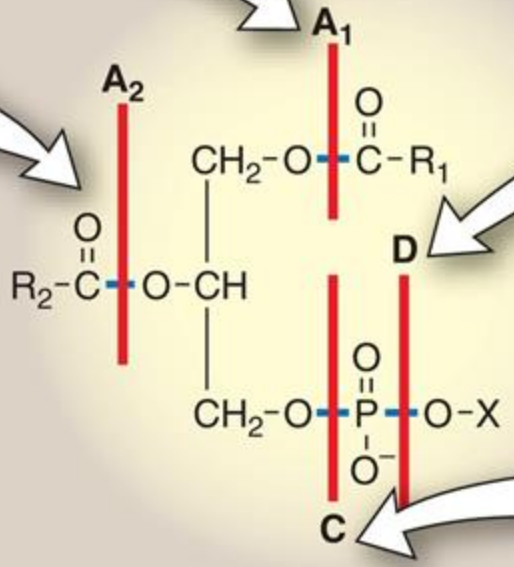
This is different than what's in the textbook

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.

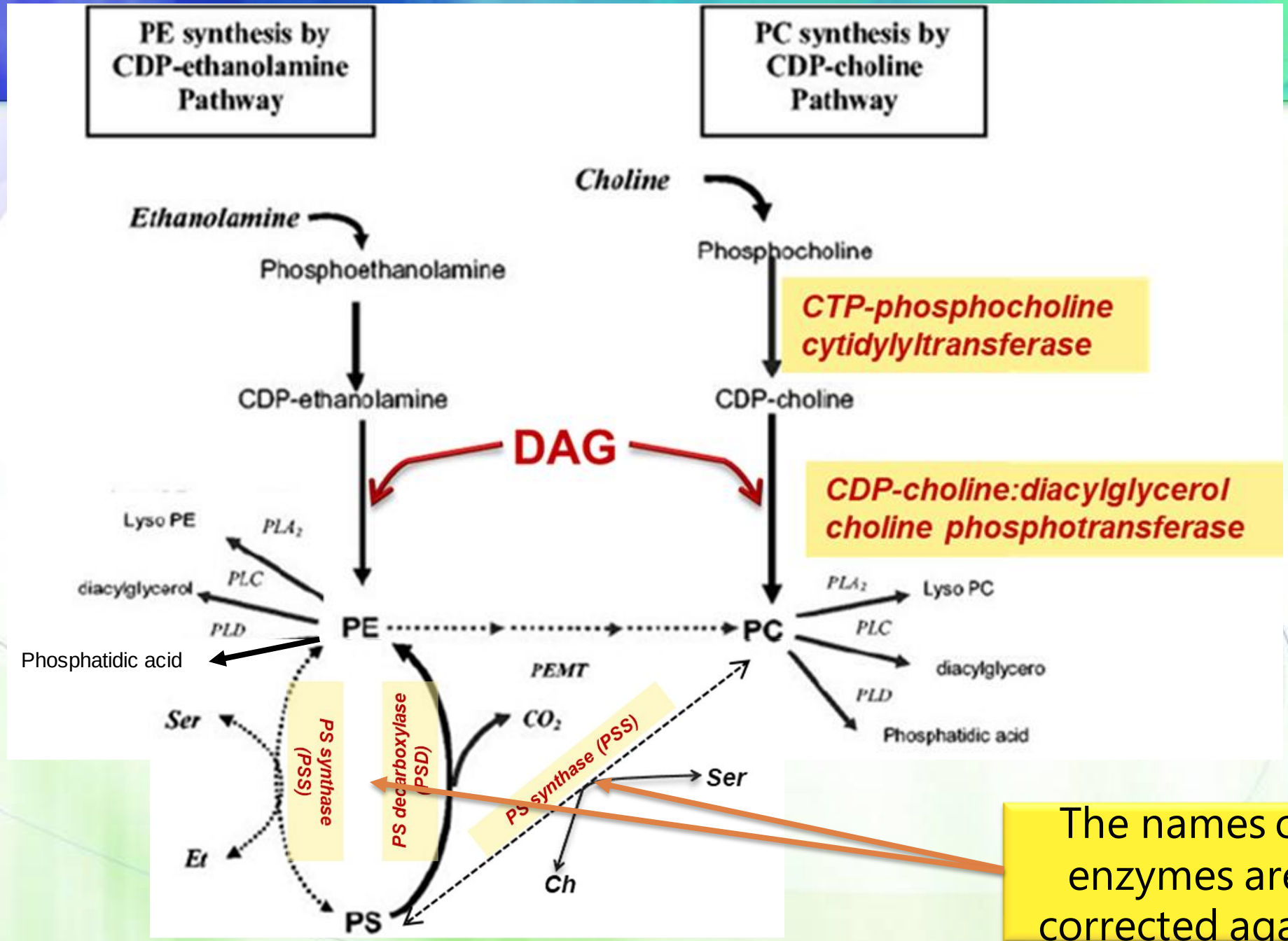


PHOSPHOLIPASE D

- *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 names of enzymes are corrected again