بسم الله الرحمن الرحيم

Phospholipid Compounds of Physiological Importance

By

Reem M. Sallam, M.D.; Ph.D.

Objectives

- Selected members of phospholipids
- Physiological importance of phospholipids
- Plospholipases:
    - Phospholipases A1, A2, C and D
    - Lysosomal phospholipase: Sphingomyelinase

Functions of Phospholipids

(A)Membrane-bound phospholipids:

Structural: Predominant lipids of cell membranes

Anchoring: Attaching some proteins to membranes

Signaling: Source of PI3 and DAG

Myelin sheath: insulator and speeds up transmission of nerve impulses

Functions of Phospholipids

CONT'D

(B) Non-membrane-bound phospholipids:

Easy re-inflation of alveoli by air: Lung surfactant

Detergent effect: Essential component of bile
Solubilize cholesterol, preventing gall stones
Emulsifying lipids, helping lipid digestion

Structural: Coat of lipoproteins

Background: Lipid Compounds

- **Heterogeneous group**
- **Relatively water-insoluble (? Exception)**
- **Soluble in non-polar solvents**

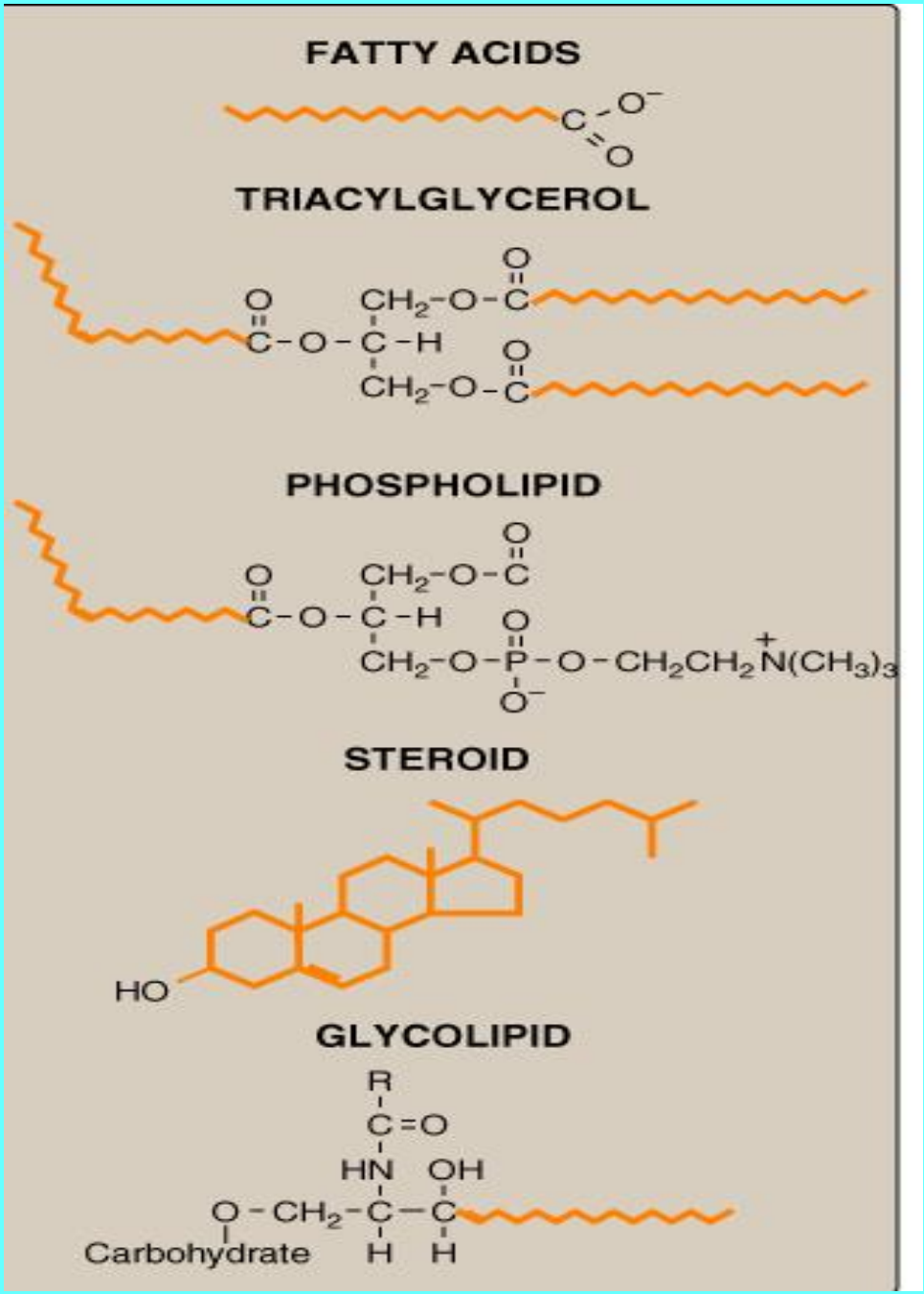
Lipid Compounds: Heterogeneous Group

A. Simple Lipids:

- Fatty acids
- Ketone bodies
- Triacylglycerol
- Cholesterol

B. Complex Lipids:

- Phospholipids
- Lipoproteins
- Glycolipids



Phospholipids

A. Glycerophospholipids

Glycerol-containing phospholipids

B. Sphingo-phospholipids:

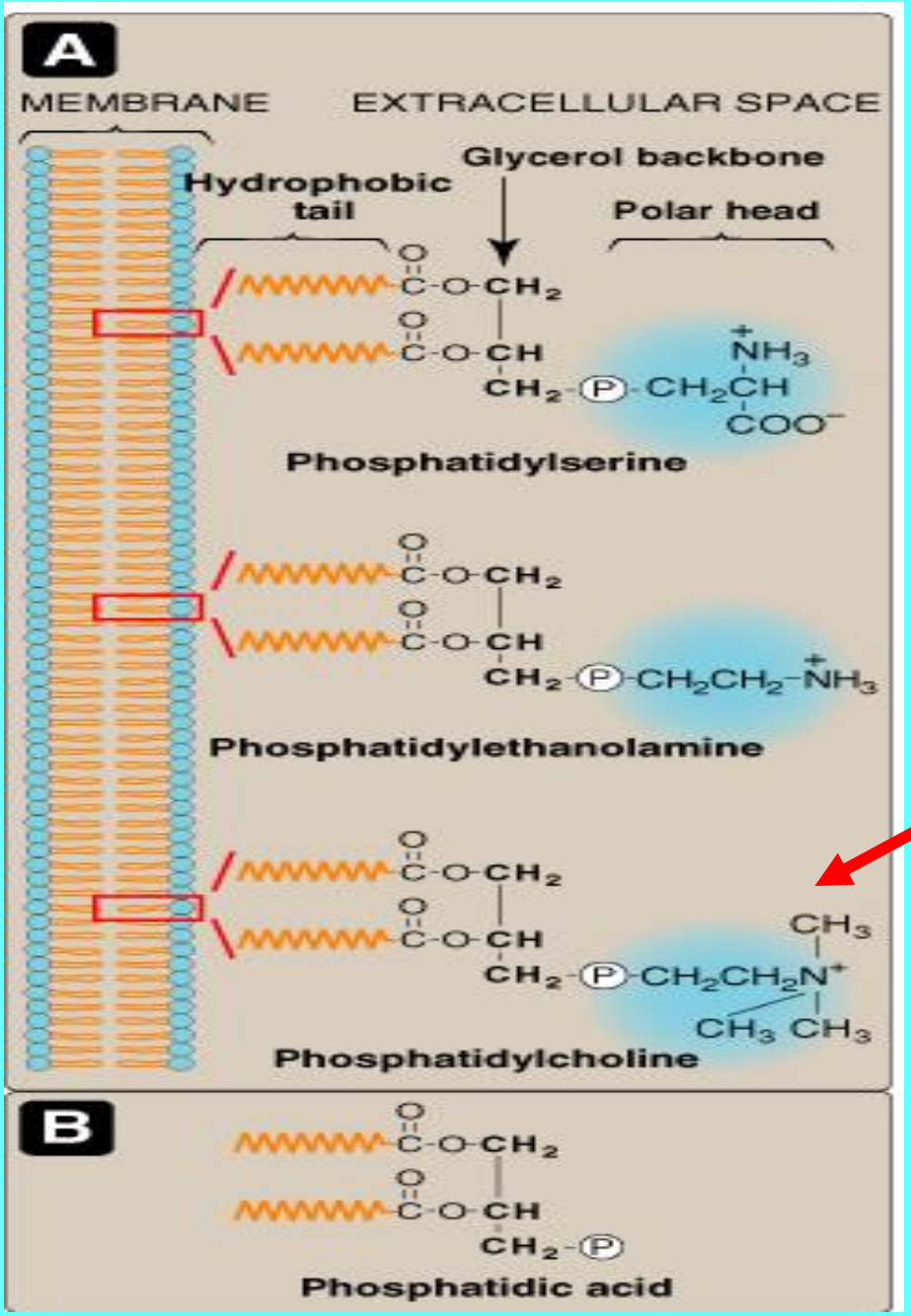
Sphingosine-containing phospholipids

Phospholipids

A. Glycerophospholipids:

1. Phosphatidylcholine (Lecithin)
   e.g., Surfactant (Dipalmitoylecithin)

2. Phosphatidylinositol
   (Signaling and anchoring molecule)



Phospholipids:

A. Glycerophospholipids

Parent Compound

Phosphatidic acid

Members:

1. Phosphatidylcholine (Lecithin)

   e.g., Surfactant

(DipalmitoylPhosphatidylcholine = DPPC= Dipalmitoylecithin)

Phospholipids: A. Glycerophospholipids

1. Dipalmitoylecithin (Lung surfactant)

Synthesis and secretion: by granular pneumocytes

Major lipid component (65%) of lung surfactant
(Remainining 35%: Other phospholipids, cholesterol & proteins)

Surfactant decreases surface tension of fluid layer lining of alveoli, reducing the pressure needed for their inflation by air, and preventing alveolar collapse (atelectasis)

Congenital Respiratory distress syndrome (RDS):
Insufficient production of lung surfactant
(especially in pre-term babies) ⟶ neonatal death

Congenital Respiratory distress syndrome (RDS)

Pre-natal diagnosis by:
Lecithin/sphingomyelin (L/S) ratio in amniotic fluid

Ratio of 2 or above indicates lung maturity and no RDS
(i.e., shift from sphingomyelin to lecithin synthesis by pneumocytes that normally occurs by 32 weeks of gestatioin)

Prevention:

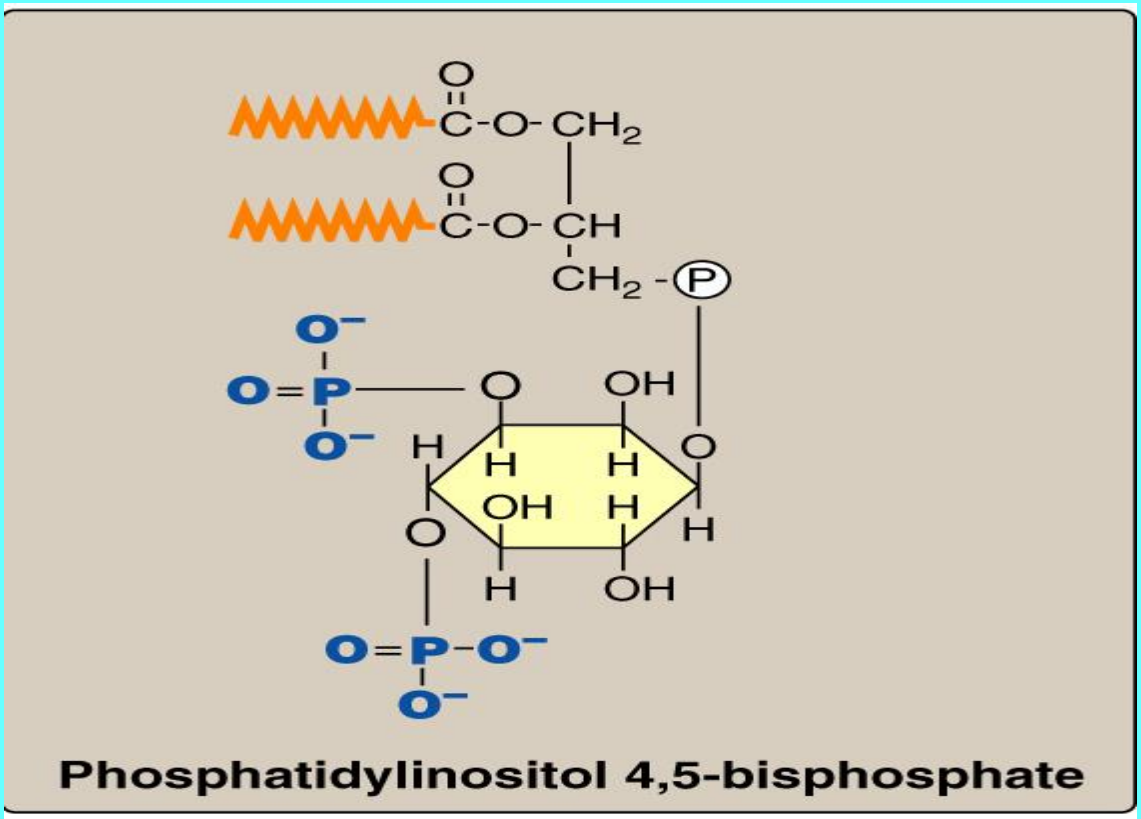
Glucocorticoids to the pregnant mother with low L/S ratio shortly before delivery

Treatment:

Intratracheal administration of surfactant to pre-term infants with RDS

Phospholipids: A. Glycerophospholipids

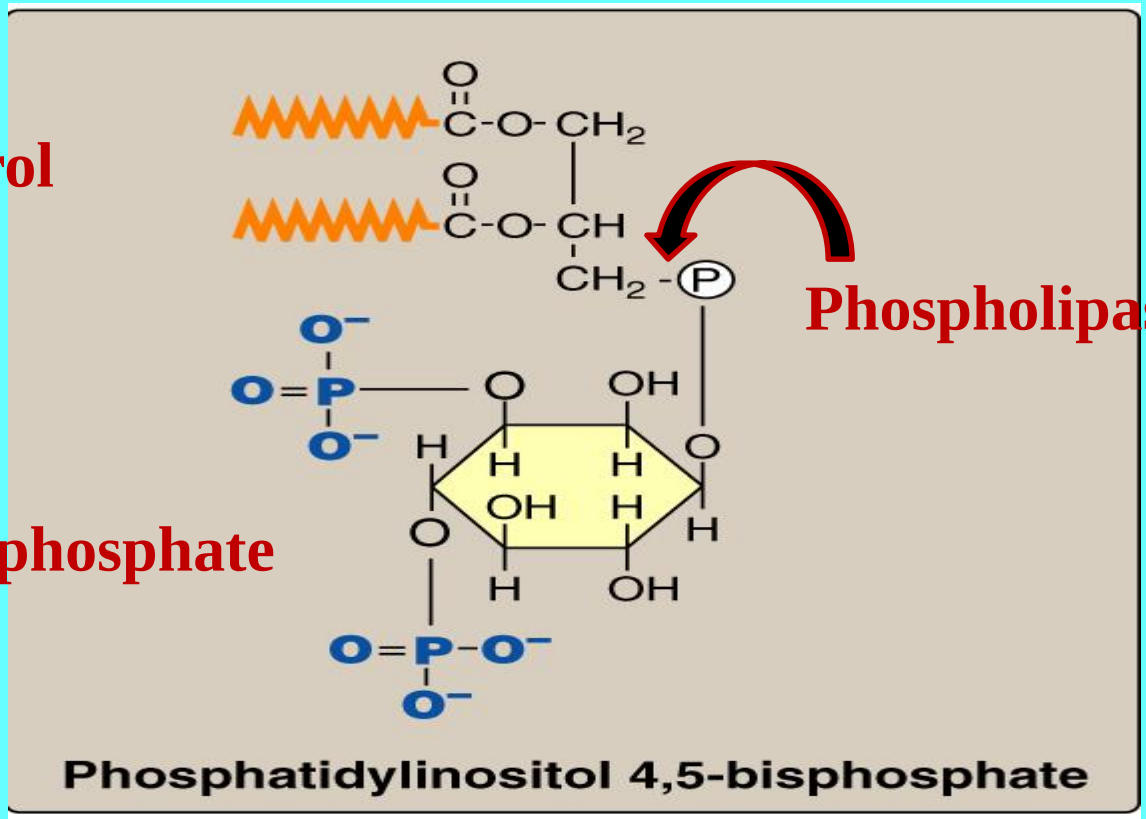
2. Phosphatidylinositol 4,5 bisphosphate (PI)



Calcium/Phosphatidylinositol System

Diacylglycerol (DAG)

Inositol Trisphosphate (IP_3)



Phosphatidylinositol System

Signal: Hormones or neurotransmitters

e.g., Acetylcholine, antidiuretic hormone (V1-receptor) and catecholamines (α_1 actions)

Receptor: G-protein coupled receptor

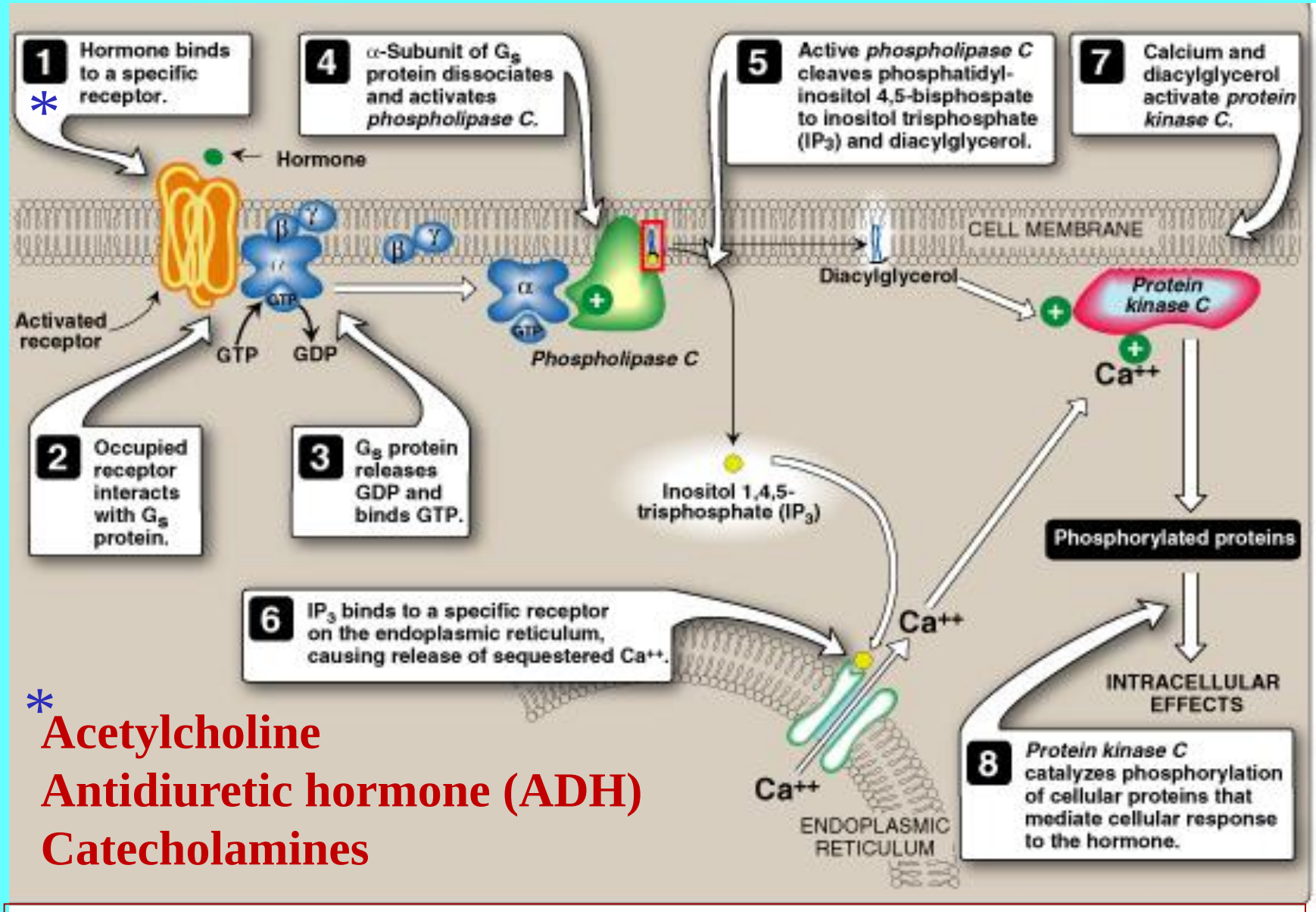
Effects: Activation of phospholipase C

Hydrolysis of phosphatidylinositol 4,5-bisphosphate

Production of IP3 ($\uparrow Ca^{2+}$) and DAG

Activation of protein kinase C

Response: Phosphorylation of cellular proteins and responses to hormones



*Acetylcholine
Antidiuretic hormone (ADH)
Catecholamines

Intracellular Signaling by Inositol trisphosphate

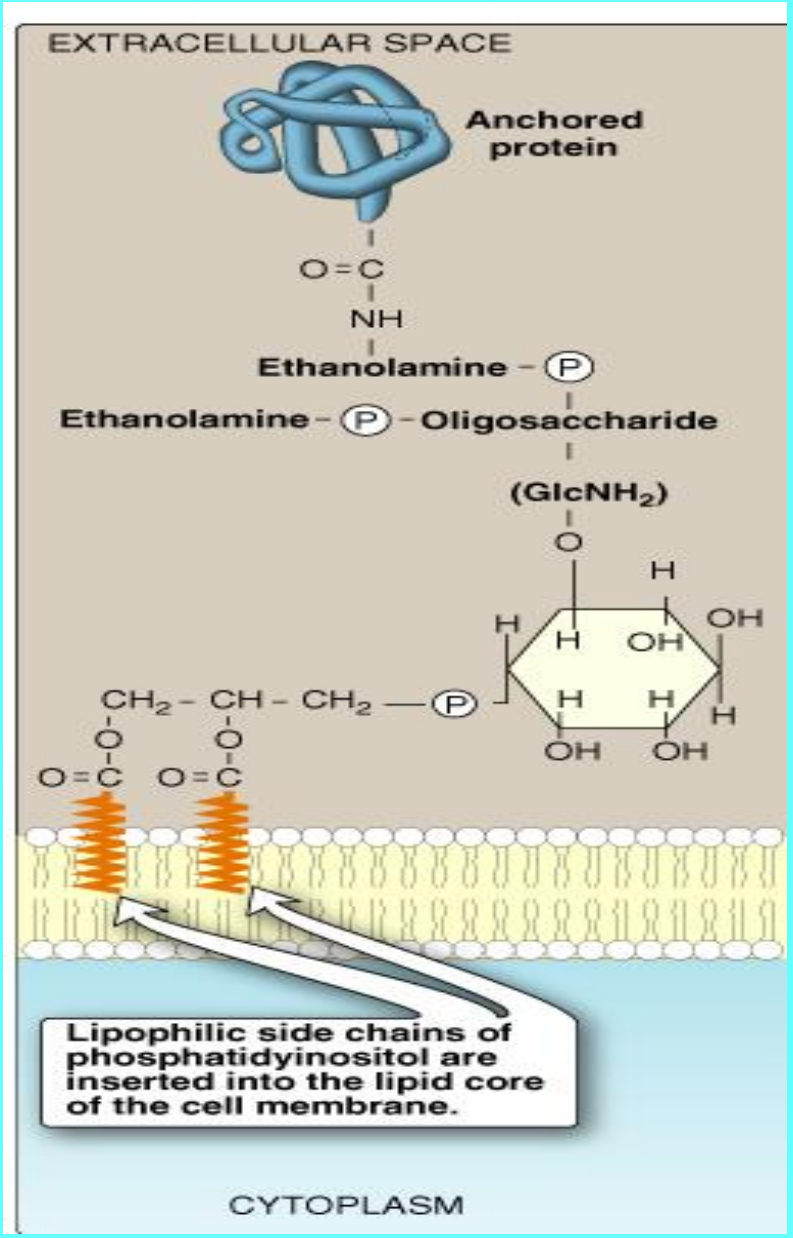
PI- Protein Anchoring

Anchoring of proteins to membranes via Carbohydrate-Phosphatidylinositol Bridge

Examples of anchored proteins:

1. **Alkaline phosphatase**
   (to the surface of small intestine)
2. **Acetylcholine esterase**
   (to postsynaptic membrane)

These proteins can be cleaved from their attachment to the membranes by phospholipase C



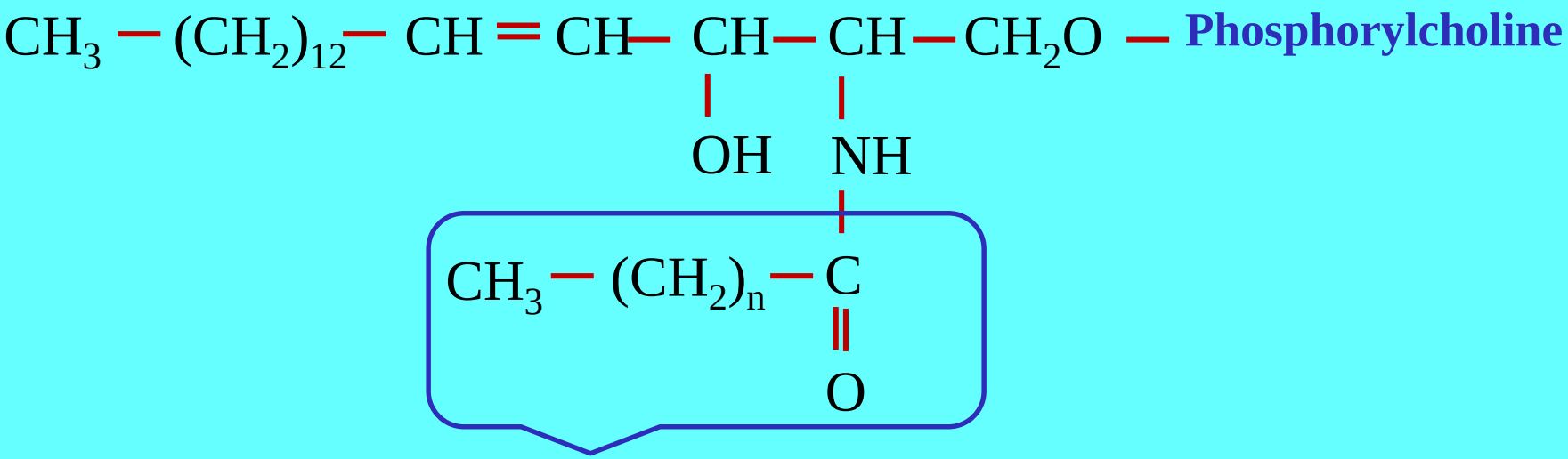
Phospholipids

B. Sphingo-phospholipids:

Sphingosine-containing phospholipids:
e.g., sphingomyelin (Myelin sheath)

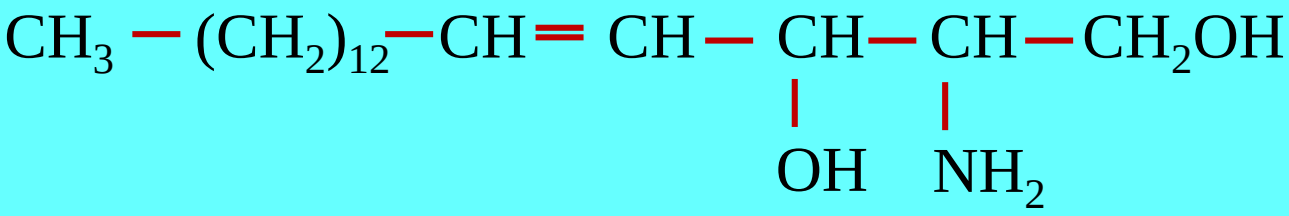
Phospholipids:
B. Sphingo-phospholipids

Sphingomyelin



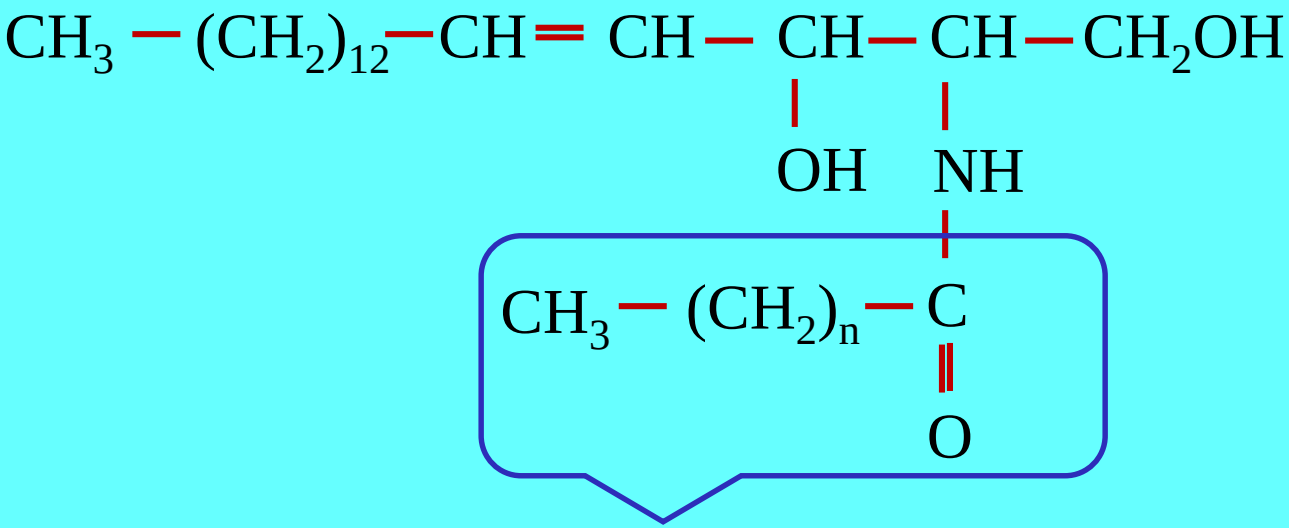
Long Chain Fatty acid

Sphingosine



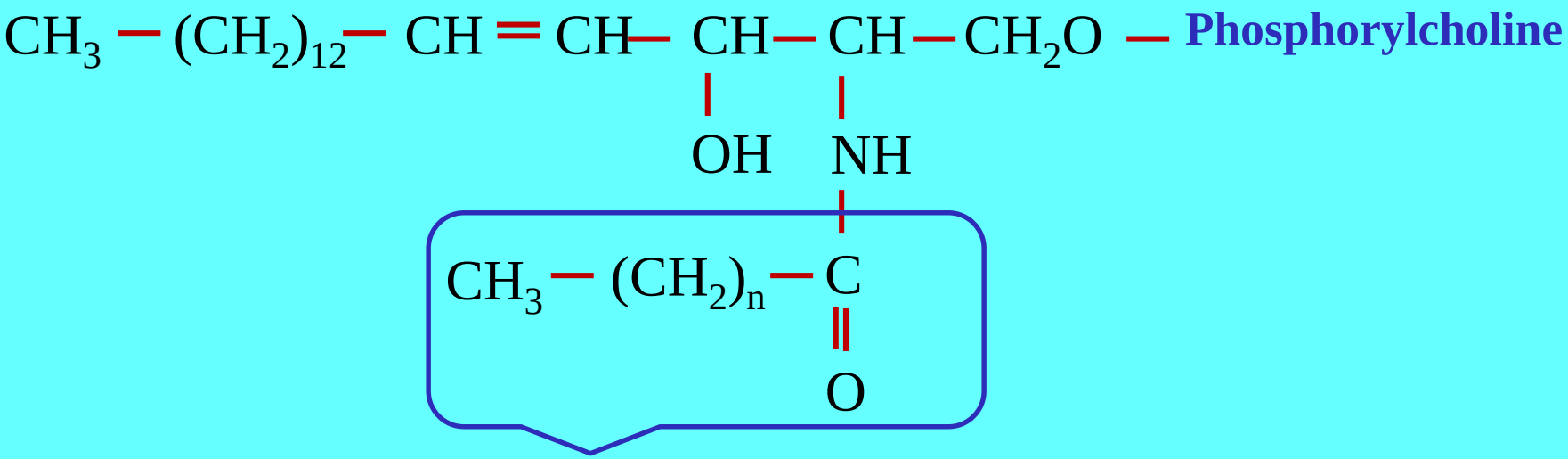
Long chain, unsaturated amino alcohol

Ceramide: Parent Sphingolipid Compound



Long Chain Fatty acid

Sphingomyelin



Long Chain Fatty acid

Structure & Function of Myelin Sheath

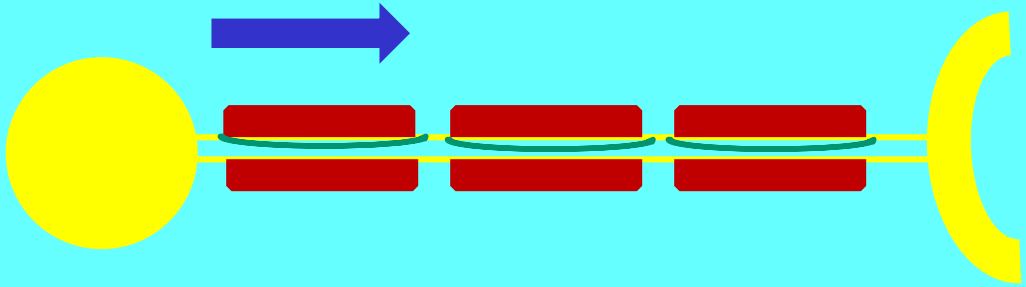
Myelin structure: Lipids (80%) → **Glycolipids (mainly)**

→ **Sphingomyelin**

Proteins (20%)

Myelin sheath insulates the nerve axon to avoid signal leakage and greatly speeds up the transmission of impulses along axons

Direction of nerve impulse



Lipoprotein Structure

Outer part (coat):

Apoproteins or apolipoproteins

Phospholipids (Why?)

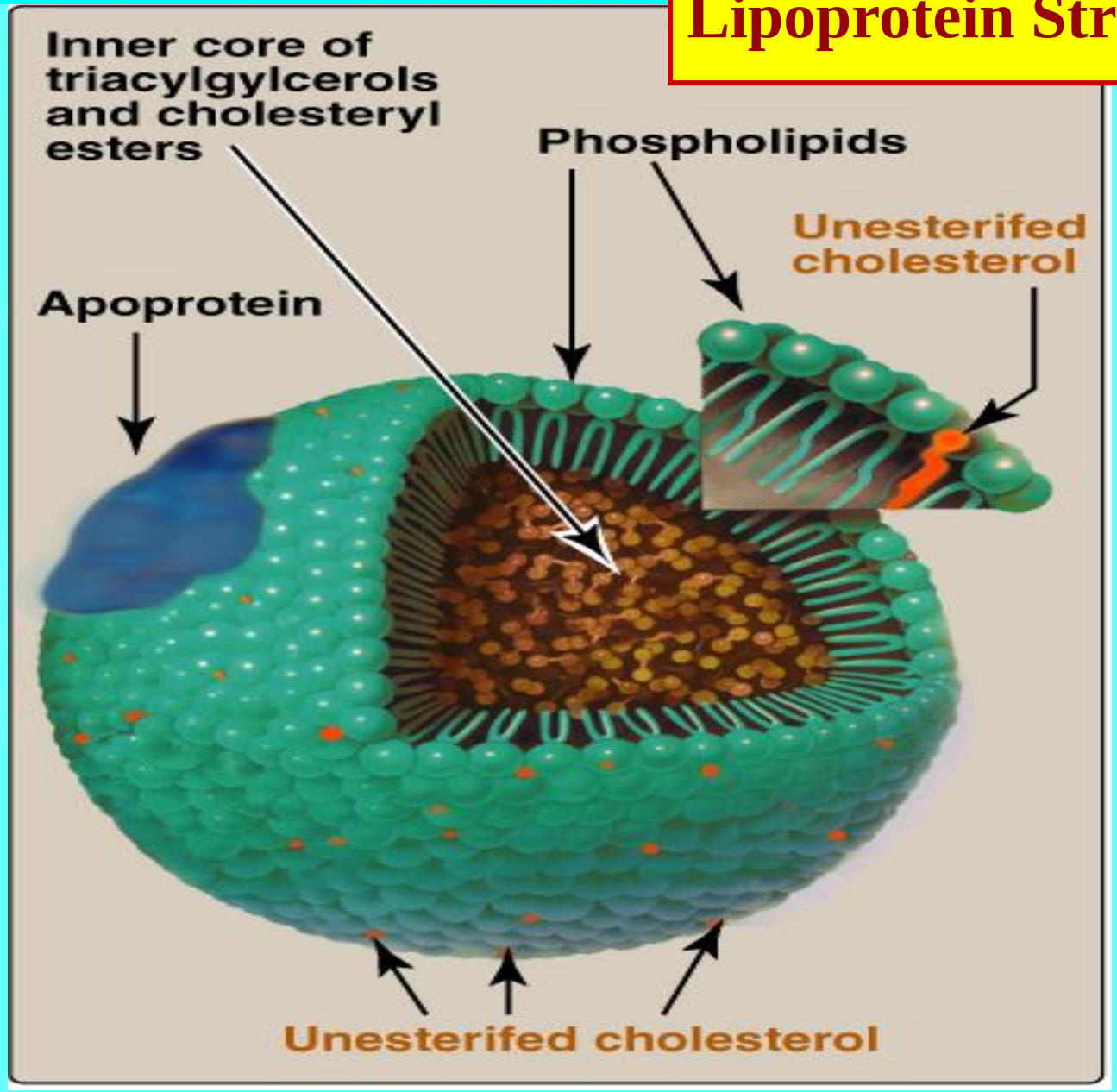
Free cholesterol

(Relatively hydrophilic, allowing transport of lipid particles of the core in the aqueous plasma)

Inner part (core):

- **According to the type of lipoproteins**
- **Different lipid components in various combinations**

Lipoprotein Structure



Phospholipases

(1) For glycerophospholipids:

Phospholipases A1, A2, C and D

Present in all tissues and pancreatic juice

Present in snake venoms and bacterial toxins

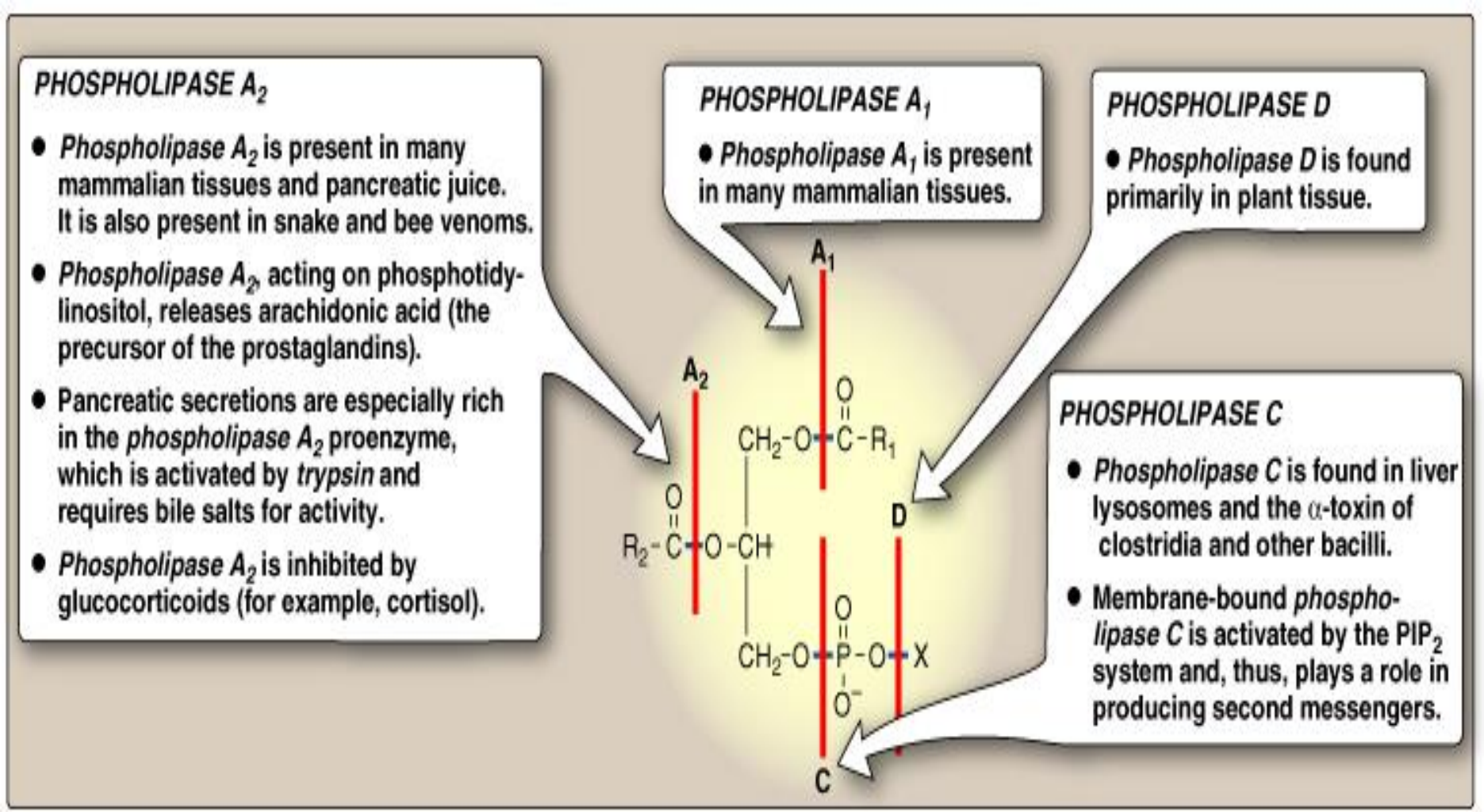
(2) For sphingophospholipids:

Lysosomal phospholipase

Sphingomyelinase

Sphingomyelin ⟶ Ceramide + Phosphocholine

Glycero-phospholipases



Functions of Phospholipases

(1) Degradation of phospholipids

- Production of second messengers
- Digestion of phospholipids by pancreatic juice
- Pathogenic bacteria degrade phospholipids of membranes and causing spread of infection

(2) Remodeling of phospholipids:

- Specific phospholipase removes fatty acid from phospholipid
- Replacement of fatty acid by alternative fatty acid using fatty acyl CoA transferase

  e.g., Binding of 2 palmitic acids in DPPC

  Binding of arachidonic to carbon 2 of PI or PC

Take Home Message

- **Phospholipids are Complex lipids**

- **Phospholipids have important physiological functions:**

  A. Membrane-bound:

  Structural

  Signalling & anchoring: e.g., PI

  Myelin sheath: e.g., sphingomyelin

  B. Non-membrane bound:

  Structural: Lipoprotein coat

  Alveolar re-inflation: Lung surfactant

  Detergent effect: Phospholipids of bile

Take Home Message

CONT'D

Phospholipases:

Phospholipases A1, A2, C and D

Lysosomal Phospholipase: Sphingomyelinase

Function of phospholipases:

Degradation of phospholipids

e.g., production of second messengers

Remodeling of phospholipids

e.g., production of DPPC (lung surfactant)