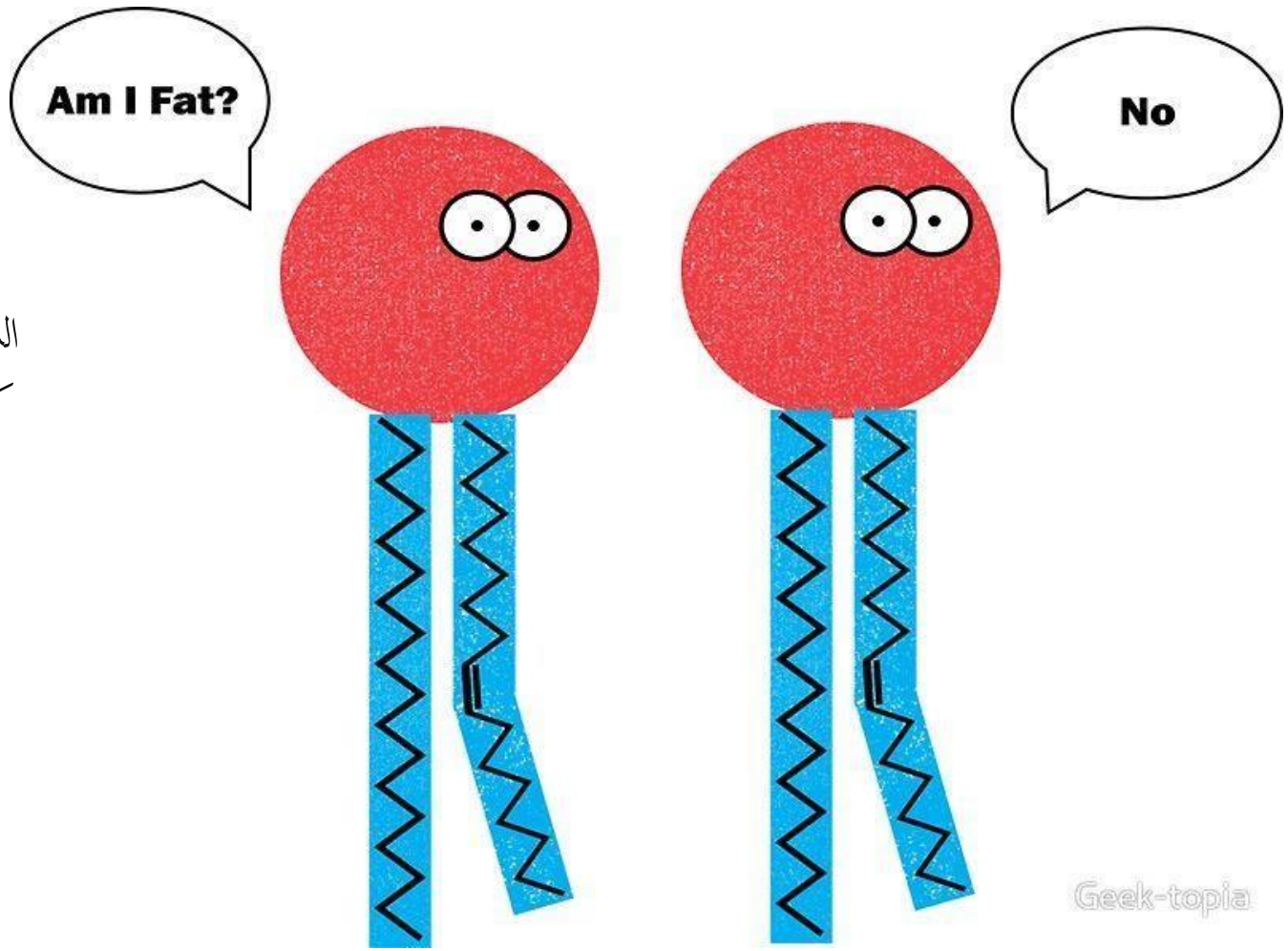
Metabolism of Glycerophospholipids



اللهم اجعل دراستي هذه طريقًا إلى العلم النافع والرزق الطيب، وسهل لي فيها كل صعب، ووفقني لما تحب وترضى، واجعلها سببًا في رفع درجاتي في الدنيا والآخرة، اللهم يا مُيسر الأمور، يسر لي دراستي، ووفقني لفهم ما أتعلمه، واجعلني من المتميزين في علمي وع عملي. اللهم لا سهل إلا ما جعلته سهلًا، وأنت تجعل الحزن إذا شئت سهلًا

Dr. Diala Abu-Hassan

Lippincott's Biochemistry, Ch. 17

Done by Leen Mamoon

Structure and Classification of Glycerophospholipids

1. Glycerol Backbone

2. Fatty Acid Chains

· Carbon 1 of the glycerol is connected to the first fatty acid via an ester bond.

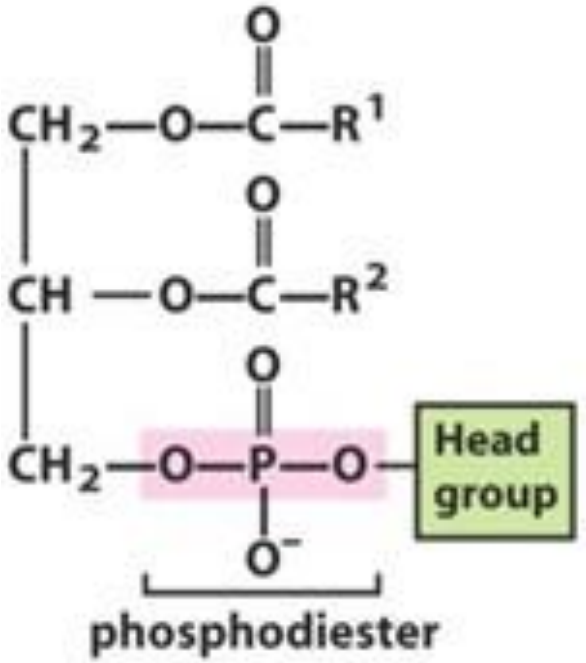
· Carbon 2 of the glycerol is connected to the second fatty acid via another ester bond.

3. Phosphate Group

· Carbon 3 of the glycerol is attached to a phosphate group.

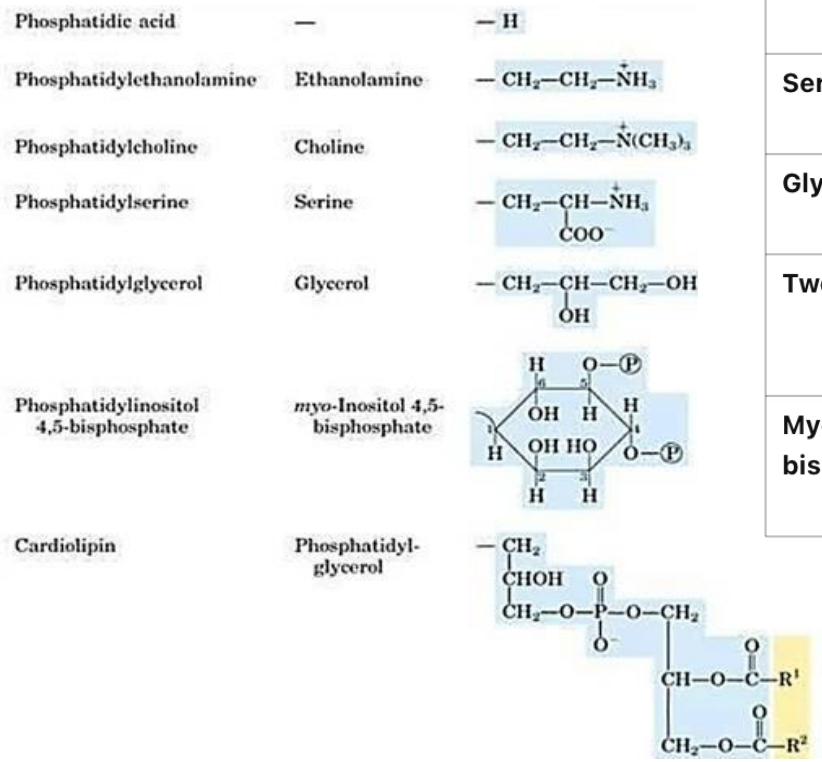
4. Head Group

The phosphate group is linked to a head group through a phosphodiester bond.
The head group can vary and determines the specific type of glycerol phospholipid…



Structure and Classification of Glycerophospholipids

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

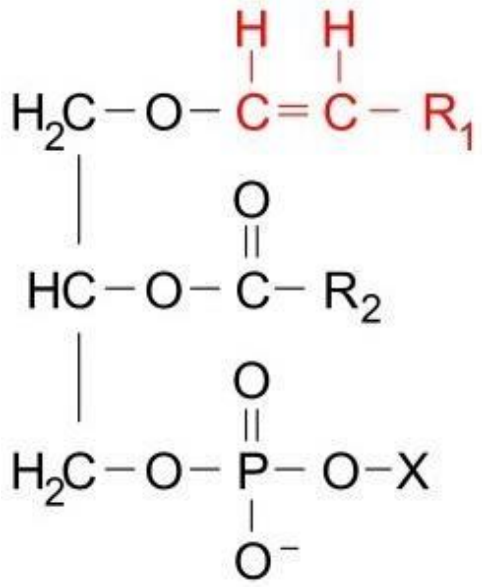


Types of Glycerol Phospholipids Based on the Head Group:

Head Group	Molecule Name	Description
Hydrogen	**Phosphatidic Acid**	Parent molecule of glycerophospholipids.
Choline	**Phosphatidylcholine**	Carbon-carbon chain connected to nitrogen, with three methyl groups.
Ethanolamine	**Phosphatidylethanolamine**	Hydrogens replace carbons in the choline group.
Serine (amino acid)	**Phosphatidylserine**	Contains the amino acid serine as the head group.
Glycerol	**Phosphatidylglycerol**	Another glycerol molecule serves as the head group.
Two Phosphatidic Acids	**Cardiolipin**	Two phosphatidic acid molecules attached to one glycerol molecule.
Myo-inositol 4,5-bisphosphate	**Phosphatidyl Myo-inositol 4,5-bisphosphate (PIP2)**	Contains myo-inositol as the head group, phosphorylated at positions 4 and 5.

- Plasmalogens

- ✓ **Some molecules are structurally similar to glycerophospholipids but differ in one key aspect.**
- ✓ **On carbon number one, instead of a fatty acid attached via an ester bond, a hydrocarbon group is attached via an ether bond.**
- ✓ **These molecules are called plasmalogens, a specific variation within this group.**

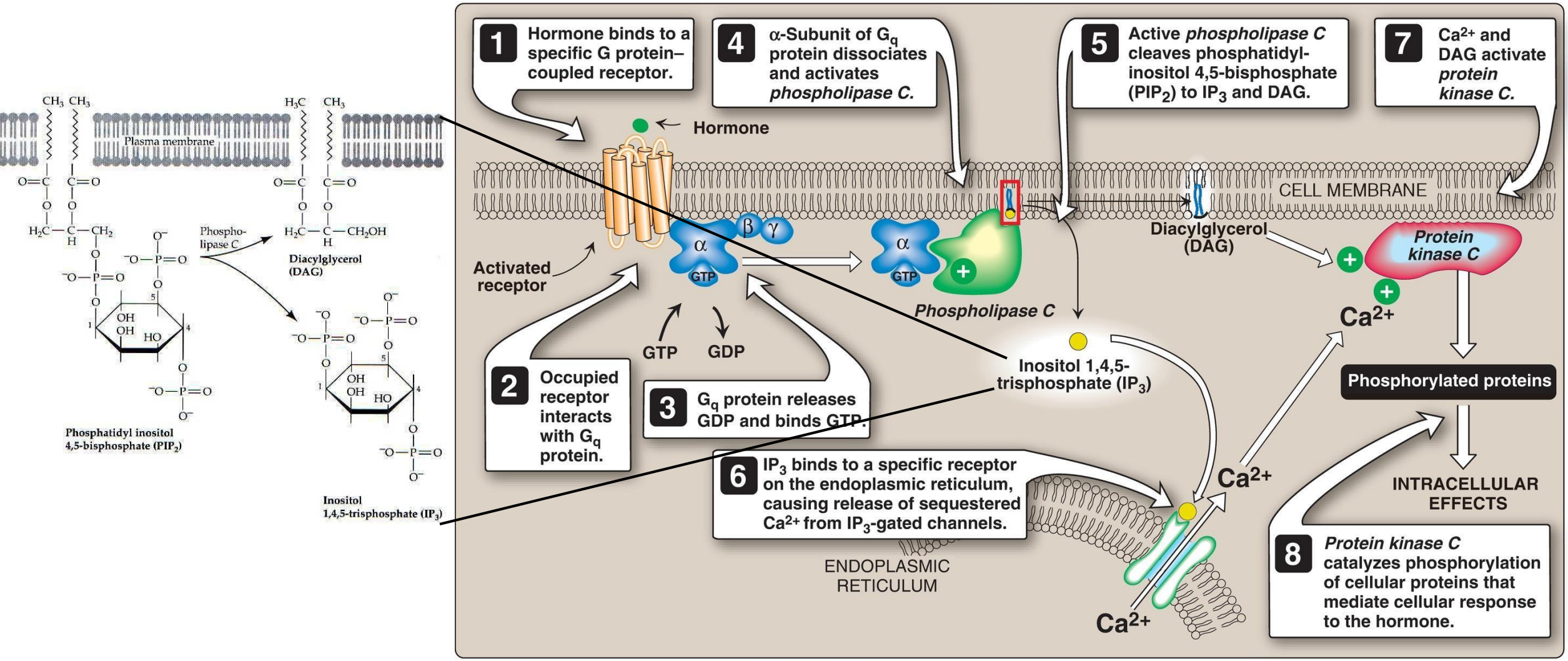


Why do we need to make glycerophospholipids?

- ✓ **1) Glycerophospholipids are crucial for the synthesis of membranes as they are major components of cellular membranes.**
- ✓ **They are more common than other molecules like sphingolipids.**
- ✓ **These lipids not only form structural components of membranes but also perform other cellular functions.**

Important functions of glycerophospholipids other than their structural function in membranes

2) Signaling by PIP2 products



Signaling by PIP2 Products (Phosphatidylinositol 4,5-bisphosphate)

1. Initial Hormone Binding and Activation:
A hormone / growth factor binds to a specific G-protein coupled receptor (GPCR) on the cell membrane.

2&3 .Receptor Activation and G-protein Interaction:

- ✓ The receptor interacts with the inactive G-protein (which is bound to GDP).
- ✓ The receptor activation causes the α-subunit to release GDP and bind GTP instead.
- ✓ This exchange triggers the dissociation of the α-subunit from the βγ complex, activating the G-protein.

In addition to the adenylyl cyclase pathway activated by G-protein coupled receptors (GPCRs), there is another way to activate this signaling pathway, which involves the activation of phospholipase C (PLC).

4. Activation of Phospholipase C:

Phospholipase C is an enzyme that catalyzes the breakdown of phospholipids in the membrane.

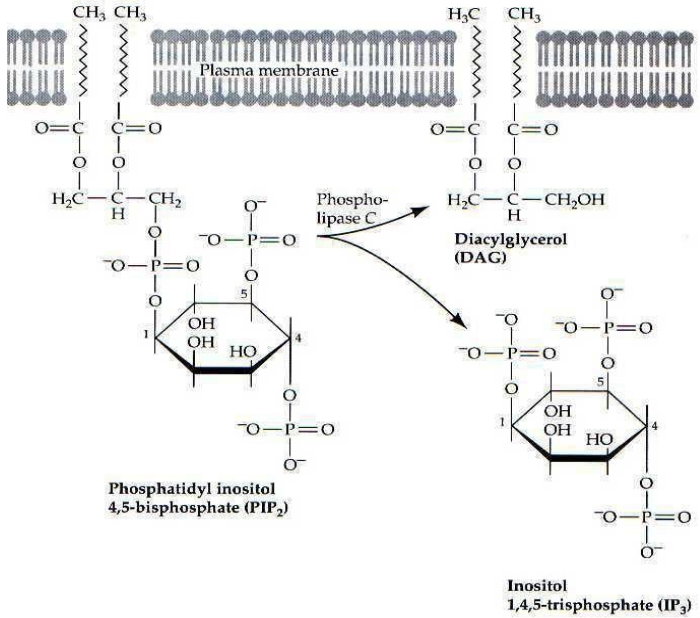
5. Cleavage of PIP2:

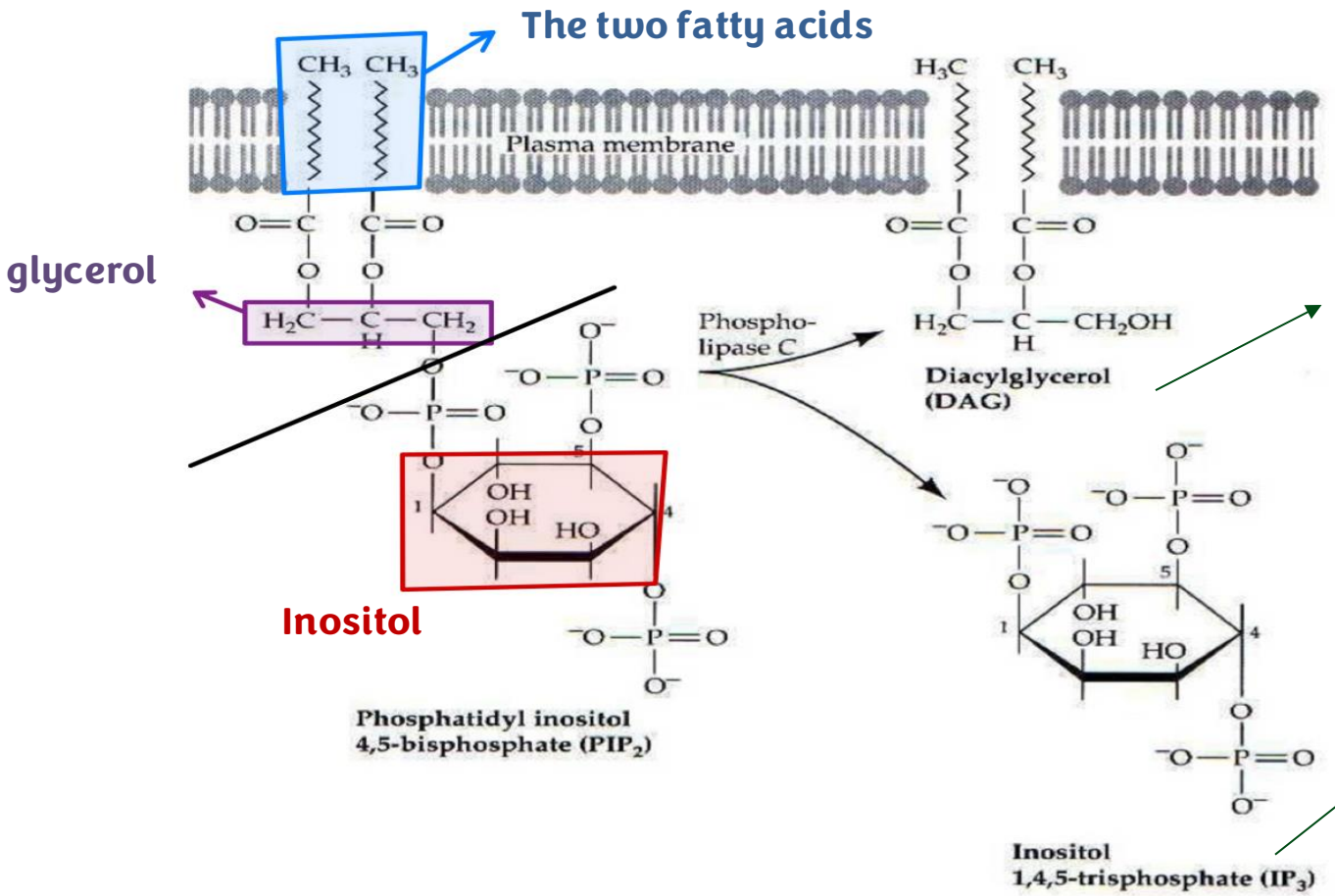
In this process, phospholipase C specifically cleaves PIP2), a phospholipid present in the cell membrane.

When cleaved, PIP2 produces two important secondary messengers:

· Inositol 1,4,5-trisphosphate (IP3)

· Diacylglycerol (DAG)





DAG (Diacylglycerol) is a lipid that inserts into the cell membrane due to the hydrophobic nature of its fatty acid chains.

- ✓ three phosphate groups attached to the inositol ring
- ✓ IP3 is highly hydrophilic, with negative charges and polar groups, which make it interact well with water-based environments. This makes it an effective second messenger.

687 -

Role of IP3:

· IP3 travels to the (ER), where it binds to specific IP3 gated channels , causing the release of Ca2+ ions from the ER into the cytoplasm.

Role of DAG:

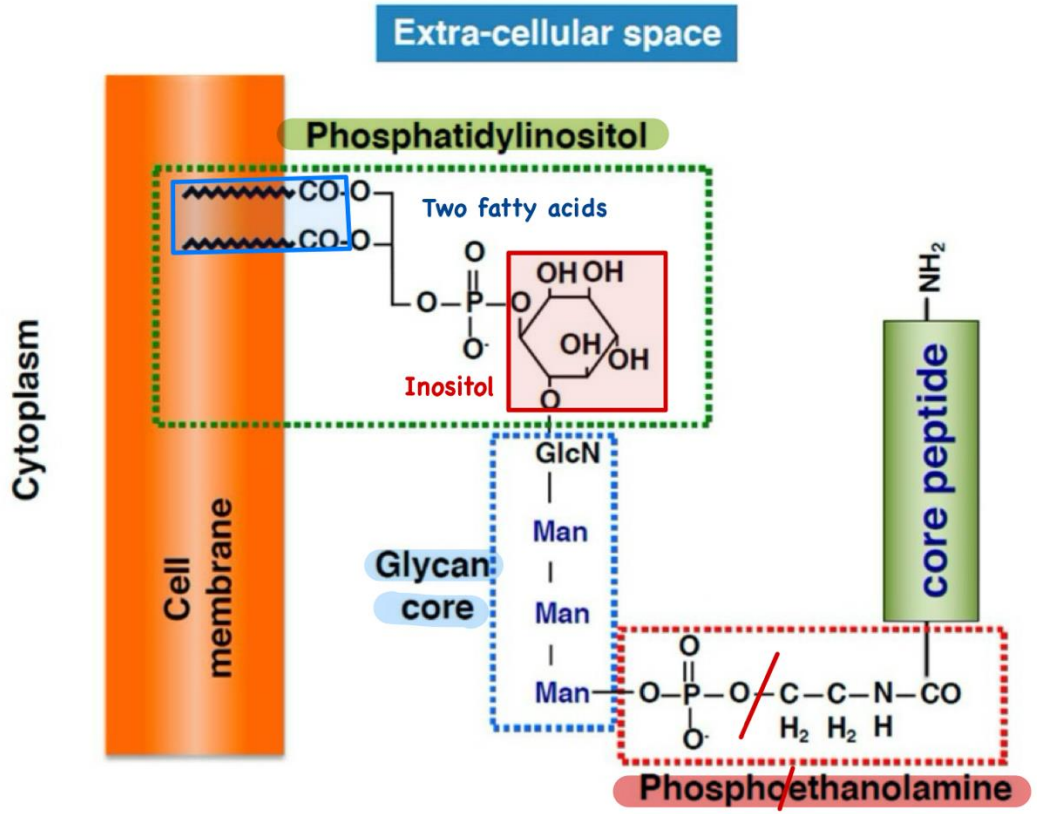
· DAG, which remains embedded in the cell membrane, works alongside the released Ca2+ to activate protein kinase C (PKC).

8.Activation of PKC:

· PKC then phosphorylates target proteins within the cell, leading to various cellular responses in response to the hormone or signal.

3) GPI for membrane attachment/Anchoring

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



· **Phosphatidylinositol is linked to the glycan core.**

· **Glycan core (peptide) is linked to phosphoethanolamine.**

· **Phosphoethanolamine is linked to the core peptide.**

Importance of GPI Anchoring:

1. Strong Attachment :

· The covalent bond between the GPI anchor and the protein provides a strong attachment of the protein to the cell membrane.

· This covalent attachment ensures stability and prevents the protein from detaching under normal cellular conditions.

2. Providing Flexibility and Mobility:

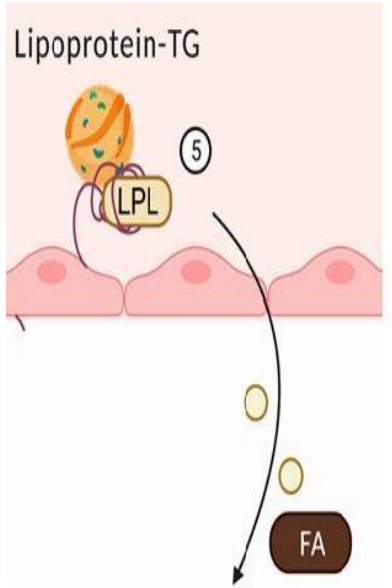
· Unlike integral membrane proteins, which move laterally within the membrane, GPI-anchored proteins can rotate 180° within the membrane.

· The anchoring of the protein through the GPI structure provides greater flexibility, allowing the protein to switch between different functional forms and locations within the cell membrane.

Example: Lipoprotein Lipase (LPL):

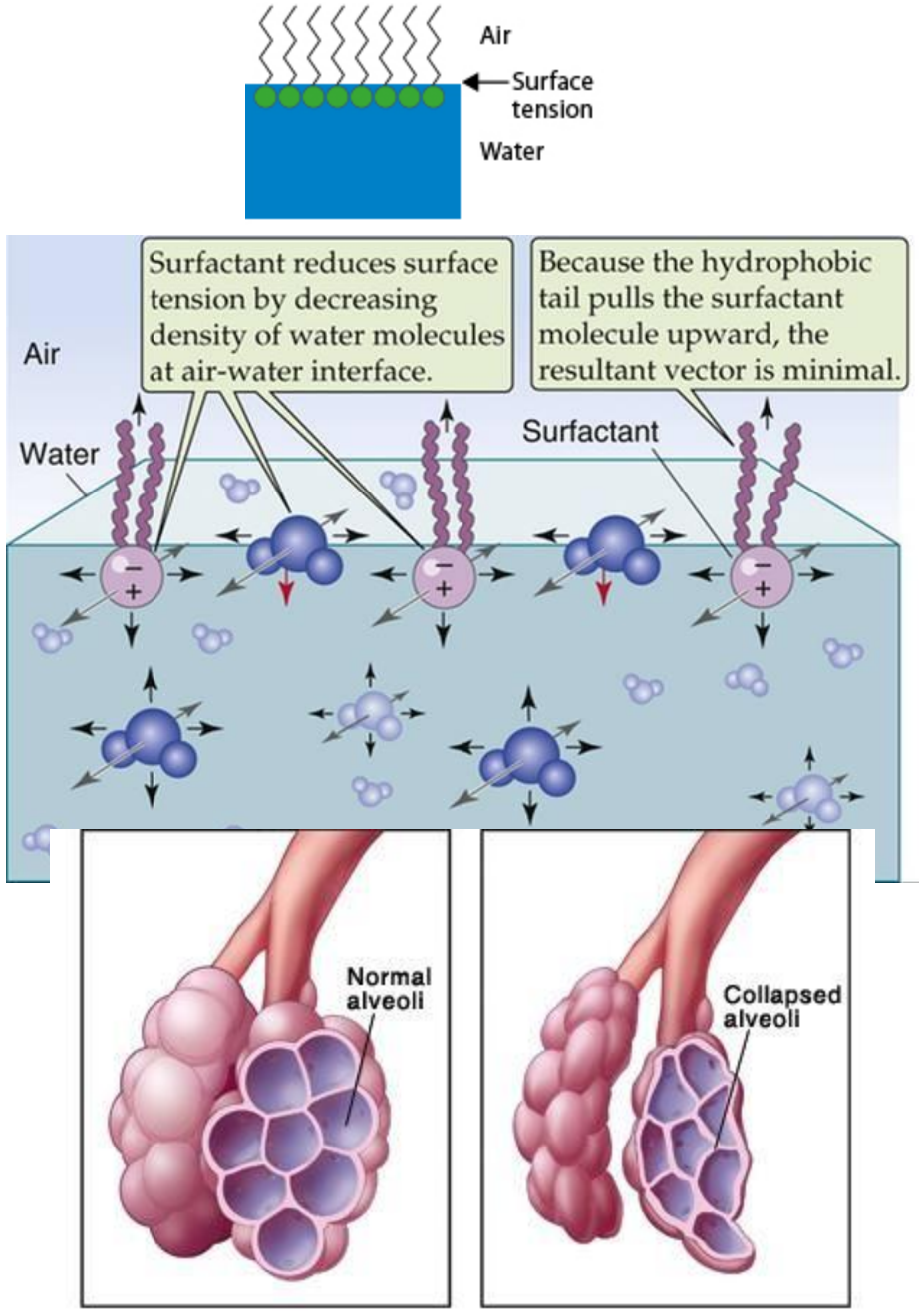
· Lipoprotein lipase (LPL) is an example of a protein anchored by GPI to the endothelial cell membrane in blood vessels.

· This flexibility allows the lipase to move across the cell membrane and degrade lipoproteins, switching between different functional types as required by the cell



4) Application: Surfactants

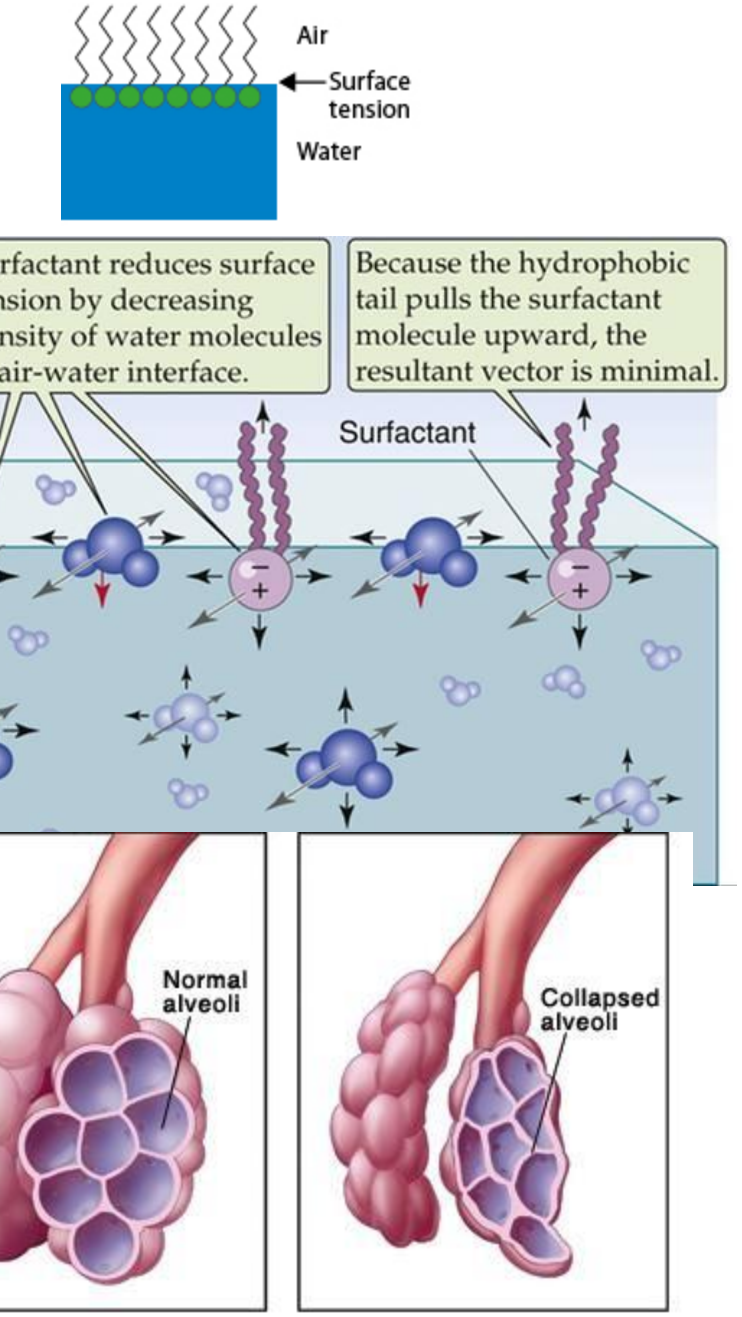
- ✓ **The lungs are composed of functional units known as alveol (The alveolus is a small sac with very thin walls) During inhalation, the alveoli inflate to fill with air, and they collapse after exhalation.**
- ✓ **When we inhale, air fills the lungs, similar to filling a balloon, along with this air, there is moisture (like water vapor).**
- ✓ **Repeated inhalation and exhalation cause the alveolus inflates and deflates, surface tension increases, which can cause the walls of the sacs to collapse.**
- ✓ **This collapse makes it harder for the alveolus to reinflate and perform gas exchange.**
- ✓ **Surfactant is a substance produced in the lungs that reduces surface tension.**



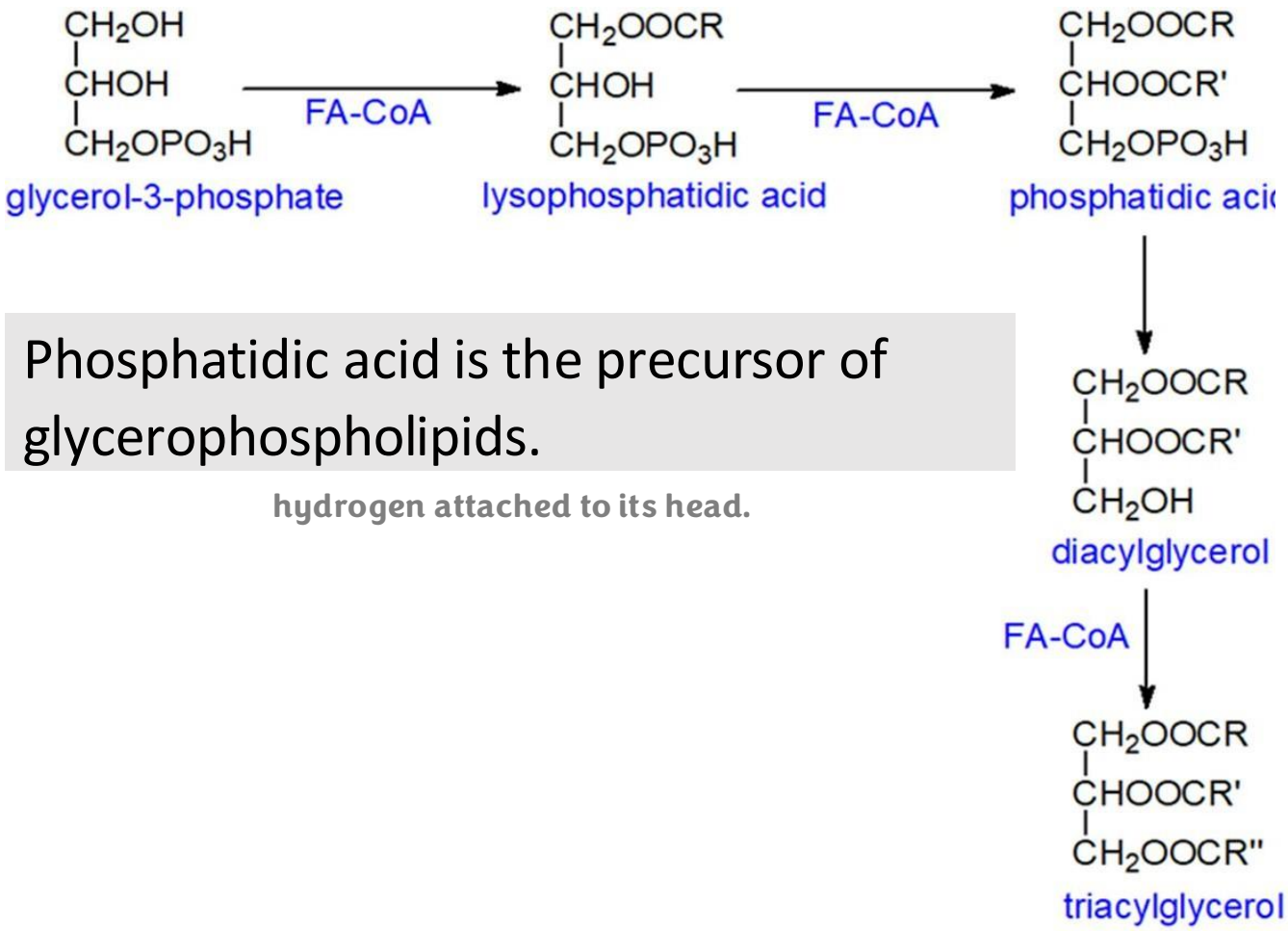
4) Application: Surfactants

- 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.

✓ **These medications are typically given within 48 hours before birth to improve fetal lung function and reduce the risks associated with premature birth.**



Synthesis of phosphatidic acid



Phosphatidic acid is the precursor of glycerophospholipids.

hydrogen attached to its head.

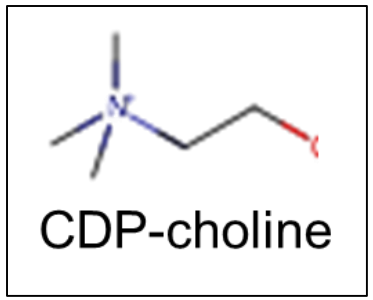
Step	Description	Products
1. Glycerol-3-phosphate Formation	- Glycerol-3-phosphate (G3P) is formed from glycerol via glycerol kinase, or from dihydroxyacetone phosphate (DHAP) through the glycolytic pathway.	Glycerol-3-phosphate (G3P)
2. Fatty Acid Attachment	- Fatty acids are attached to glycerol-3-phosphate to form lysophosphatidic acid (LPA).	Lysophosphatidic acid (LPA)
3. Phosphatidic Acid Formation	- A second fatty acid is added to LPA to form phosphatidic acid (PA).	Phosphatidic acid (PA)
4. Phosphatidic Acid to Diacylglycerol (DAG)	- Phosphatidic acid (PA) is dephosphorylated to form diacylglycerol (DAG).	Diacylglycerol (DAG)
5. Triglyceride Formation	- Diacylglycerol (DAG) reacts with fatty acyl-CoA to form triglycerides (TAG).	Triglycerides (TAG)

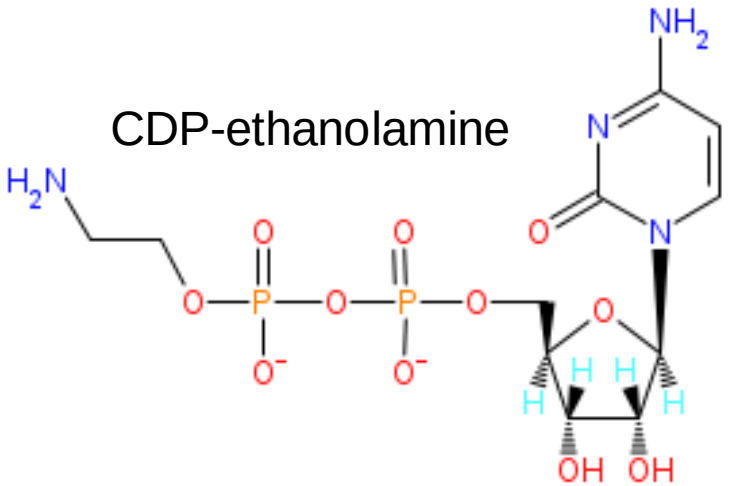
Synthesis

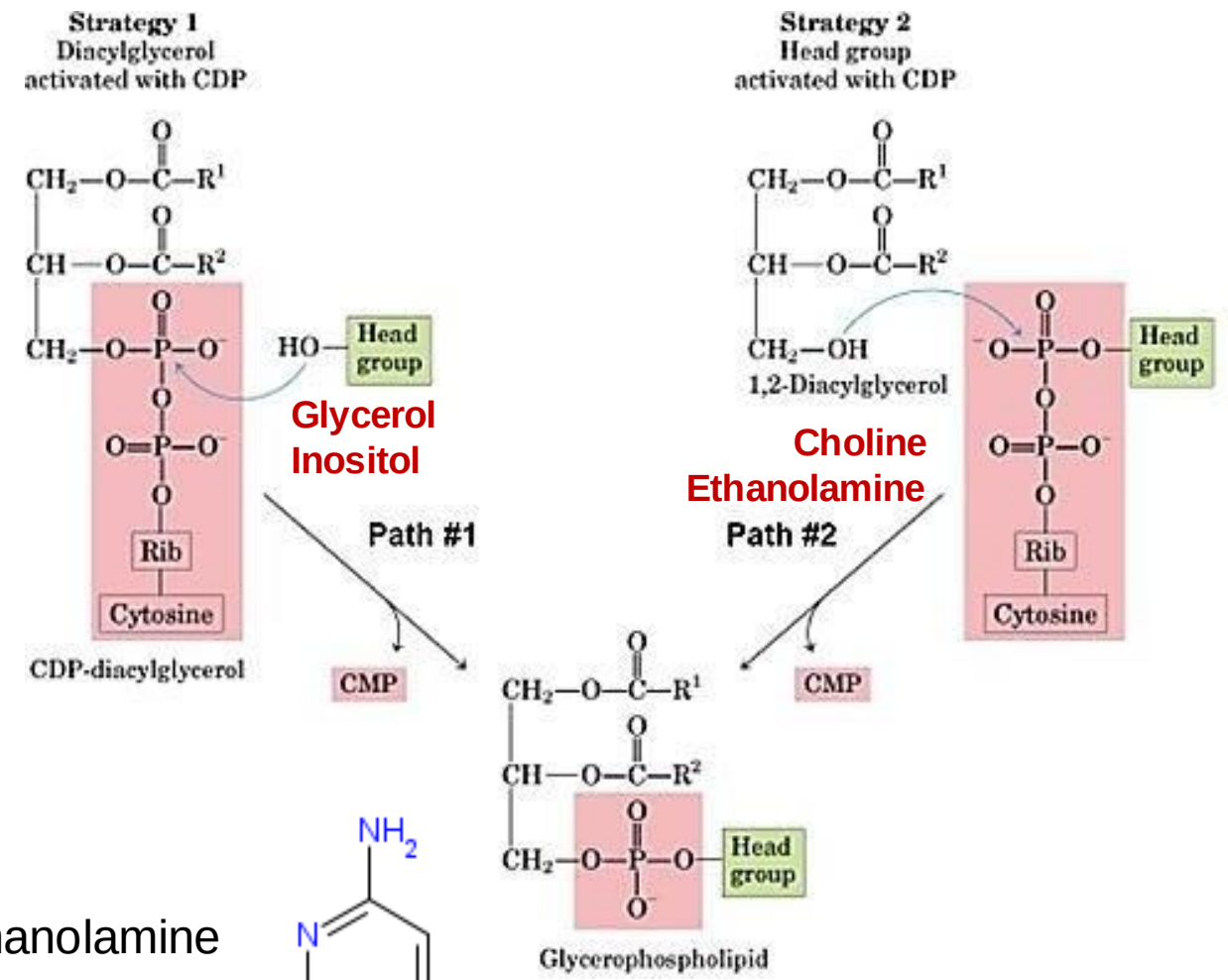
- Location: smooth ER
  - Except for ether lipids
- Activation by CDP is necessary. Either:
  - CDP-DAG (glycerol, inositol)
  - CDP-alcohol (choline, ethanolamine)
- Sources of choline and ethanolamine
  - diet
  - synthesis
  - re-cycling from the turnover of pre-existing phospholipids

  For example **Phosphatidylethanolamine** –– **Phosphatidylcholine**
- Diet is still essential since

demand > supply







Steps for Synthesizing Different Types of Glycerophospholipids: . CDP-alcohol (choline, ethanolamine)

1. Start with Diacylglycerol (DAG)
This is the parent molecule formed after the initial steps of glycerophospholipid synthesis.

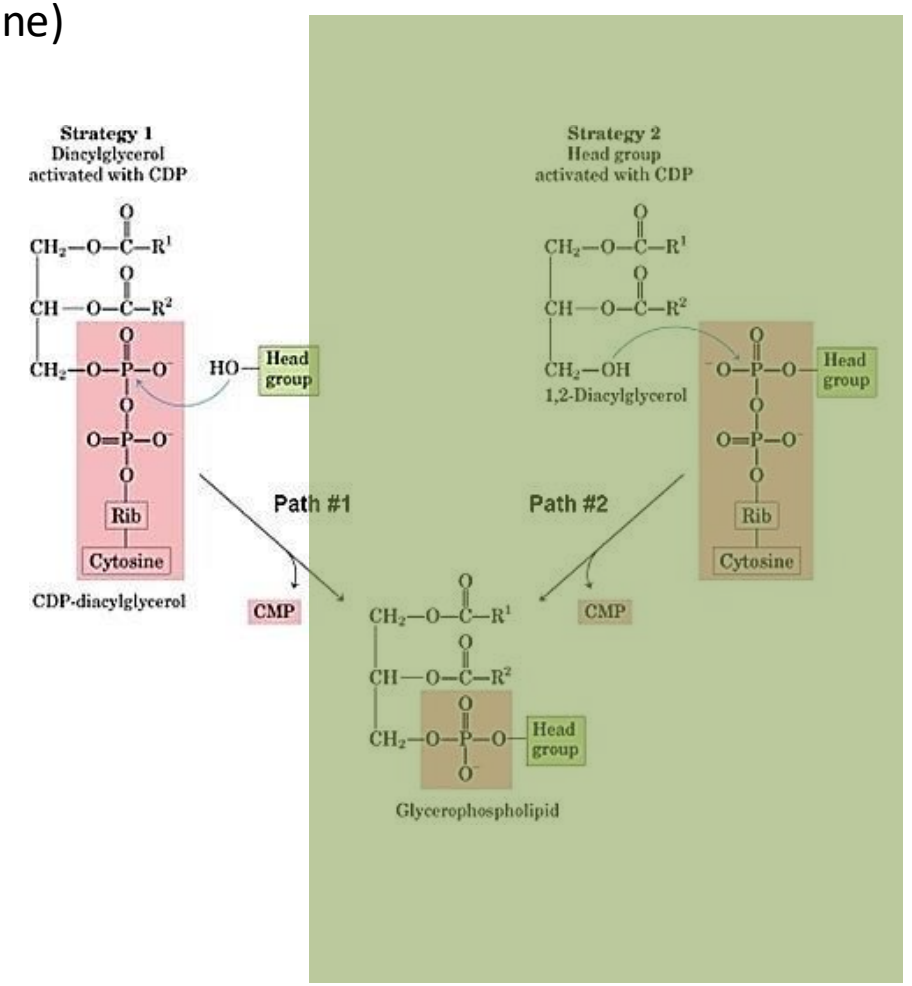
2. Activation of the Head Group: this step we will talk about it in next slides
· Choline or ethanolamine by themselves are not reactive enough to attach to diacylglycerol (DAG).
· Phosphorylation (by kinase) adds a phosphate group to the head group, making it phosphorylated choline or phosphorylated ethanolamine
· This is a necessary preparation step to further activate the head group.

3. Use CDP Nucleotide for Head Group Activation
CDP (Cytidine Diphosphate) nucleotide carries the head group (either ethanolamine or choline)

4.Transfer the Head Group to DAG
Transferase enzymes facilitate the attachment of the head group to DAG.

5. Cleavage of the Phosphate Group and Cytosine
The phosphate group and the cytosine (from the CDP nucleotide) are cleaved(CMP molecule (Cytidine monophosphate)) This releases the nucleotide.

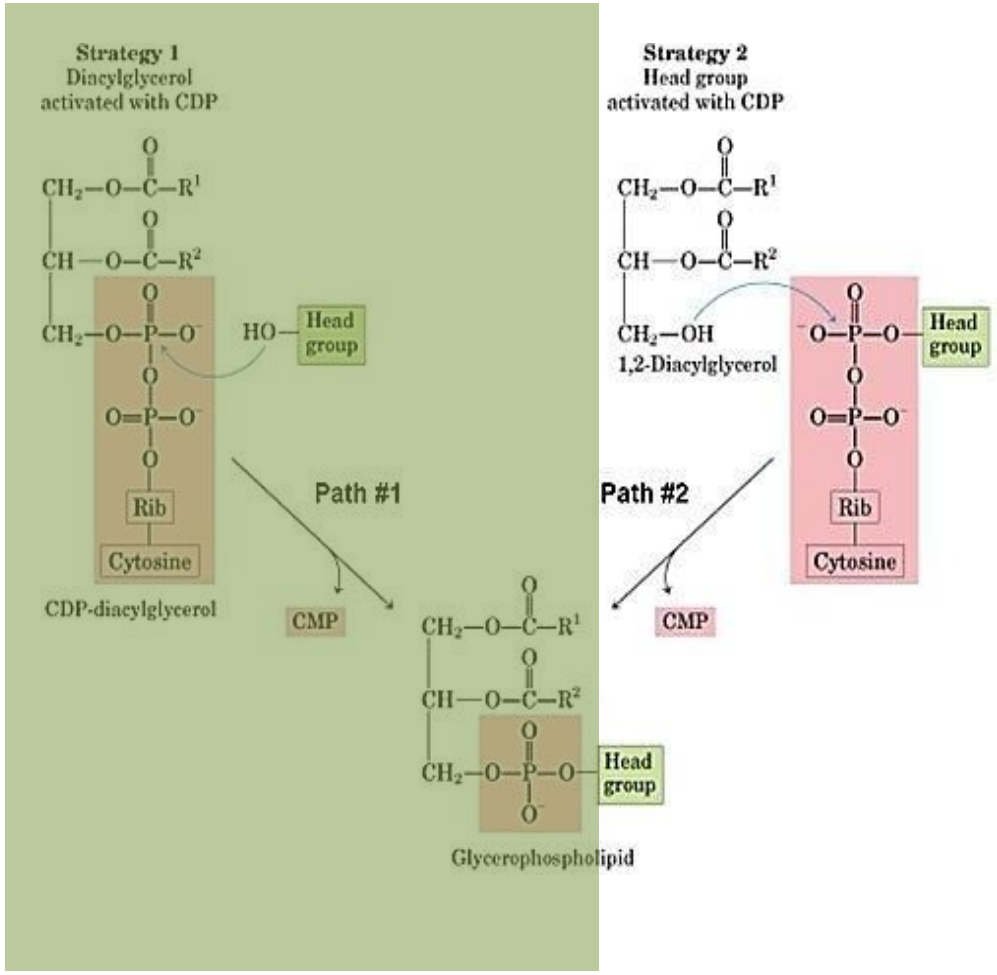
6.Finally
After the head group is added to DAG and the CDP nucleotide is cleaved, the result is either:
· Phosphatidylcholine (PC) if the head group is choline.
· Phosphatidylethanolamine (PE) if the head group is ethanolamine.



Steps for Synthesizing Different Types of Glycerophospholipids: CDP-DAG (glycerol, inositol)

Other pathway

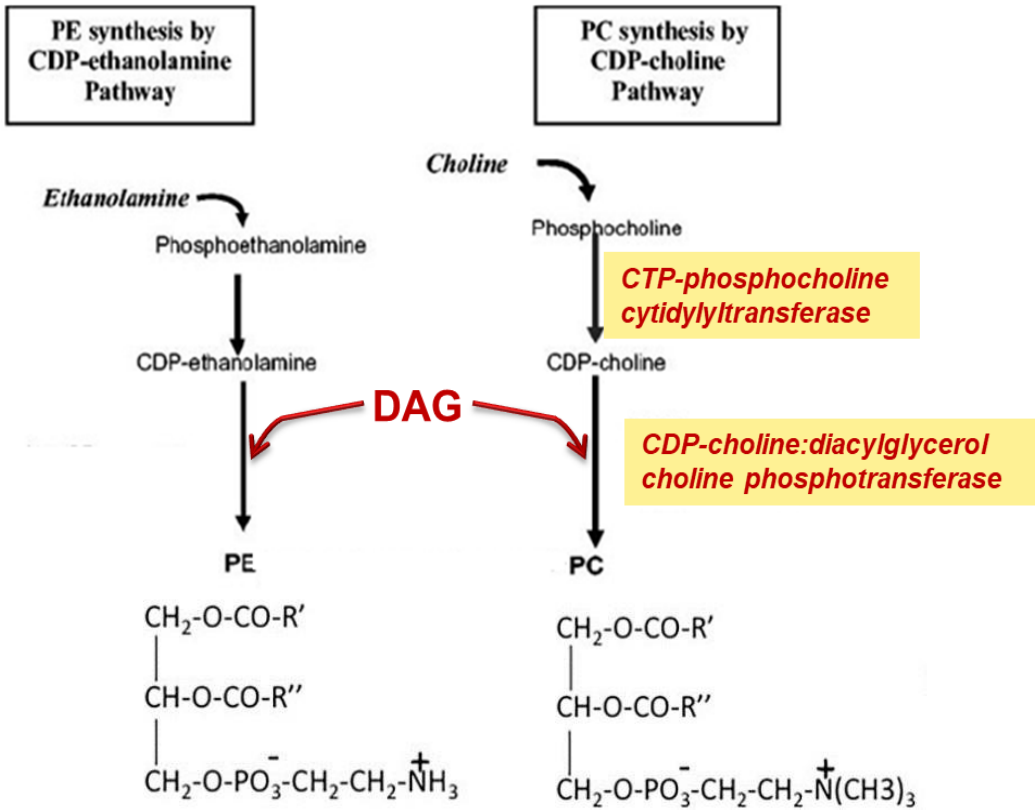
Step	Reaction
1. Formation of CDP-DAG	CDP activates DAG, forming CDP-DAG.
2. Head group attachment	Transferase attaches the head group (inositol, ethanolamine, etc.) to CDP-DAG.
3. CMP cleavage	CMP (cytidine, ribose, and phosphate) is removed, leaving the head group attached.
4. Final product formation	The head group and DAG form the specific glycerophospholipid (e.g., PI, PG).



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.

We've already talked about that.



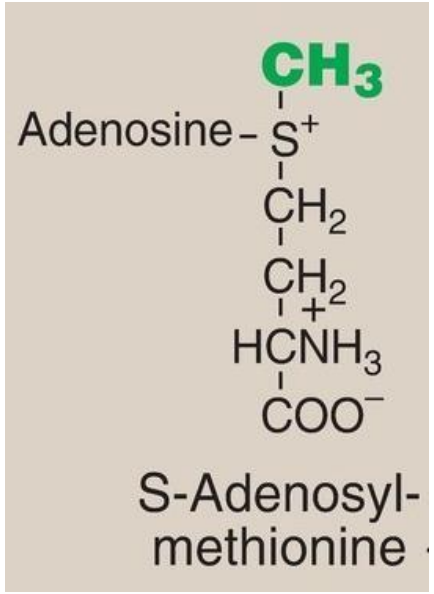
- **In both the CDP-Alcohol Pathway and the CDP-DAG Pathway, CTP (Cytidine Triphosphate) is the molecule that provides the energy required for activation.**
- **When CTP participates in the reaction, it transfers cytidine and two phosphate groups to the target molecule (DAG or the head group).**
- **In the process, one phosphate group is lost, converting CTP to CDP.**

Pathway	Activation	Role of CDP
CDP-DAG Pathway	CDP activates DAG	DAG becomes reactive to attach the head group (inositol, etc.).
CDP-Alcohol Pathway	CDP activates the head group	The head group becomes reactive to attach to DAG.

➢ Synthesis of ph-choline from ph-ethanolamine

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

Phosphatidylethanolamine N – methyltransferase (PEMT)



Phosphatidylethanolamine (PE) is the initial molecule containis a two carbon backbone withan amine group (-NH2) , Methylation of PE converts it into Phosphatidylcholine (PC).

. Methylation involves replacing the hydrogen atoms on the amine group with methyl groups (-CH3) to form a choline head group , Each hydrogen atom in the amine group (-NH2) is replaced with a methyl group in a stepwise manner (3 steps in total) to form Phosphatidylcholine (PC). The reaction is catalyzed by Phosphatidylethanolamine Methyltransferase (PEMT) ,

Source of Methyl Groups:

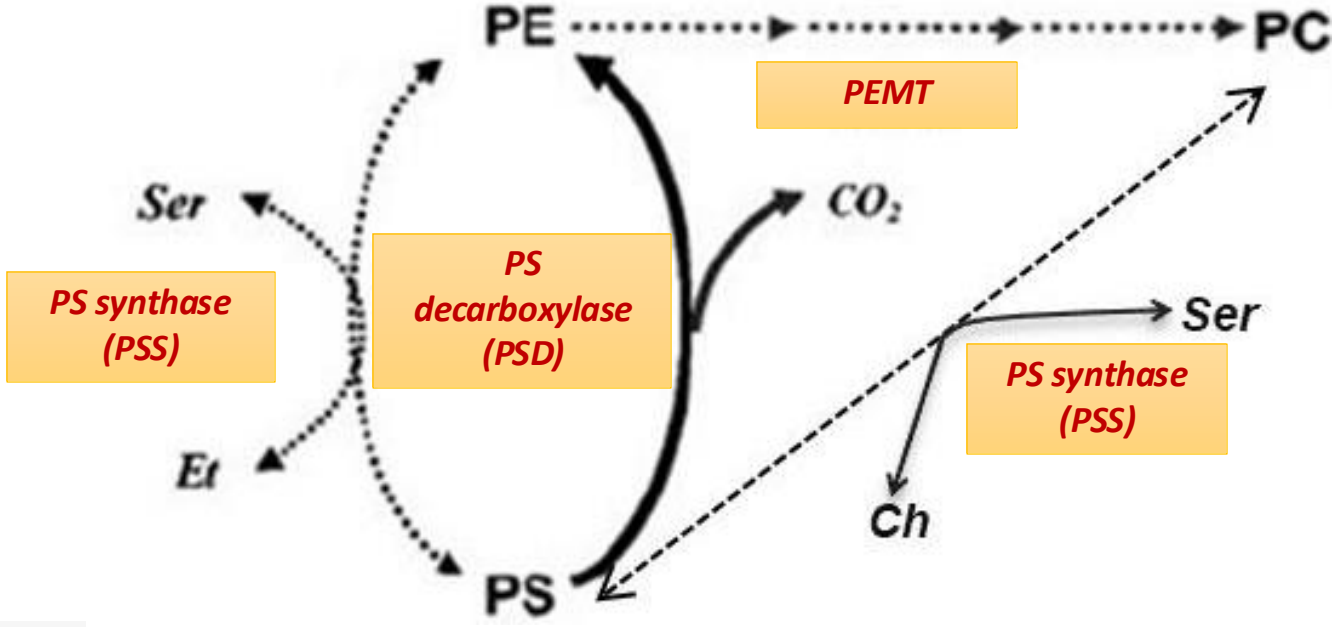
· SAM (S-adenosylmethionine) is the primary donor of methyl groups during methylation reactions , SAM is synthesized from methionine (an amino acid) and ATP.

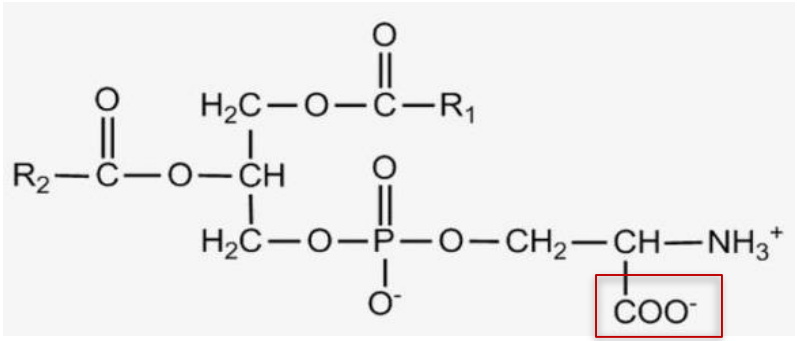
· Methionine contains a sulfur atom bonded between two carbon atoms , The terminal carbon is cleaved and used as the donor for the methyl group during methylation reactions.

· Vitamin B9 (Folate) can also carry single-carbon units in various forms (e.g., methyl, formyl) . However, in this specific reaction, methyl groups are primarily donated by SAM.

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) (reversible)

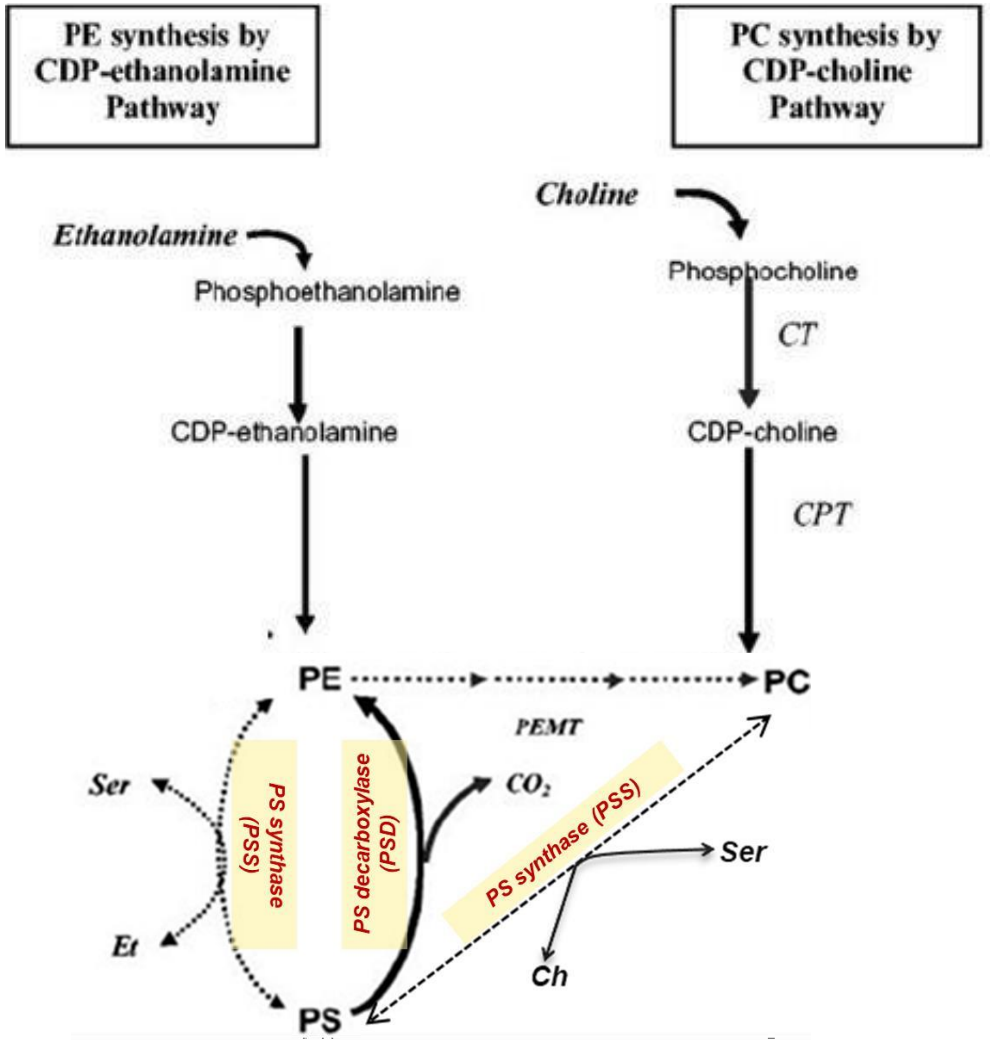




phosphatidylserine

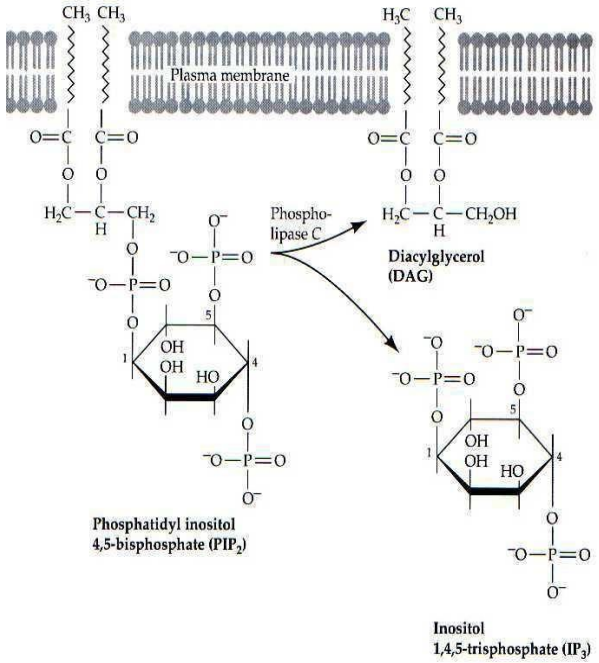
Pathway	Enzyme/Mechanism	Result
PS → PE (Decarboxylation)	Phosphatidylserine Decarboxylase (PSD)	Phosphatidylethanolamine (PE)
PE → PC (Methylation)	Phosphatidylethanolamine Methyltransferase (PEMT) + S-adenosylmethionine (SAM)	Phosphatidylcholine (PC)
PS Exchange	Phosphatidylserine Synthase (PSS) (Reversible)	Phosphatidylserine (PS) can be exchanged with PE or PC

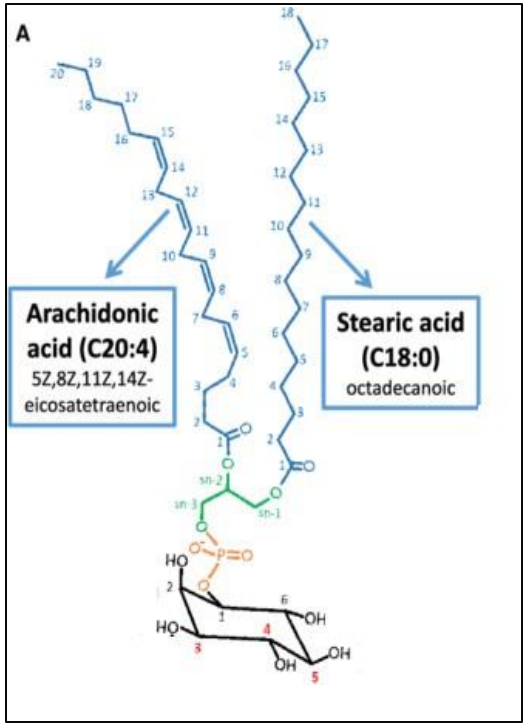
Summary of synthesis pf PE, PC, and PS

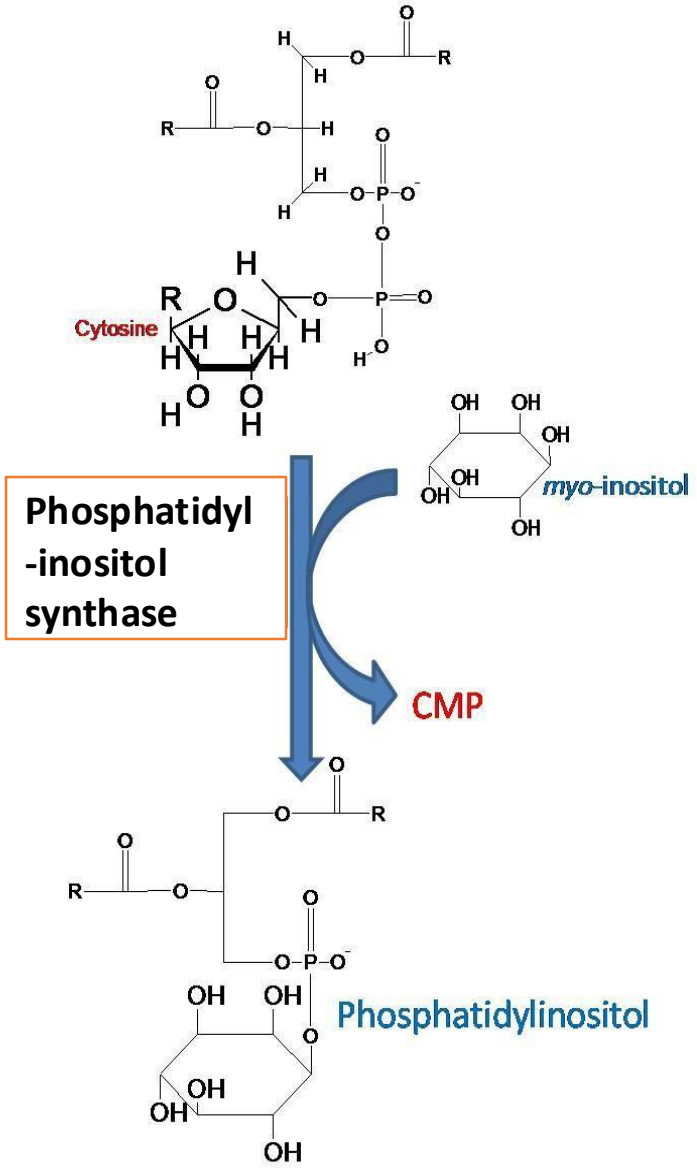


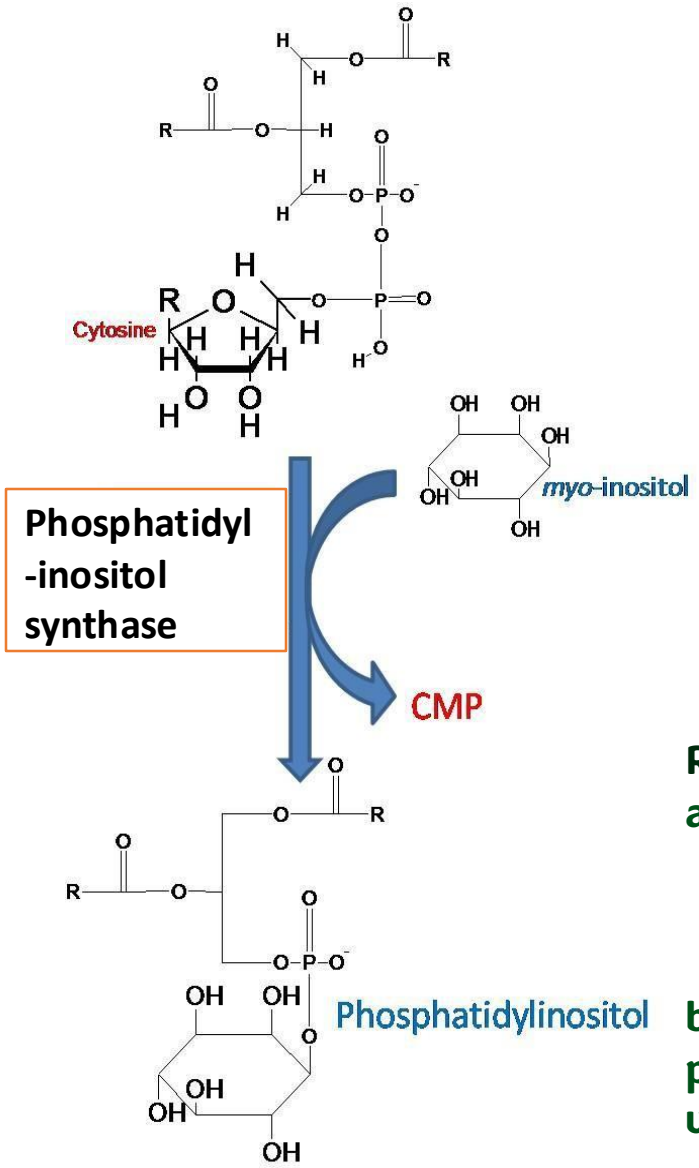
Synthesis of ph-inositol

- 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.









Step	Description
1. Activation of DAG	DAG is activated by CDP, forming **CDP-DAG** (activated form of DAG).
2. Addition of Inositol	Inositol is added to the phosphate group on DAG through the action of **phosphatidylinositol synthase**.
3. CMP Removal	CMP is removed, resulting in the production of **Phosphatidylinositol (PI)**.

Roles of Phosphatidylinositol:

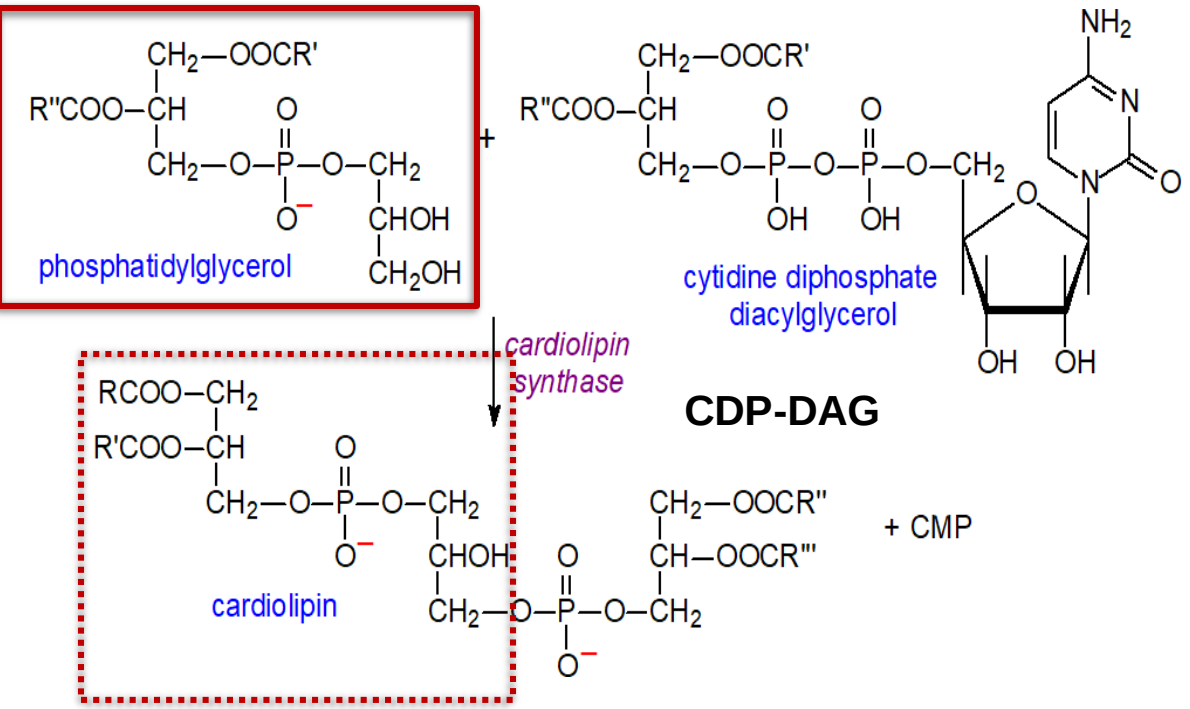
a) **GPI Anchor Formation: PI is essential for the formation of glycosylphosphatidylinositol (GPI) anchors, which attach proteins to the plasma membrane.**

b) Signaling Pathways: PI plays a crucial role in cell signaling, especially as a precursor for PIP2 (Phosphatidylinositol 4,5-bisphosphate), which is involved in various intracellular signaling pathways.

c) Arachidonic Acid Reservoir: The fatty acid composition of PI is mainly arachidonic acid and stearic acid, making it a significant source of arachidonic acid, which is crucial for inflammatory signaling and other metabolic processes.

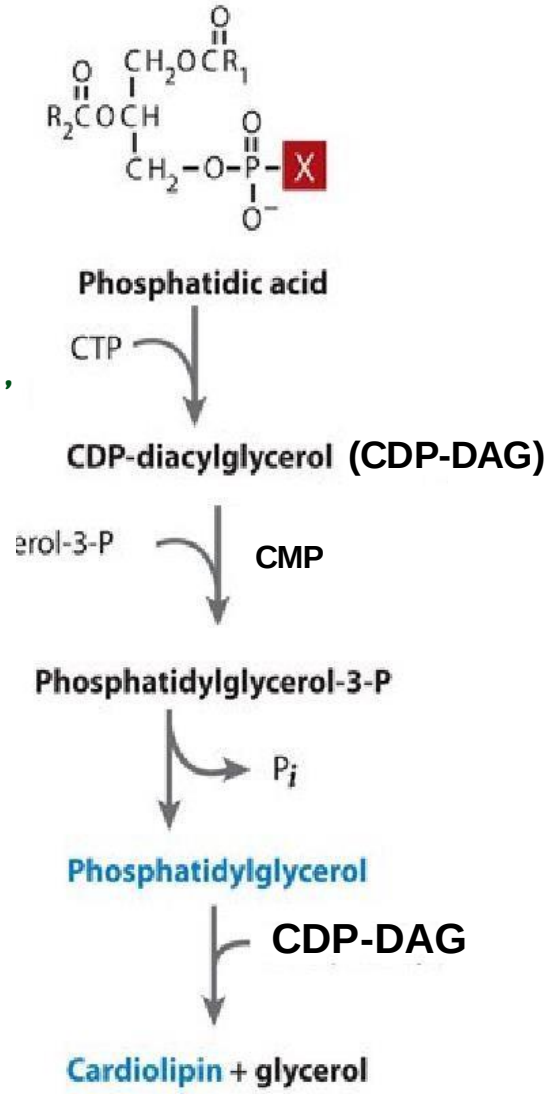
Phosphatidylglycerol and cardiolipin

- 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.



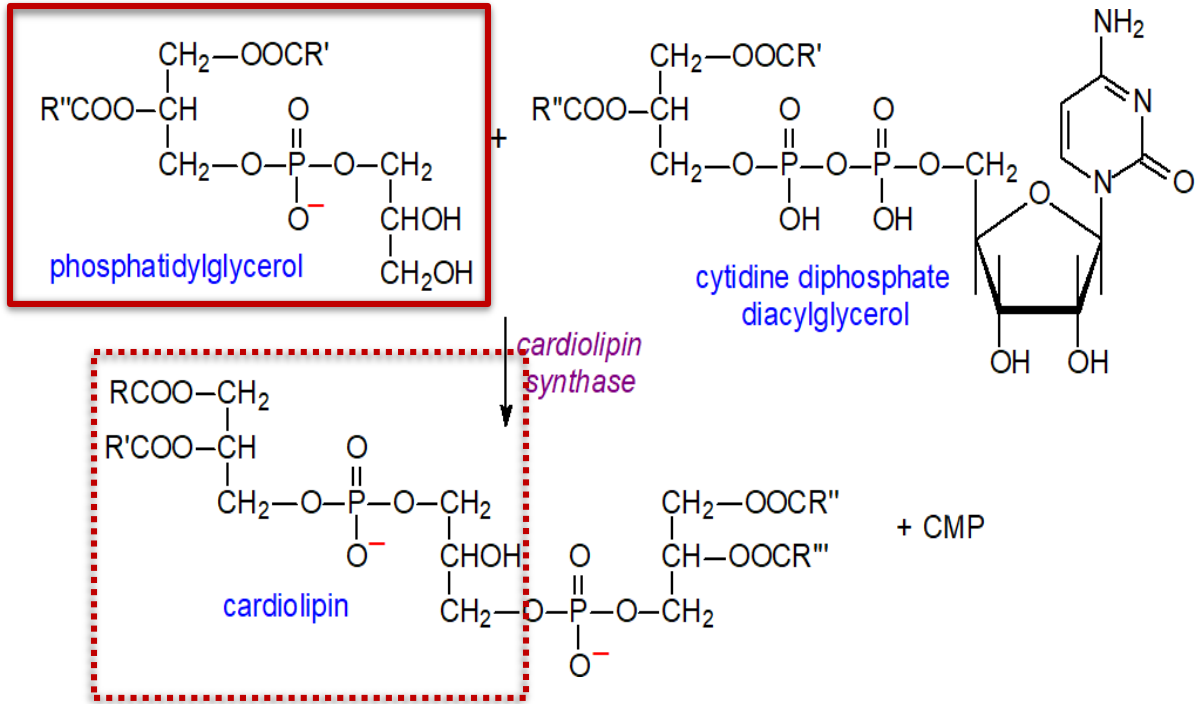
Same as PI in mechanism (as both are alcohols) , they differ only in the last step

Step	Process Description
1. Activation of Diacylglycerol (DAG)	**Diacylglycerol (DAG)** is activated by **CDP** to form **CDP-DAG** (Cytidine diphosphate diacylglycerol).
2. Addition of Glycerol Head Group	**Glycerol-3-phosphate** is added to **CDP-DAG** through the action of **Phosphatidylglycerol synthase (PGS)** to form **Phosphatidylglycerol-3-phosphate (PGP)**.
3. Dephosphorylation of Phosphatidylglycerol-3-phosphate (PGP)	The phosphate group is removed from **Phosphatidylglycerol-3-phosphate (PGP)** by **Phosphatase**, resulting in the formation of **Phosphatidylglycerol (PG)**.



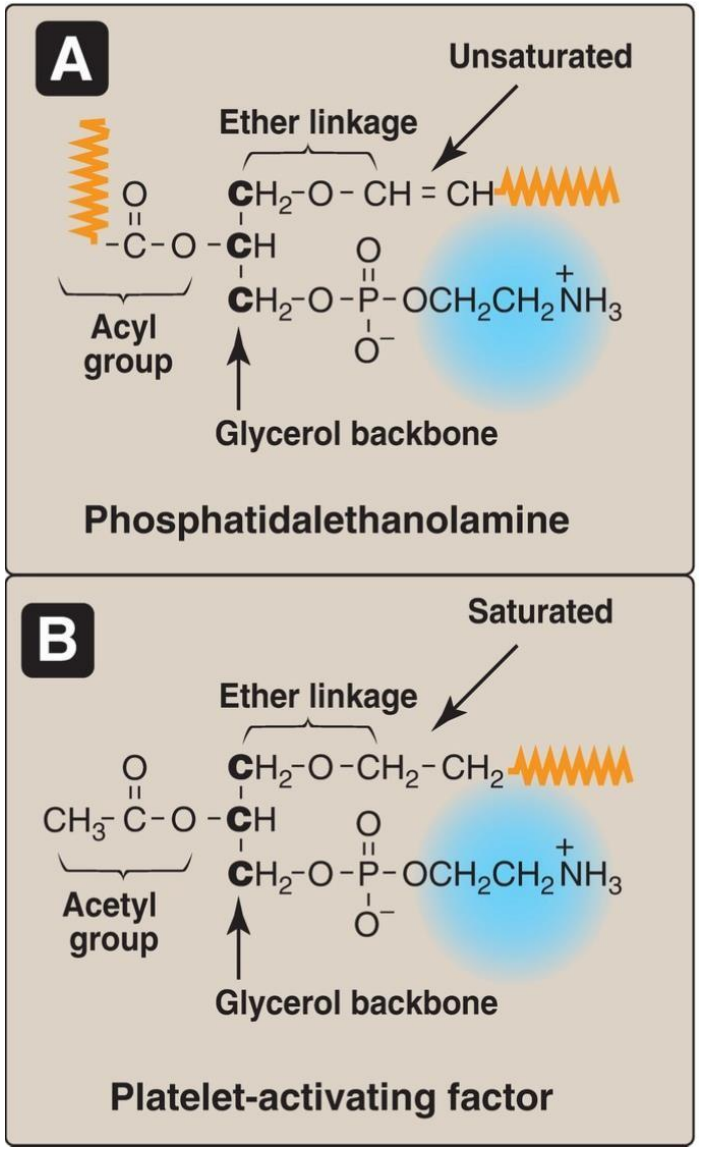
Cardiolipin is a unique phospholipid found in the inner mitochondrial membrane. It has a distinctive structure, formed by combining two phosphatidic acid molecules attached to a single glycerol backbone.

Step	Description
1. **Activation of Phosphatidic Acid**	**Phosphatidic acid** is activated to **CDP-diacylglycerol** (CDP-DAG) through a process similar to other CDP-diacylglycerol pathways.
2. **Removal of CMP**	The **CDP** group is removed from CDP-DAG, releasing **CMP** (Cytidine monophosphate).
3. **Addition of Phosphatidic Acid to Phosphatidylglycerol**	**Phosphatidic acid** (activated) is added to **phosphatidylglycerol** through the action of **cardiolipin synthase (CLS)**, linking the two molecules together.
4. **Formation of Cardiolipin**	The final product is **cardiolipin**, consisting of **2 phosphatidic acids** attached to a **glycerol** backbone.



Ether glycerophospholipids

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



- ✓ **The key difference in plasmalogens is the ether linkage between the glycerol backbone and the hydrocarbon chain (not fatty acid), as opposed to the usual fatty acid ester linkage found in most glycerophospholipids.**
- ✓ **The hydrocarbon chain must be unsaturated, with the double bond located between the first and second carbons.**
- ✓ **The process begins with the synthesis of normal phospholipids (PC or PE), followed by the replacement of the fatty acid at the first position with a hydrocarbon chain.**

- 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

Differences in PAF:

1. **Ethanolamine head group**
2. **FA on C2 is an Acetyl group (very short)**
3. **Ether linkage is present but the hydrocarbon chain is saturated (no double bond after the ether linkage)**

Degradation of Phospholipids

Phospholipid degradation involves various enzymes, primarily phospholipases, which break down phospholipids in different ways depending on the purpose..

Removes the fatty acid attached to carbon 1 of the glycerol backbone

which can serve as a precursor for diacylglycerol.

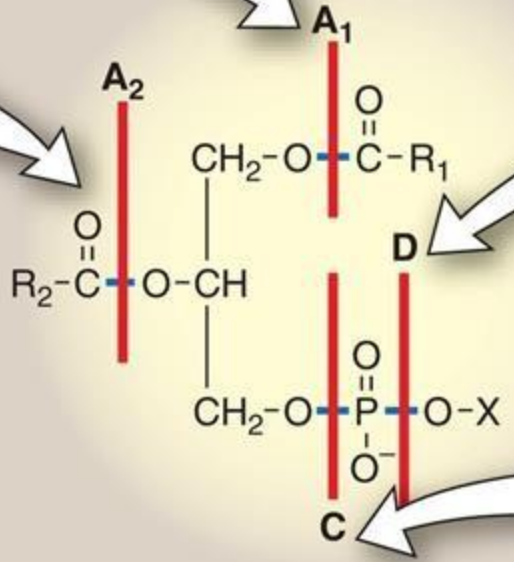
Removes the fatty acid attached to carbon 2.

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.