بسم الله الرحمن الرحيم

Phospholipid Compounds of Physiological Importance

By

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Objectives

By the end of this lecture, students are expected to:

- Discuss selected members of phospholipids
- Describe the physiological importance of phospholipids with specific examples
- Distinguish various Plospholipases and describe their roles:
  - 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 IP3 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: Ketone bodies)

Soluble in non-polar solvents

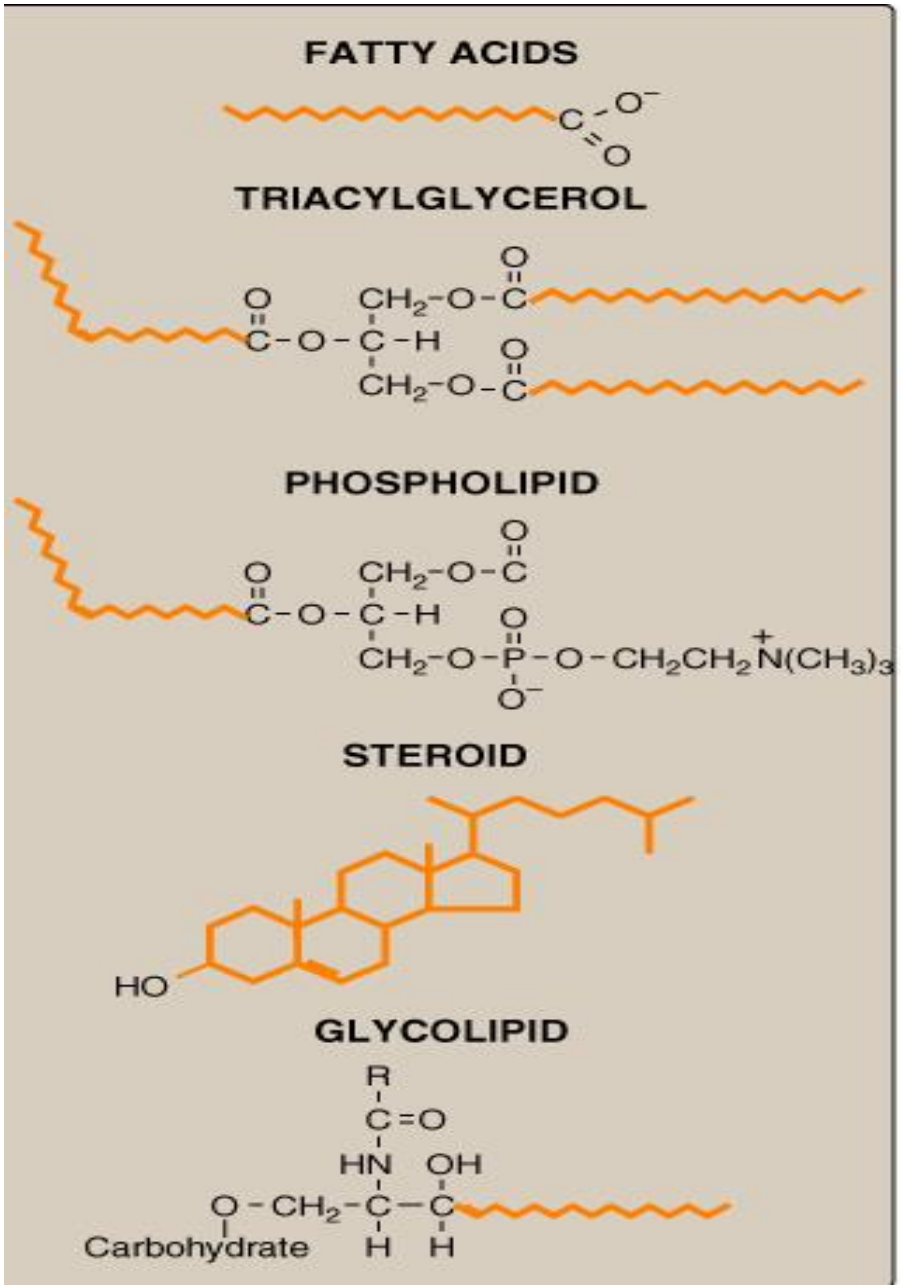
Lipid Compounds: Heterogeneous Group

A. Simple Lipids:

- Fatty acids
- Ketone bodies
- Triacylglycerol
- Cholesterol

B. Complex Lipids:

- Phospholipids
- Lipoproteins
- Glycolipids



Phospholipids

A. Glycerophospholipids

- Glycerol-containing phospholipids
- Degraded and remodeled by phospholipases

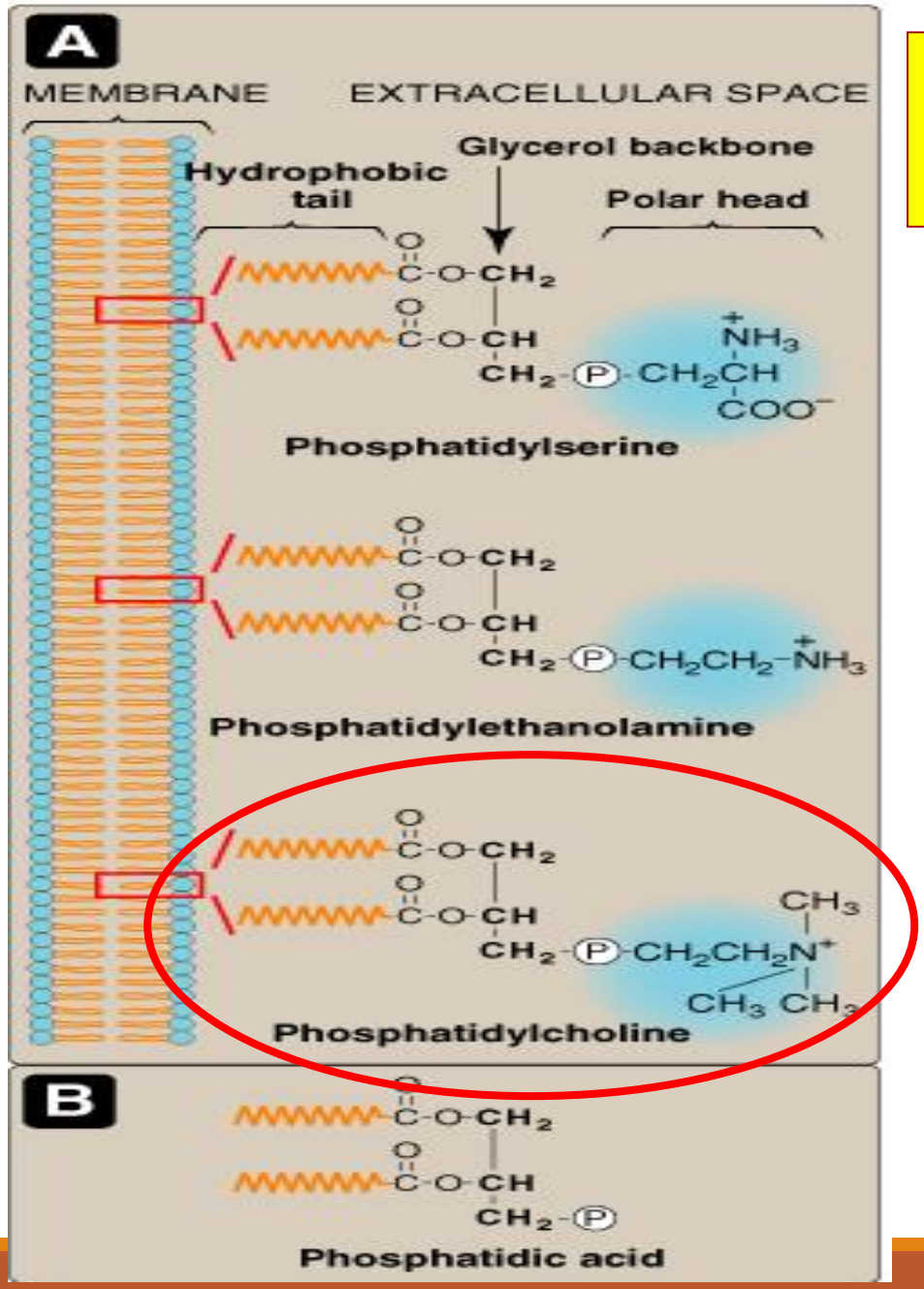
B. Sphingo-phospholipids:

- Sphingosine-containing phospholipids
- Degraded by lysosomal phospholipase (sphingomyelinase)

Phospholipids

A. Glycerophospholipids:

1. Phosphatidylcholine (Lecithin)
   e.g., Surfactant (Dipalmitoylecithin)
2. Phosphatidylinositol (Signaling & Anchoring molecule)



Phospholipids:
Glycerophospholipids

Parent Compound:
Phosphatidic acid

Members:

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

Phospholipids: Glycerophospholipids

1. Dipalmitoylecithin (Lung surfactant)

Synthesis and secretion: by granular pneumocytes

It is the major lipid component of lung surfactant (65%) (Remaining 35% is: 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 wks. of gestation)

Prevention:

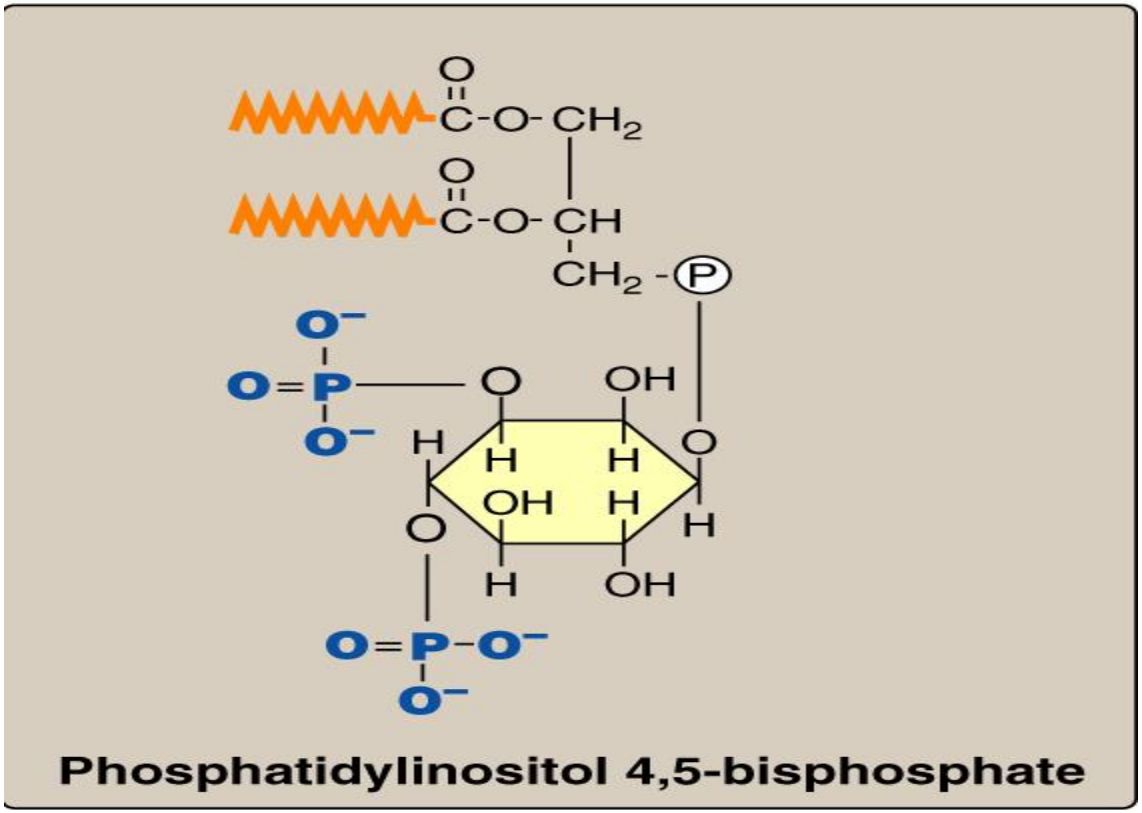
Glucocorticoids to the pregnant mother with low L/S ratio shortly before delivery

Treatment:

Intratracheal administration of surfactant to pre-term infants with RDS

Phospholipids: Glycerophospholipids

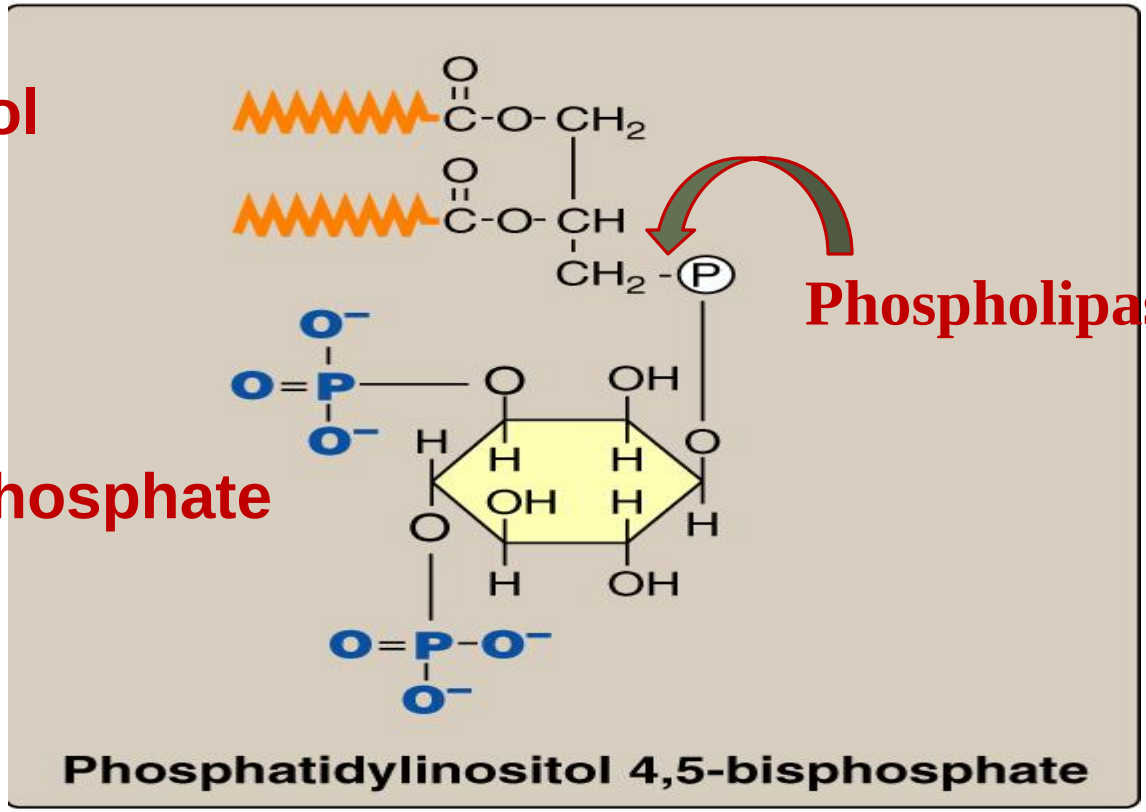
2. Phosphatidylinositol 4,5 bisphosphate (PI)



Calcium/Phosphatidylinositol System

Diacylglycerol (DAG)

InositolTrisphosphate (IP_3)



Phosphatidylinositol System

Role in signaling

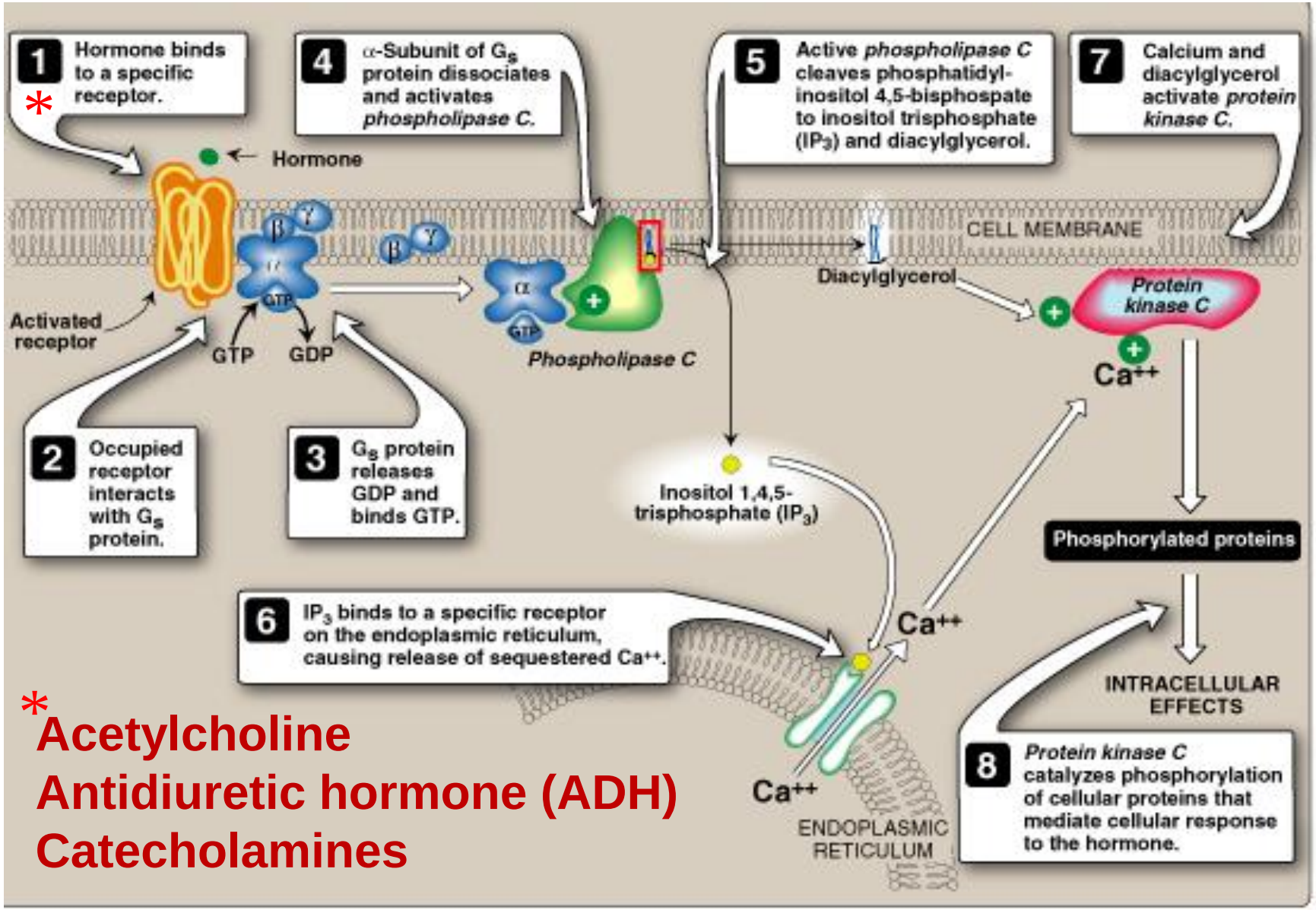
Signal: Hormones or neurotransmitters
e.g., Acetylcholine, antidiuretic hormone (V1-receptor) and catecholamines (α_1 actions)

Receptor: G-protein coupled receptor

Effects:

Activation of phospholipase C
Hydrolysis of phosphatidylinositol 4,5-bisphosphate→
Production of IP3 (↑ 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

Phosphatidylinositol

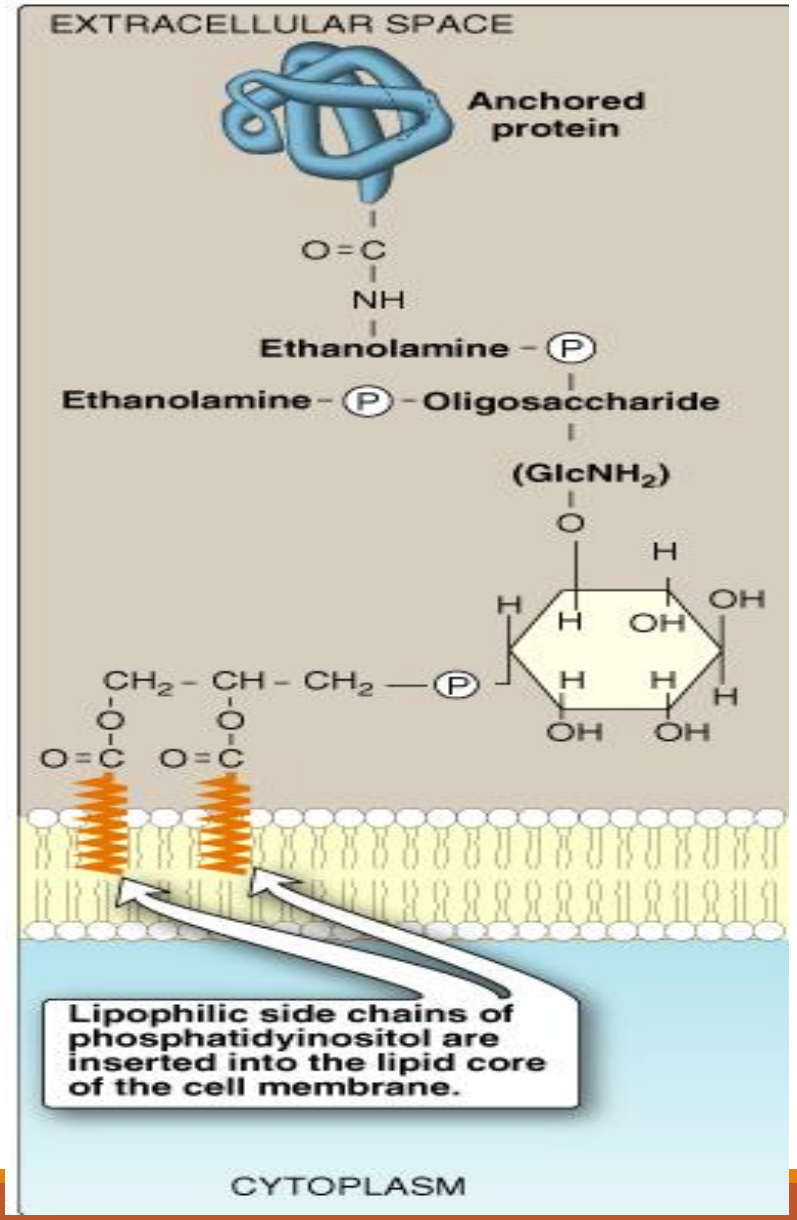
Role in Protein Anchoring

Anchoring of proteins to membranes via Carbohydrate-Phosphatidylinositol Bridge

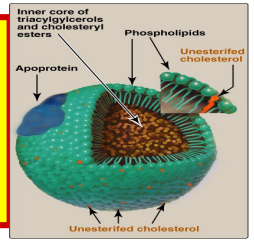
Examples of anchored proteins:

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



Lipoprotein Structure



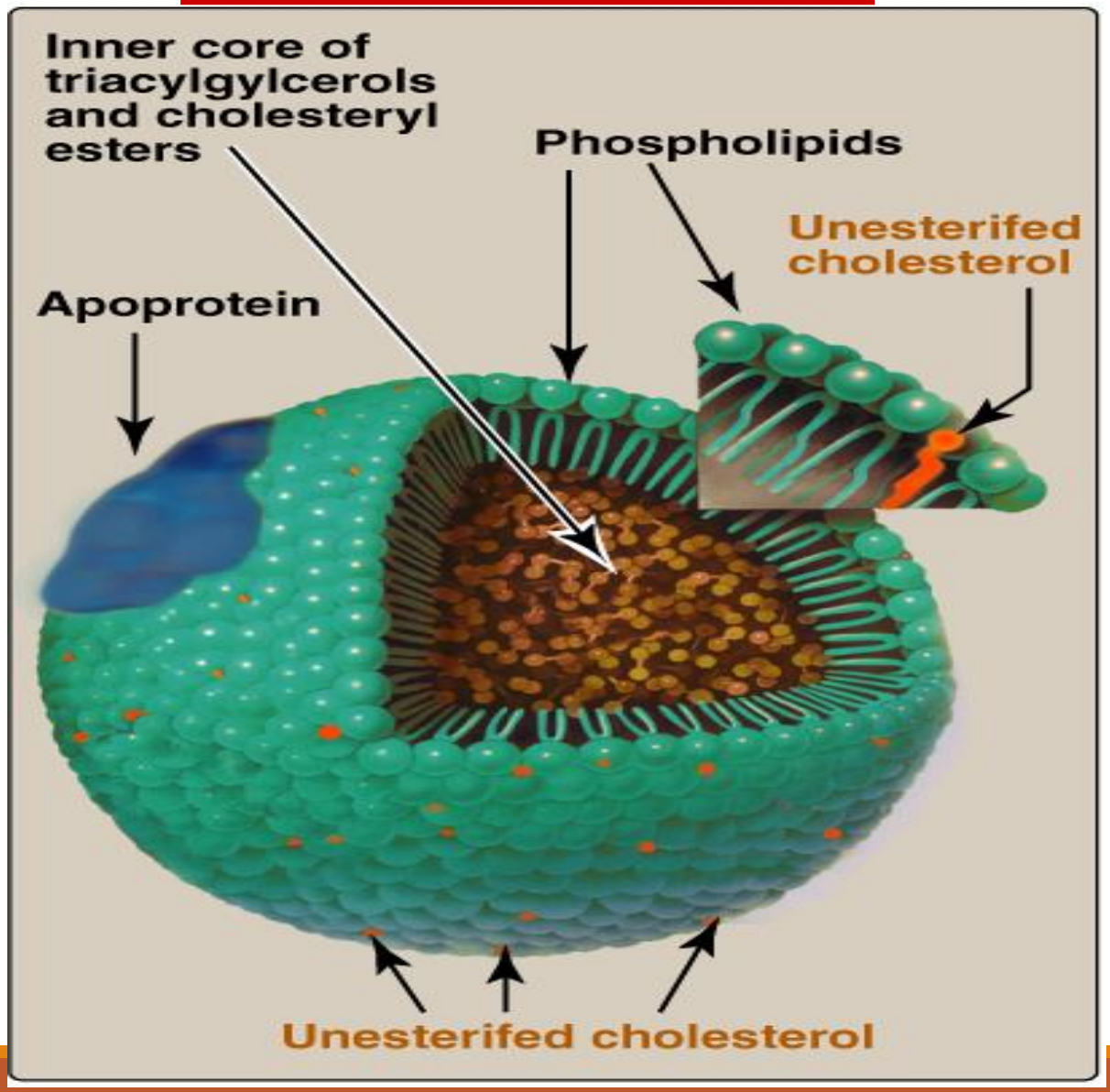
Outer part (coat):

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



HDL has the highest content of phospholipids among all classes of lipoproteins

Different classes of lipoproteins:

1- Chylomicrons
2- Low density lipoproteins (LDL)
3. High density lipoproteins (HDL)
4- Very low density lipoproteins (VLDL)

HDL has the highest content of Phospholipids.

Phosphatidyl choline (lecithin) acts as a source for fatty acids necessary for esterification of cholesterol on the surface of HDL by lecithin-cholesterol acyl transferase (LCAT/PCAT)

Phospholipases

(1) For glycerophospholipids:

Phospholipases A1, A2, C and D

Present in all tissues and pancreatic juice

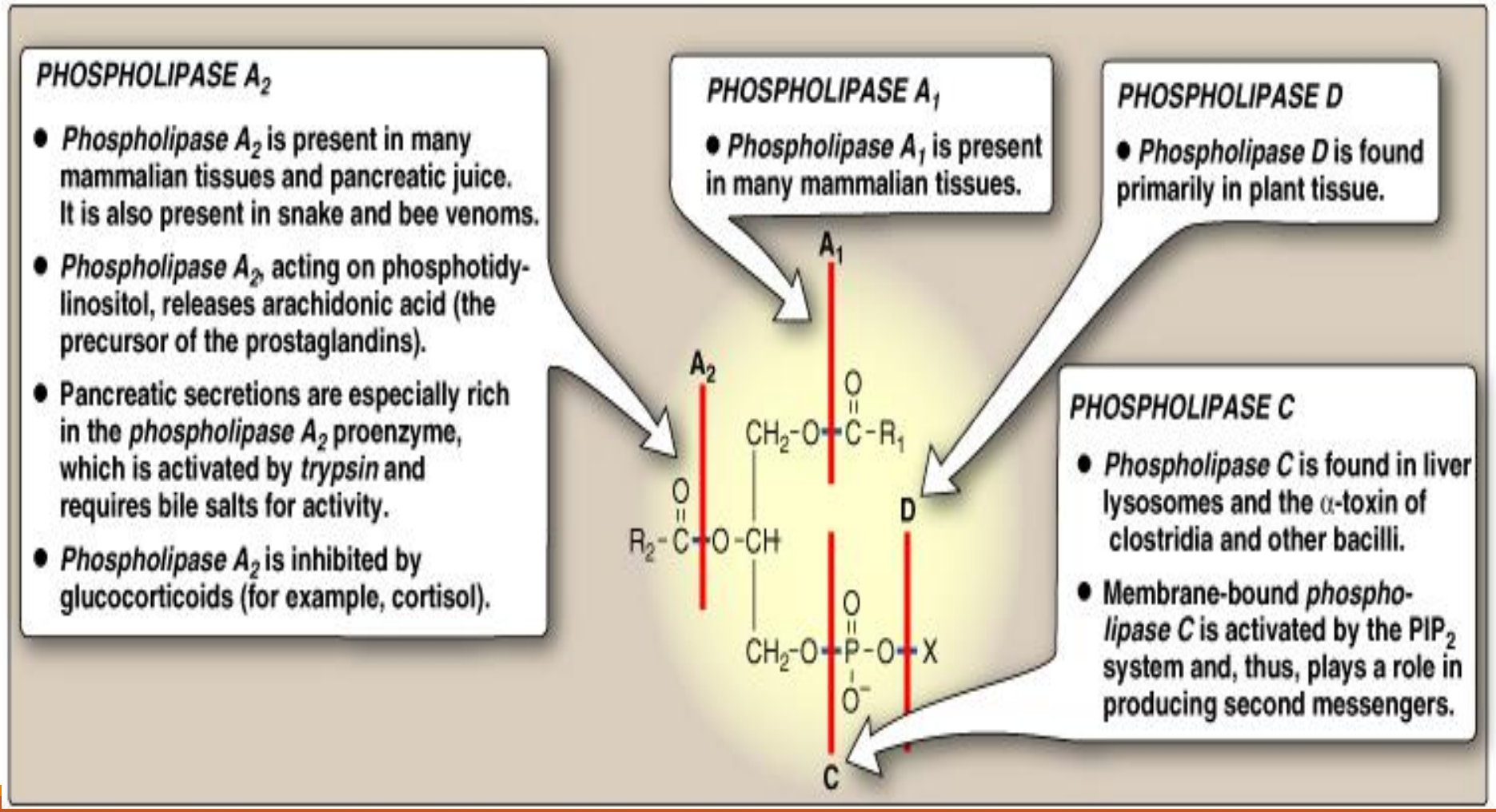
Present in snake venoms and bacterial toxins

Phospholipase A2 is important for the remodeling of phospholipids to produce the lung surfactant

(2) For sphingophospholipids:

Lysosomal phospholipase (Sphingomyelinase)

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 (e.g. Phospholipase A2 is important for the remodeling of phospholipids to produce the lung surfactant
- Replacement of fatty acid by alternative fatty acid using fatty acyl CoA transferase
- e.g., Binding of 2 palmitic acids in Dipalmitoylphosphatidylcholine (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

Signaling & 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)