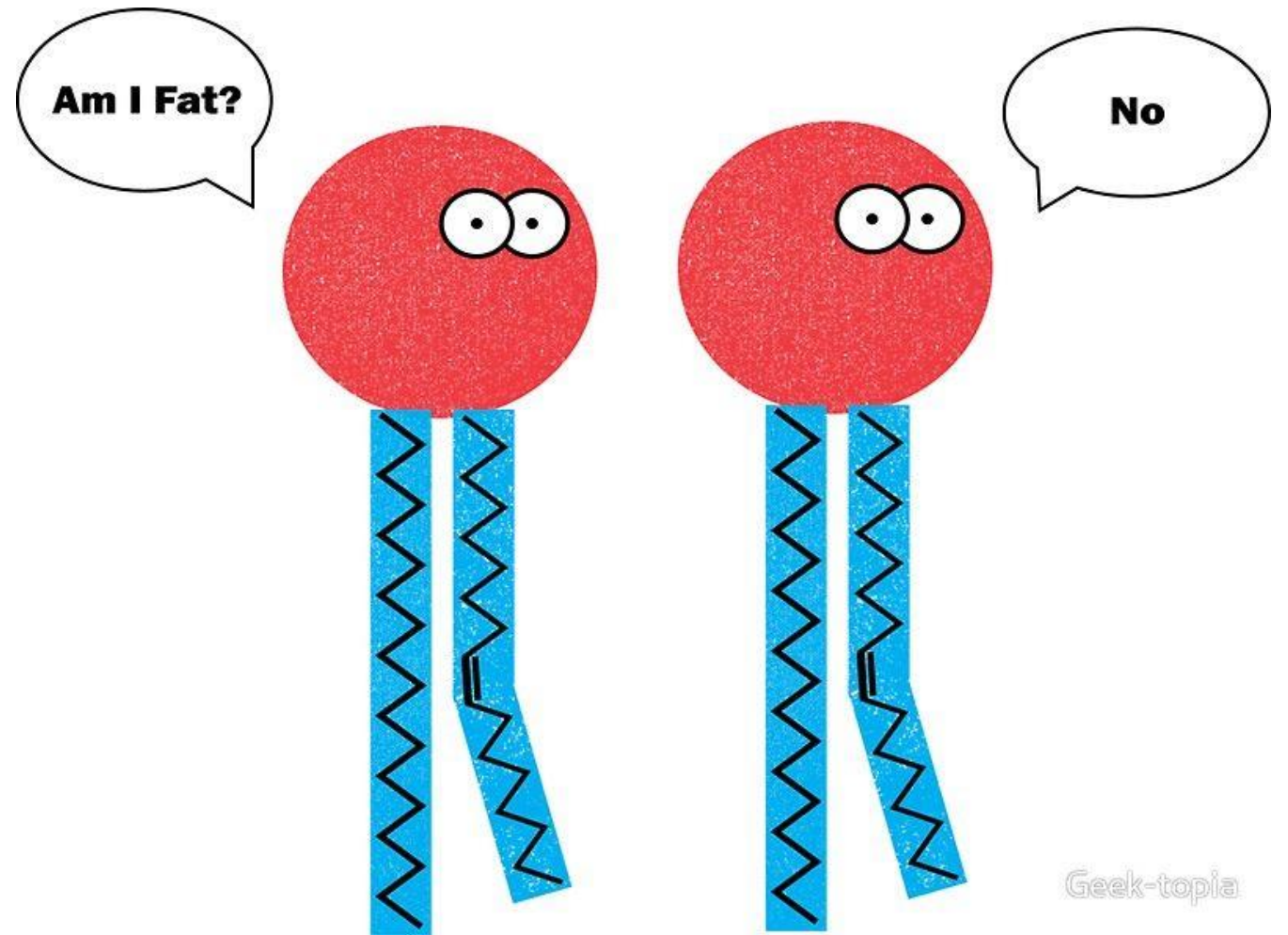


# Metabolism of Glycerophospholipids

Dr. Diala Abu-Hassan

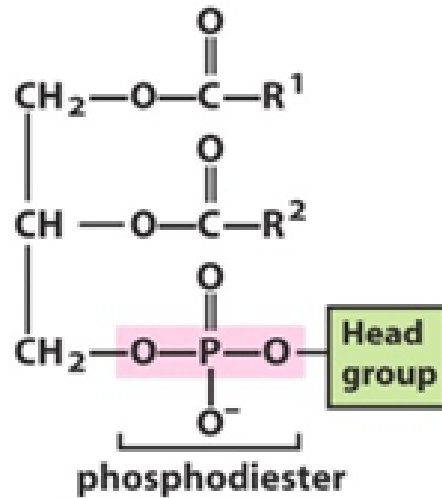
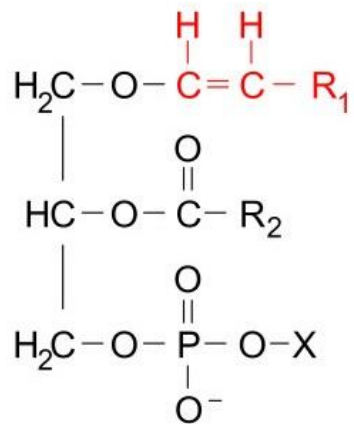
Lippincott's Biochemistry, Ch. 17

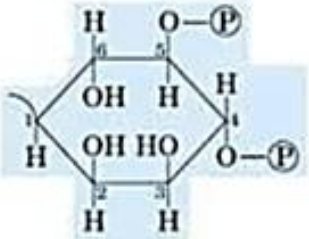


Geek-topia

# Structure and Classification of Glycerophospholipids

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

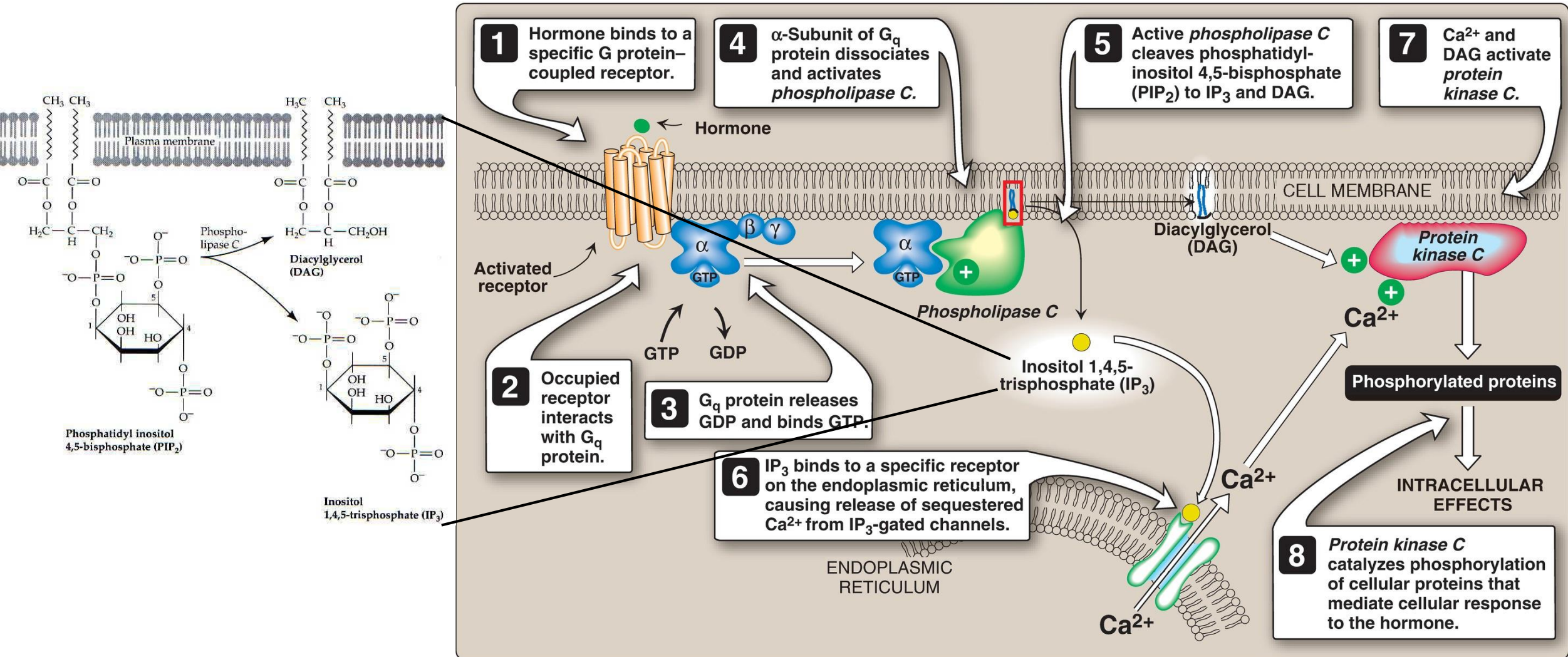


Phosphatidic acid	—	— H
Phosphatidylethanolamine	Ethanolamine	— CH <sub>2</sub> —CH <sub>2</sub> —NH <sub>3</sub> <sup>+</sup>
Phosphatidylcholine	Choline	— CH <sub>2</sub> —CH <sub>2</sub> —N <sup>+</sup> (CH <sub>3</sub> ) <sub>3</sub>
Phosphatidylserine	Serine	— CH <sub>2</sub> —CH(NH <sub>3</sub> <sup>+</sup> )—COO <sup>-</sup>
Phosphatidylglycerol	Glycerol	— CH <sub>2</sub> —CH(OH)—CH <sub>2</sub> —OH
Phosphatidylinositol 4,5-bisphosphate	<i>myo</i> -Inositol 4,5-bisphosphate	
Cardiolipin	Phosphatidylglycerol	$  \begin{array}{c}  \text{CH}_2 \\    \\  \text{CHOH} \\    \\  \text{CH}_2-\text{O}-\text{P}(=\text{O})(\text{O}^-)-\text{O}-\text{CH}_2 \\    \\  \text{CH}-\text{O}-\text{C}(=\text{O})-\text{R}^1 \\    \\  \text{CH}_2-\text{O}-\text{C}(=\text{O})-\text{R}^2  \end{array}  $

# Why do we need to make glycerophospholipids?

Important functions of glycerophospholipids other than their structural function in membranes

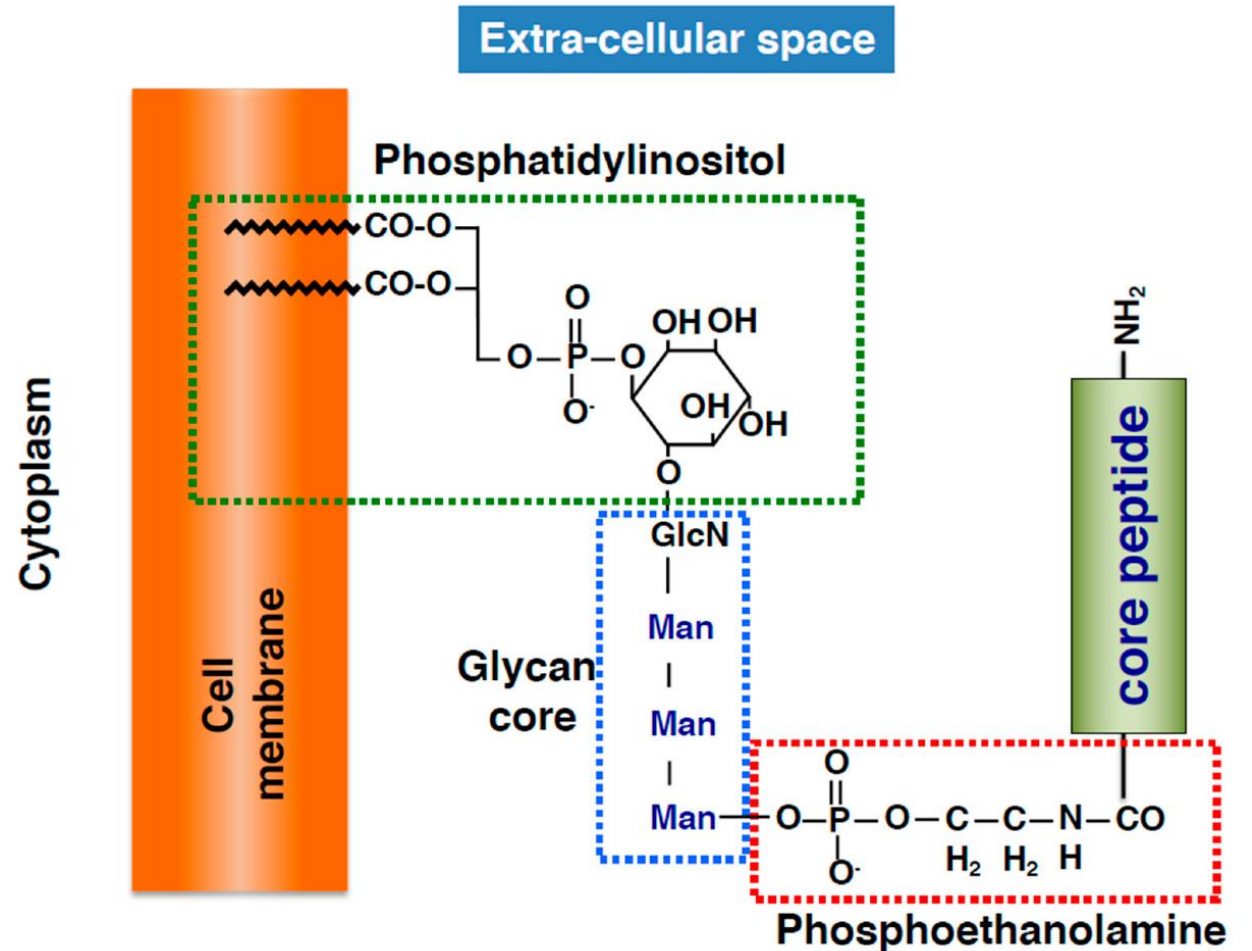
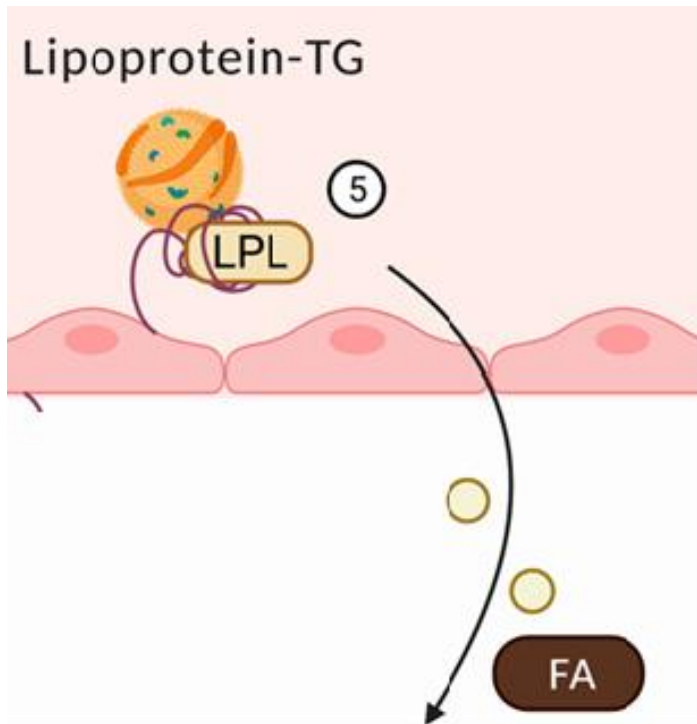
# Signaling by PIP2 products





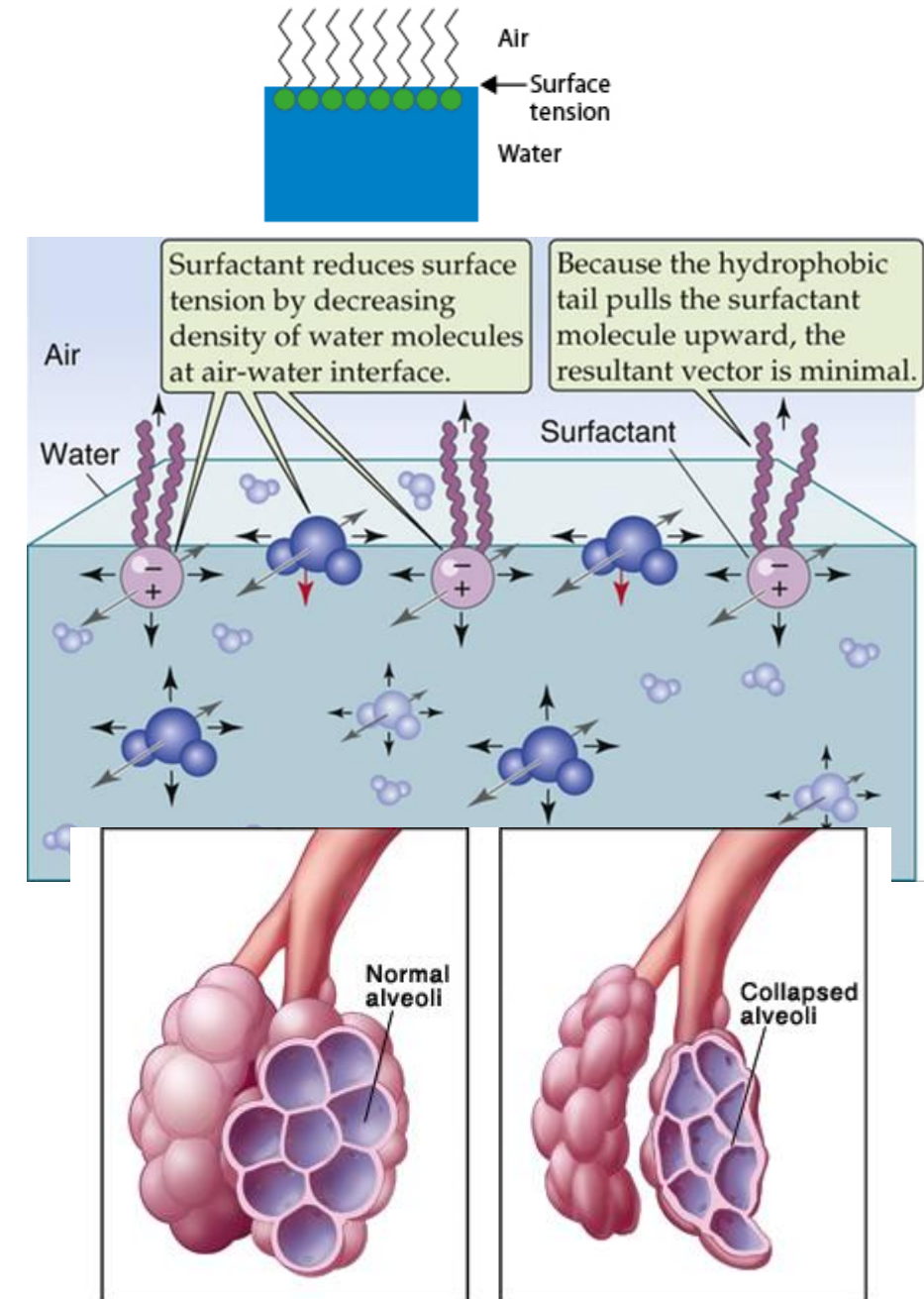
# GPI for membrane attachment

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

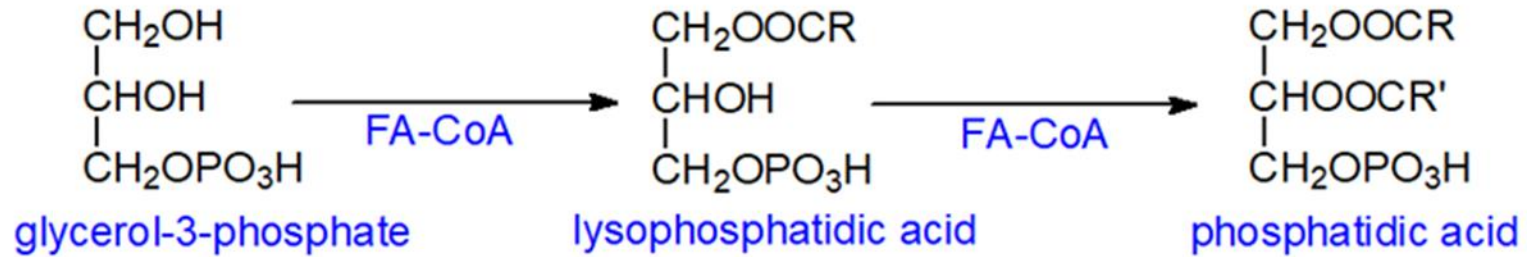


# Application: Surfactants

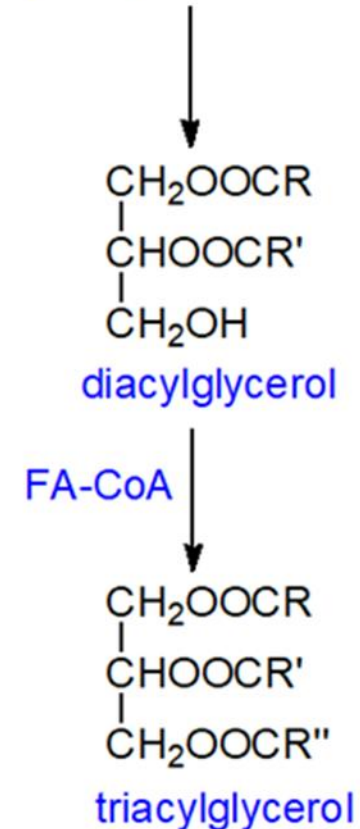
- Surfactants are a complex mixture of lipids (90%) and proteins (10%) that make the extracellular fluid layer lining the alveoli and are secreted by type II pneumocytes in the lungs.
- Dipalmitoylphosphatidylcholine (DPPC) is the major lipid in surfactants.
- Surfactants serve to decrease the surface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



# Synthesis of phosphatidic acid

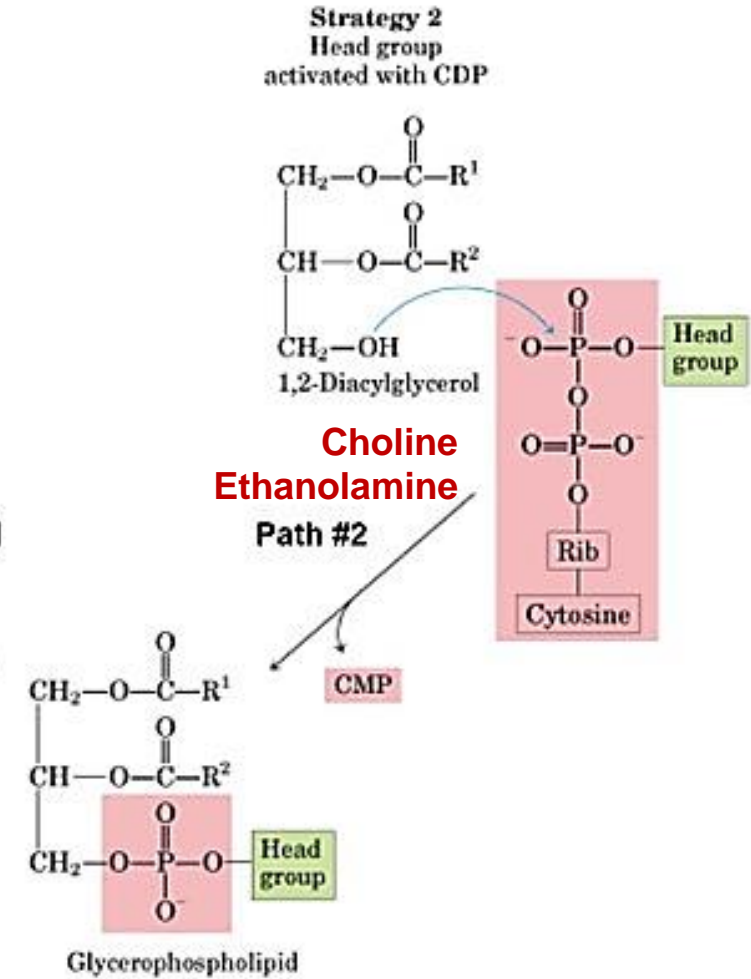
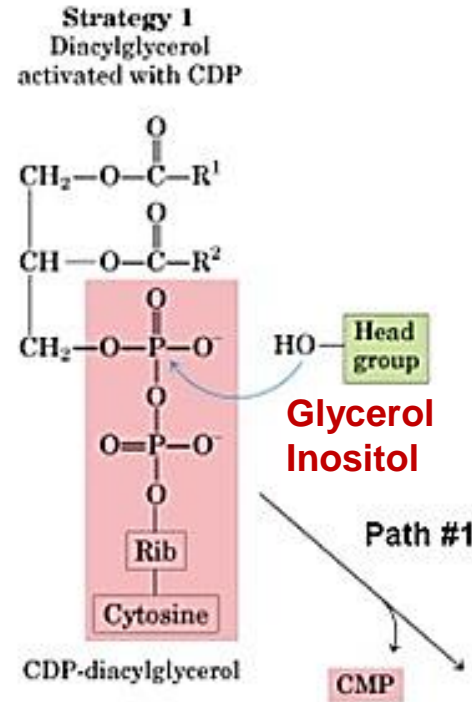
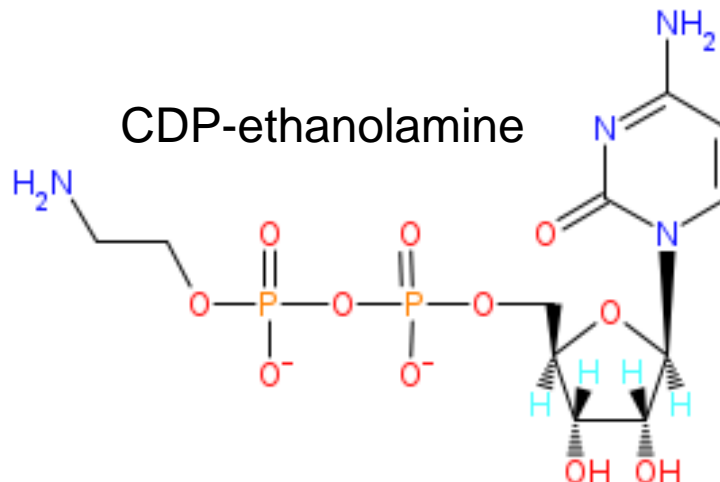
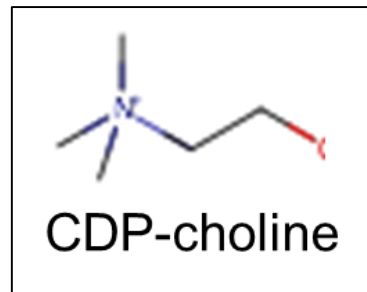


Phosphatidic acid is the precursor of glycerophospholipids.



# Synthesis

- Location: smooth ER
  - Except for ether lipids
- Activation by CDP is necessary. Either:
  - CDP-DAG (glycerol, inositol)
  - CDP-alcohol (choline, ethanolamine)
- Sources of choline and ethanolamine
  - diet
  - synthesis
  - re-cycling from the turnover of pre-existing phospholipids
- Diet is still essential since **demand > supply**





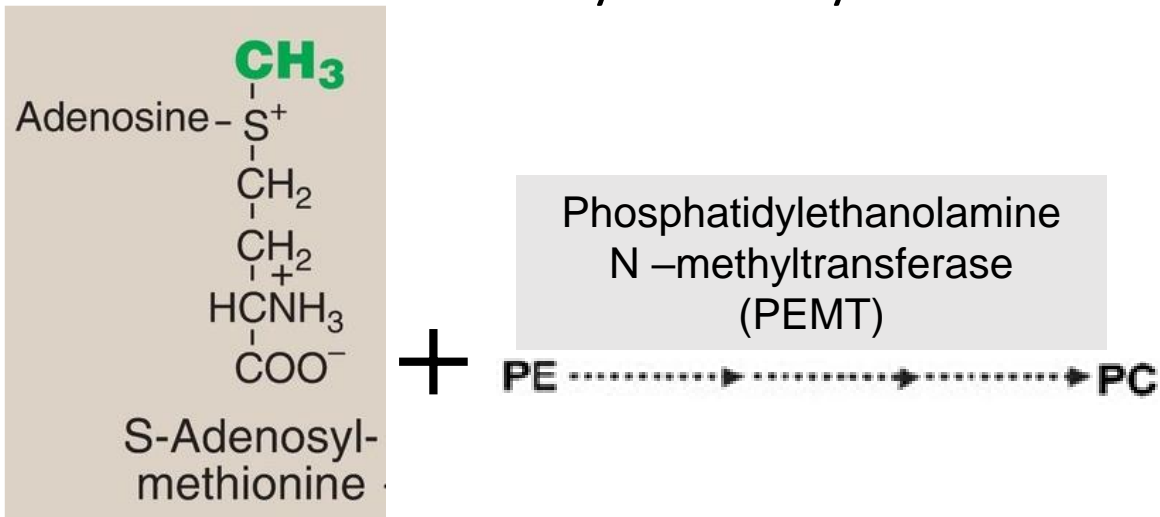
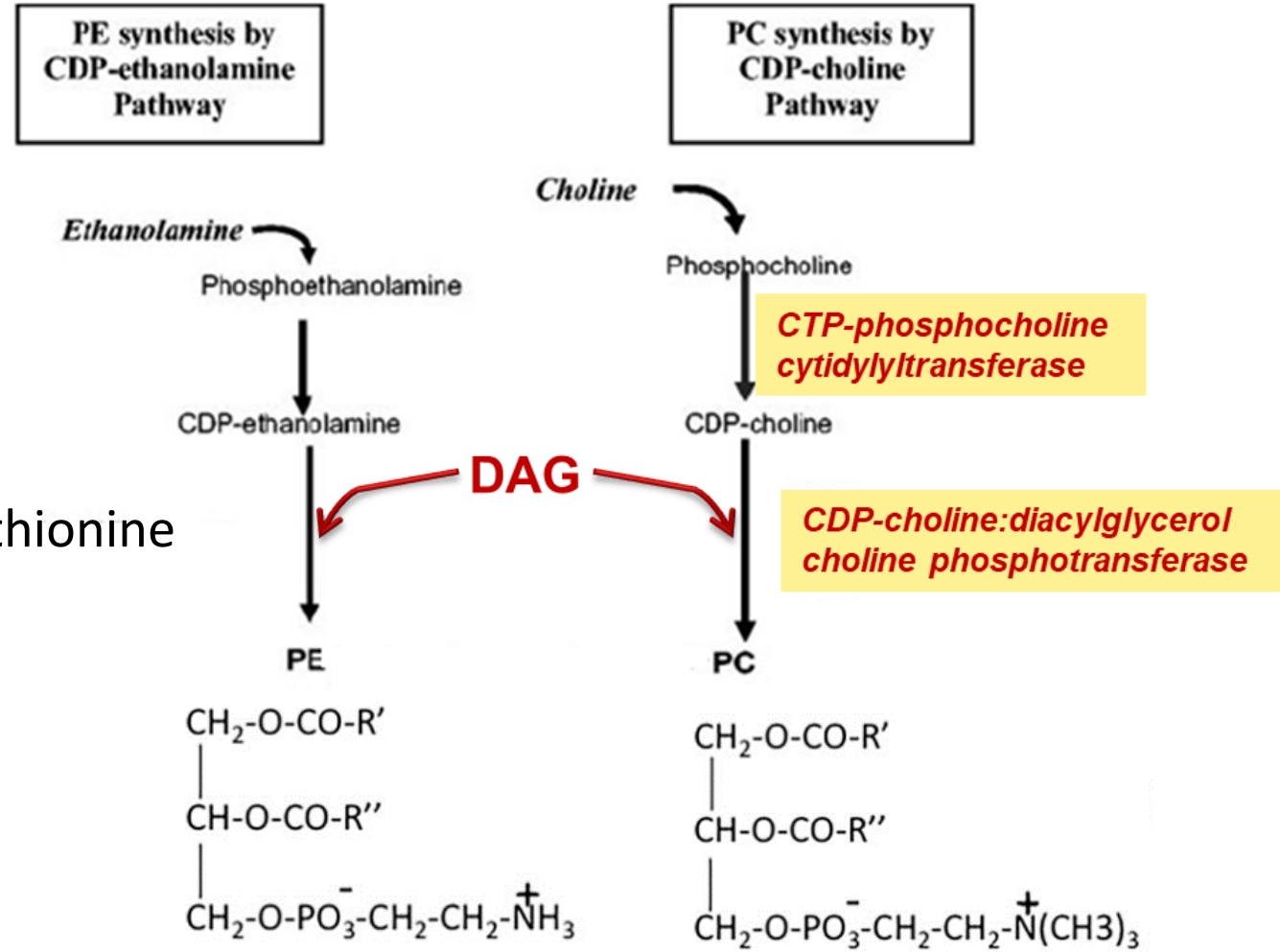
# Synthesis of *ph*-choline and *ph*-ethanolamine

- 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.

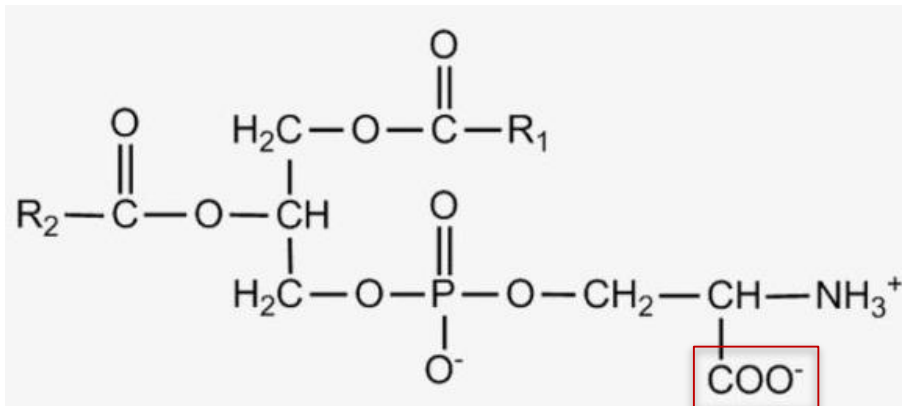
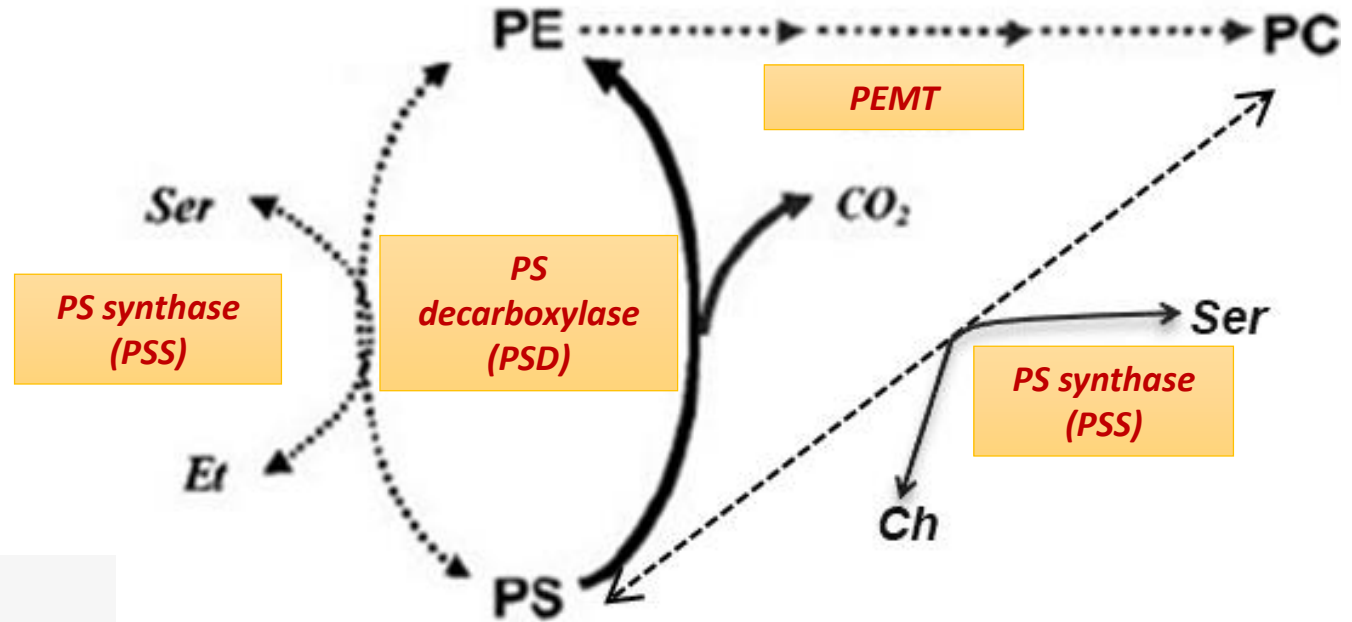
## ➤ Synthesis of *ph*-choline from *ph*-ethanolamine

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



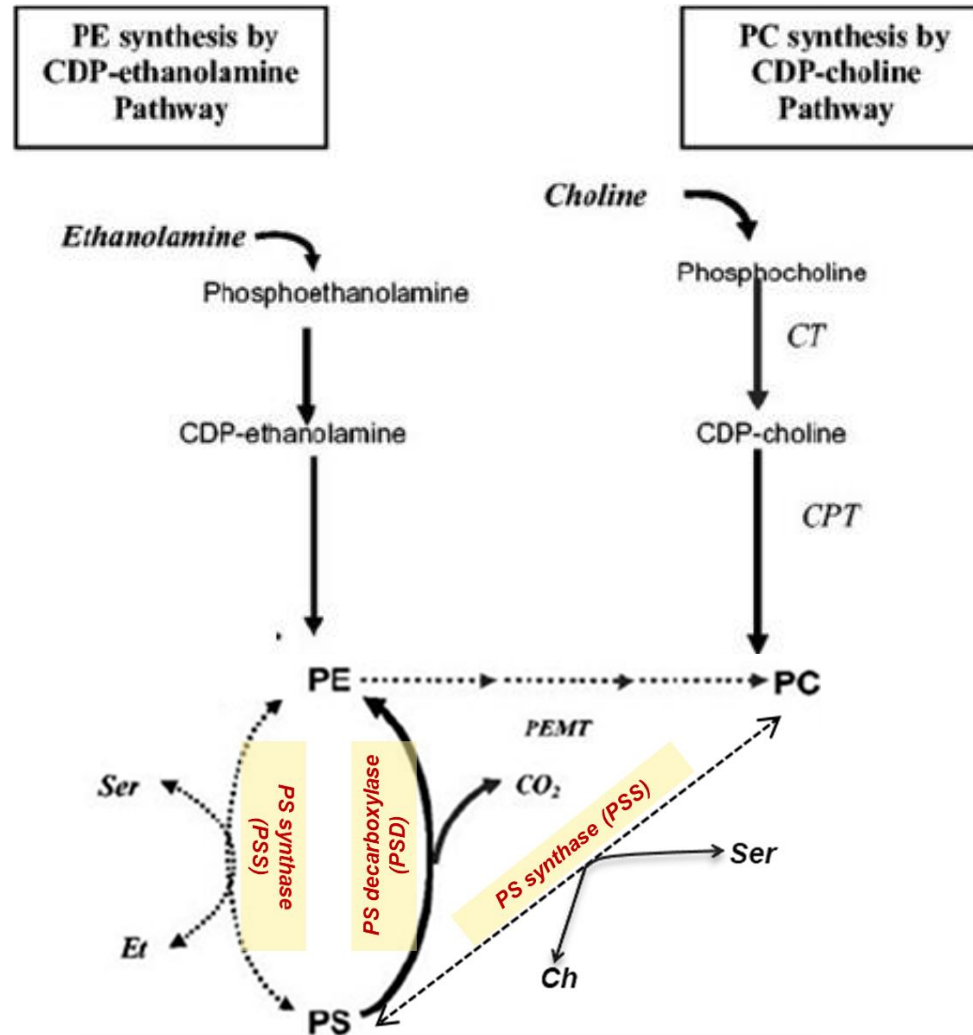
# Synthetic pathways for and from ph-serine

- 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). It can be methylated by PEMT to PC
- PS is exchanged from PE or PC by PS synthases (PSS).



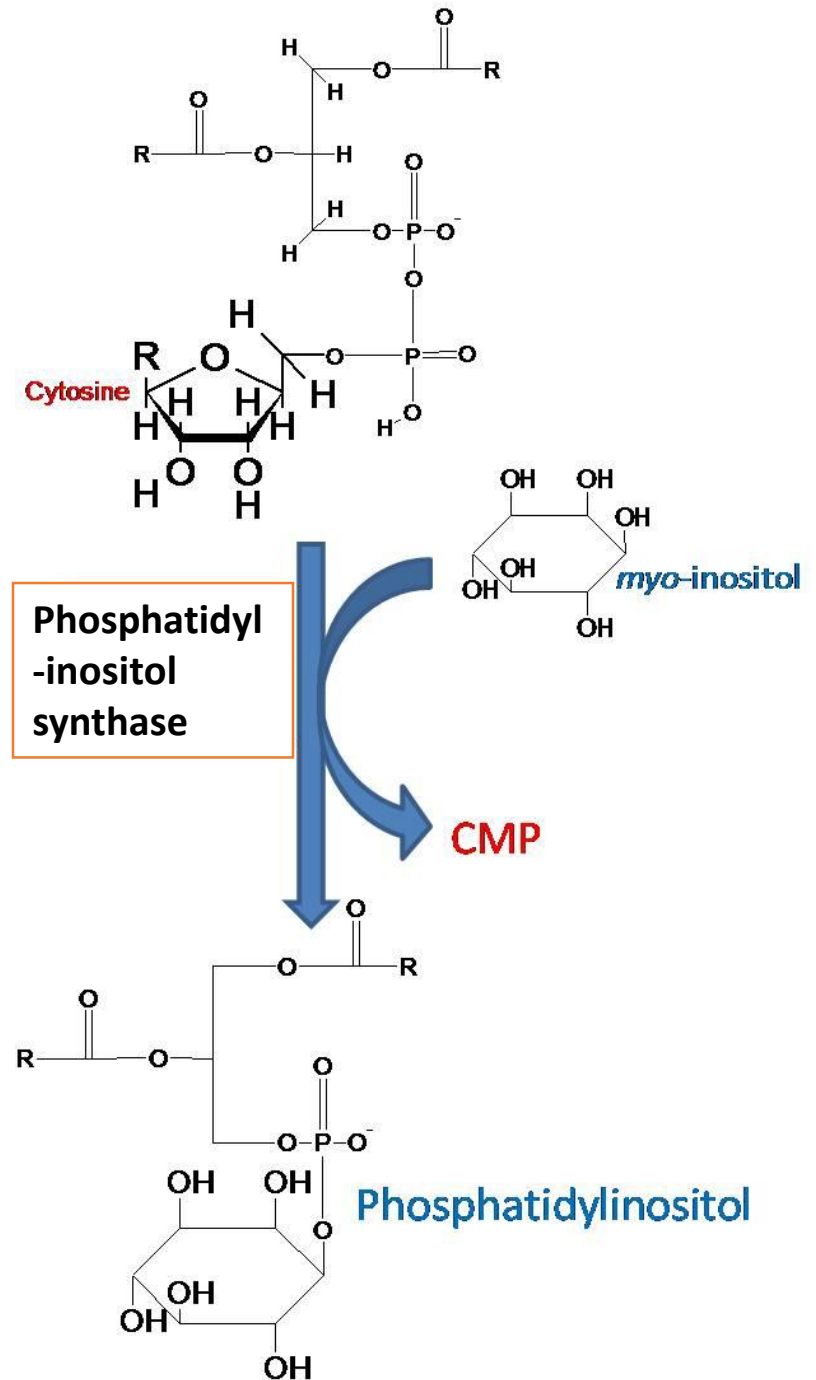
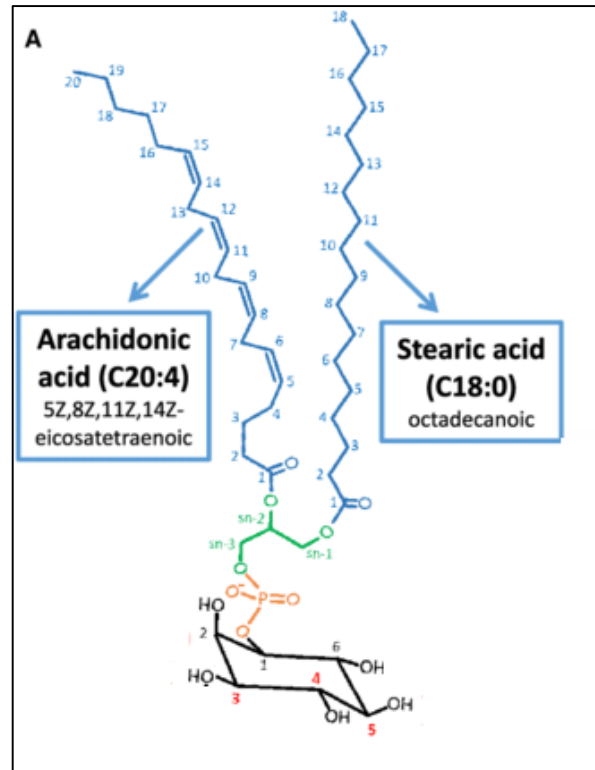
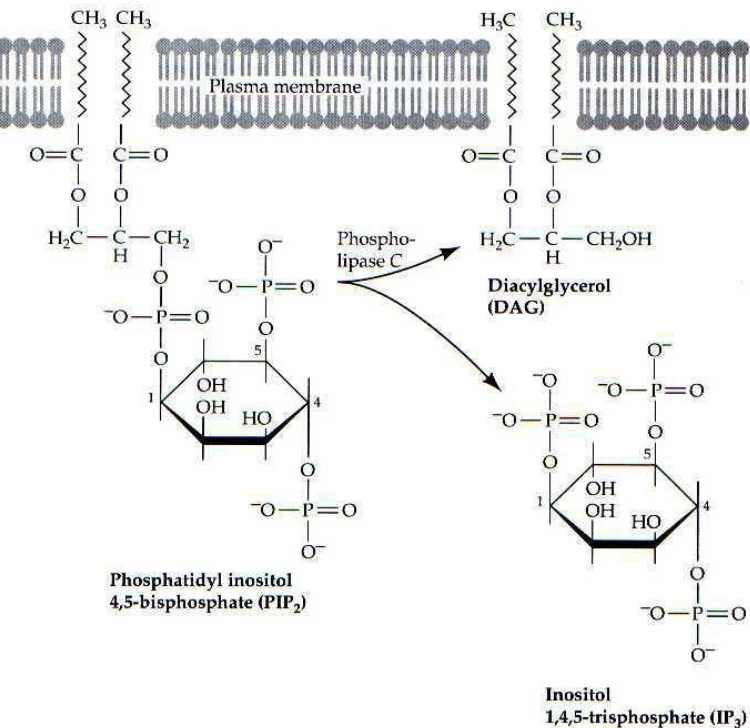
phosphatidylserine

# Summary of synthesis of PE, PC, and PS



# Synthesis of ph-inositol

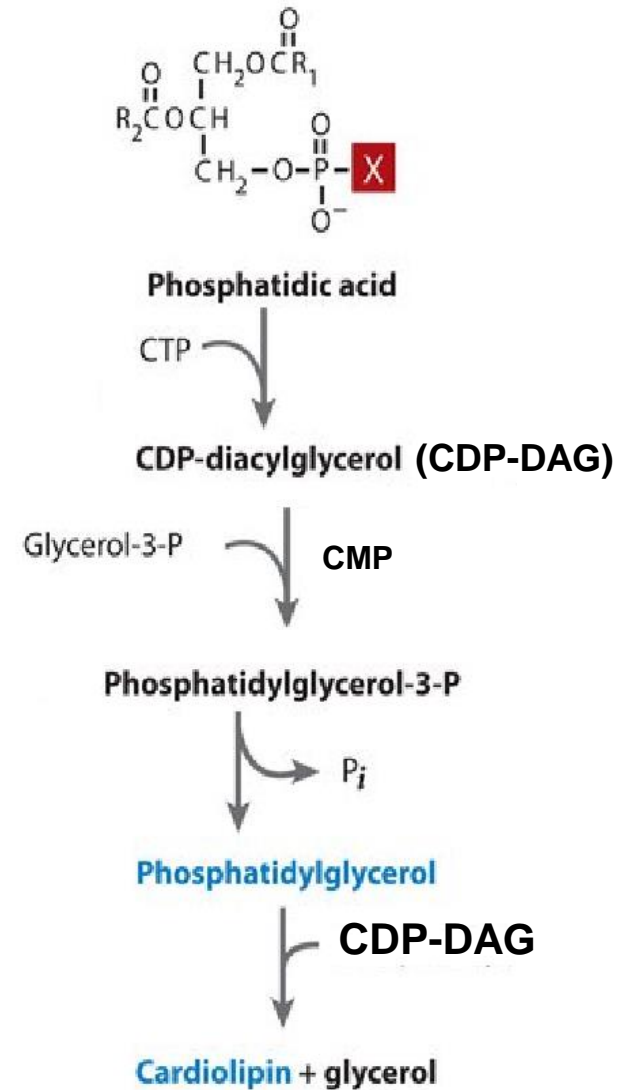
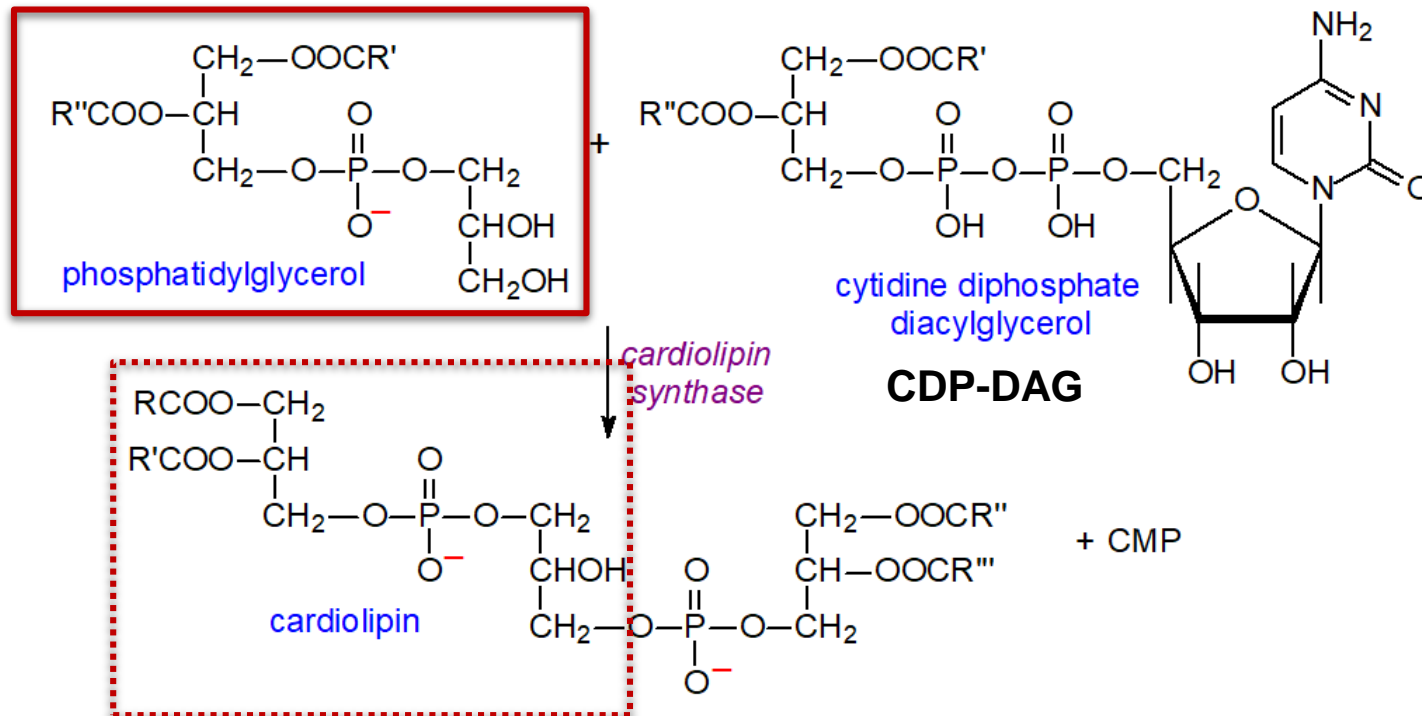
- Inositol is combined with CDP-DAG by PI synthase to produce phosphatidylinositol.
- It is a reservoir of arachidonate.
- It also produces signaling molecules when cleaved by phospholipase C.





# Phosphatidylglycerol and cardiolipin

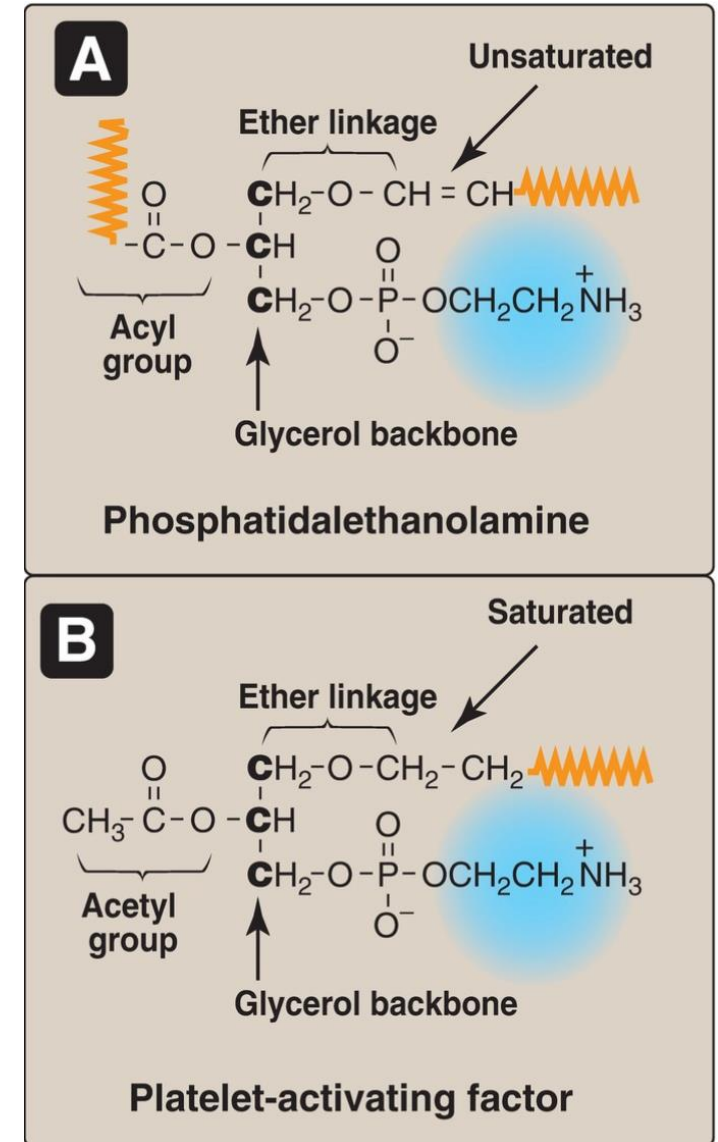
- Phosphatidylglycerol is synthesized from CDP-DAG and glycerol 3-phosphate.
- Cardiolipin is synthesized by the transfer of DAG from CDP-DAG to a pre-existing molecule of phosphatidylglycerol.



# Ether glycerophospholipids

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

- Plasmalogens: Phosphatid<sup>A</sup>ethanolamine (abundant in nerve tissue, is similar in structure to phosphatid<sup>y</sup>ethanolamine.
  - Phosphatid<sup>a</sup>choline (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



# Degradation of Phospholipids

## PHOSPHOLIPASE $A_2$

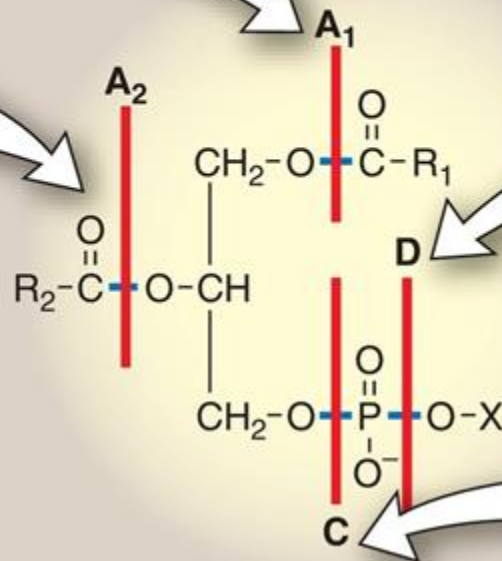
- *Phospholipase A<sub>2</sub>* is present in many mammalian tissues and pancreatic juice. It is also present in snake and bee venoms.
- Pancreatic secretions are especially rich in the *phospholipase A<sub>2</sub>* proenzyme, which is activated by *trypsin* and requires bile salts for activity.
- *Phospholipase A<sub>2</sub>*, acting on phosphatidylinositol, releases arachidonic acid (the precursor of the eicosanoids).
- *Phospholipase A<sub>2</sub>* is inhibited by glucocorticoids (for example, cortisol).

## PHOSPHOLIPASE $A_1$

- *Phospholipase A<sub>1</sub>* 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  $\alpha$ -toxin of clostridia and other bacilli.
- Membrane-bound *phospholipase C* is activated by the PIP<sub>2</sub> system and, thus, plays a role in producing second messengers.