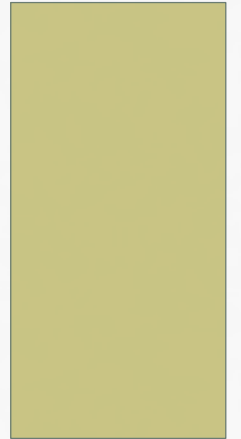


RESPIRATORY BLOCK

**PHOSPHOLIPIDS OF
CLINICAL SIGNIFICANCE**

DR. USMAN GHANI



OBJECTIVES

By the end of this lecture the First Year students will be able to:

- Identify the types and functions of phospholipids
- Discuss the physiological importance of phospholipids
- Understand the role of glycerophospholipids in lung surfactant and their clinical implications in respiratory distress syndrome (RDS)
- Identify the classes and physiological functions of phospholipase enzymes

OVERVIEW

- Types and functions of phospholipids
- Glycerophospholipids: Types, functions and role in lung surfactant, cell signaling and protein anchoring
- Respiratory distress syndrome (RDS)
- Sphingophospholipids
- Phospholipids in lipoprotein particles
- Phospholipases: Types and functions

PHOSPHOLIPIDS

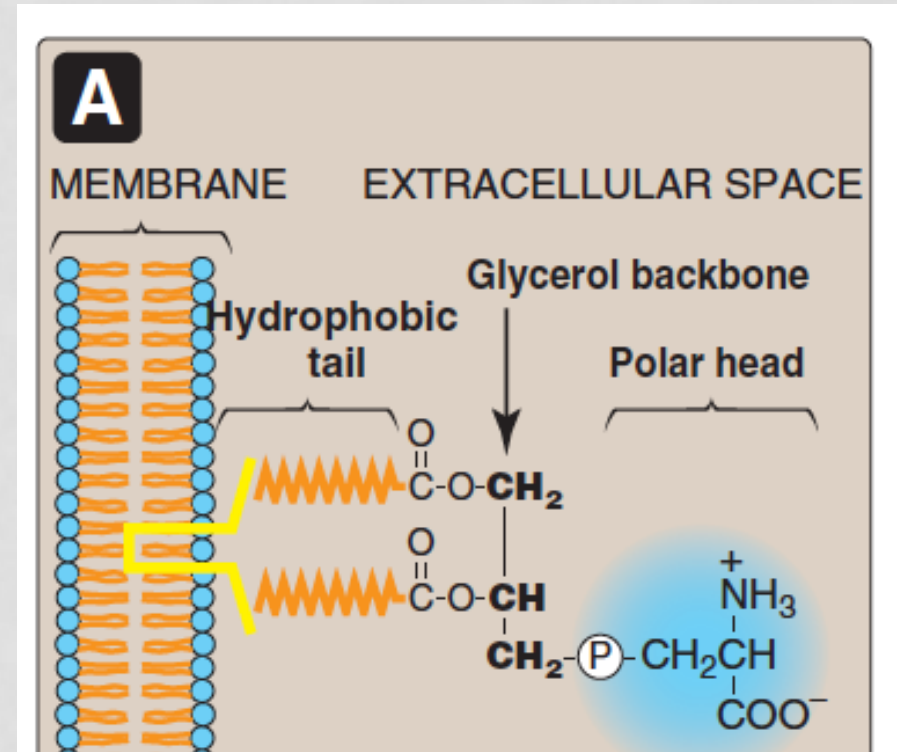
- Phospholipids are polar, ionic compounds that contain an alcohol group attached either to:
 - Diacylglycerol or
 - Sphingosine
- Major lipids of cell membranes

Two classes:

- Glycerophospholipids
- Sphingophospholipids

PHOSPHOLIPIDS

- Their hydrophobic (non-polar) portion of is attached to the membrane
- Their hydrophilic (polar) portion extends outward interacting with the aqueous environment

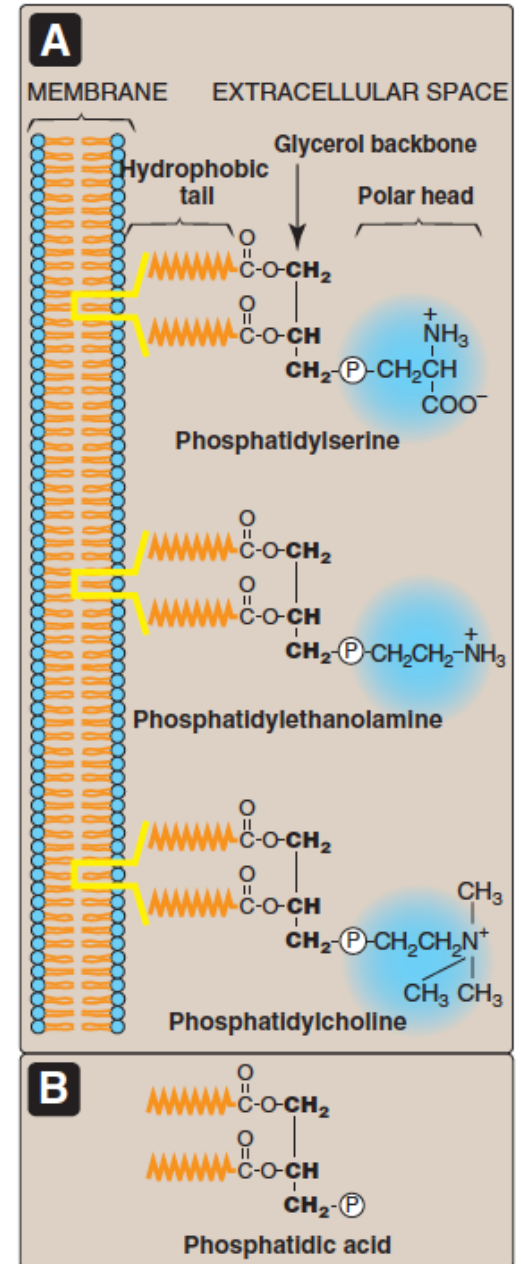


FUNCTIONS OF PHOSPHOLIPIDS

- Membrane-bound phospholipids act as:
 - Reservoir for intracellular messengers
 - Anchors to cell membranes
- Nonmembrane-bound phospholipids act as:
 - Lung surfactant
 - Components of bile (as detergents to solubilize cholesterol)

GLYCEROPHOSPHOLIPIDS

- Also called phosphoglycerides
- Contain glycerol
- A major class of phospholipids
- All contain phosphatidic acid (PA)
- PA is the simplest phospholipid



GLYCEROPHOSPHOLIPIDS

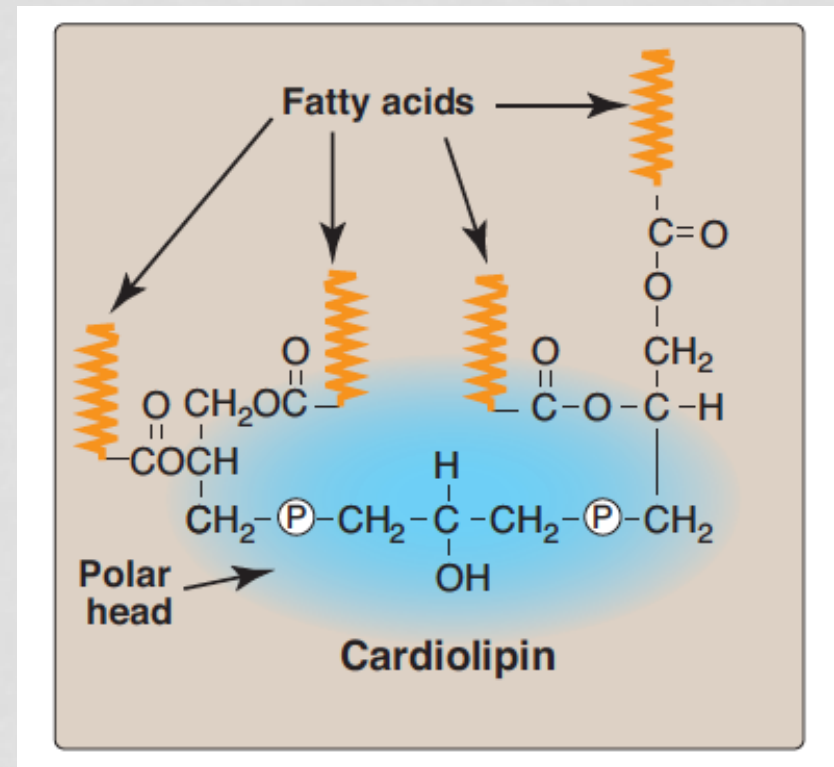
Phospholipids are derived from PA such as:

Serine + PA	Phosphatidylserine (PS)	Cell signaling Blood clotting
Ethanolamine + PA	Phosphatidylethanolamine (PE) (cephalin)	
Choline + PA	Phosphatidylcholine (PC) (lecithin)	Lung surfactant
Inositol + PA	Phosphatidylinositol (PI)	Cell signaling
Glycerol + PA	Phosphatidylglycerol (PG)	Lung surfactant

SOME EXAMPLES

Cardiolipin

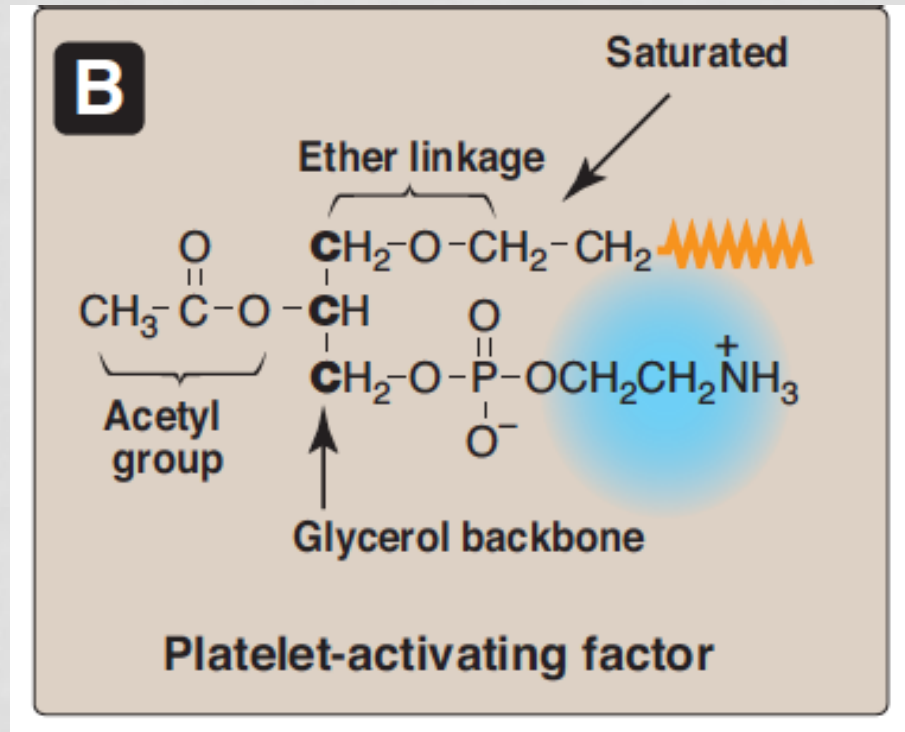
- Two molecules of PA joined to an additional molecule of glycerol through PO₄ groups
- In the inner mitochondrial membrane
- Function: maintenance of respiratory complexes of electron transport chain



SOME EXAMPLES

Platelet activating factor (PAF)

- Binds to cell surface receptors
- Triggers thrombotic and acute inflammatory reaction



ROLE OF PC IN LUNG SURFACTANT

- Lung surfactant is a complex mixture of:
 - Lipids (90%) including **Dipalmitoylphosphatidylcholine** (DPPC)
 - Proteins (10%)
- Alveolar cells of the lungs are lined by the extracellular fluid layer
- Alveolar cells secrete DPPC (a major lung surfactant)

ROLE OF PC IN LUNG SURFACTANT

- Surfactant decreases the surface tension of the fluid layer
- Reduces pressure needed to re-inflate alveoli
- Prevents alveolar collapse (atelectasis)

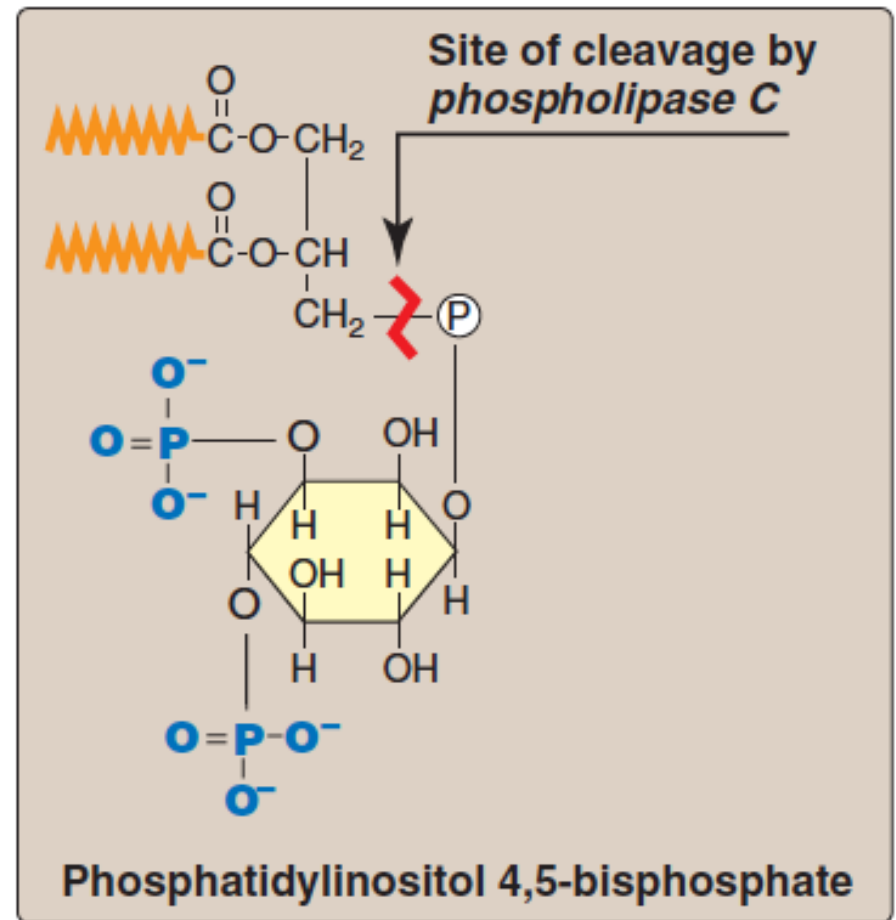
ROLE OF PC IN LUNG SURFACTANT

Respiratory distress syndrome (RDS)

- In preterm infants due to deficiency of lung surfactant
- A major cause of neonatal death
- Treatment: Glucocorticoids to mother to promote lung maturation
- In adults due to damaged alveoli by infection or trauma

ROLE OF PI IN CELL SIGNALING

- Plays important role in intracellular signaling
- PI is part of calcium-phosphatidyl inositol system



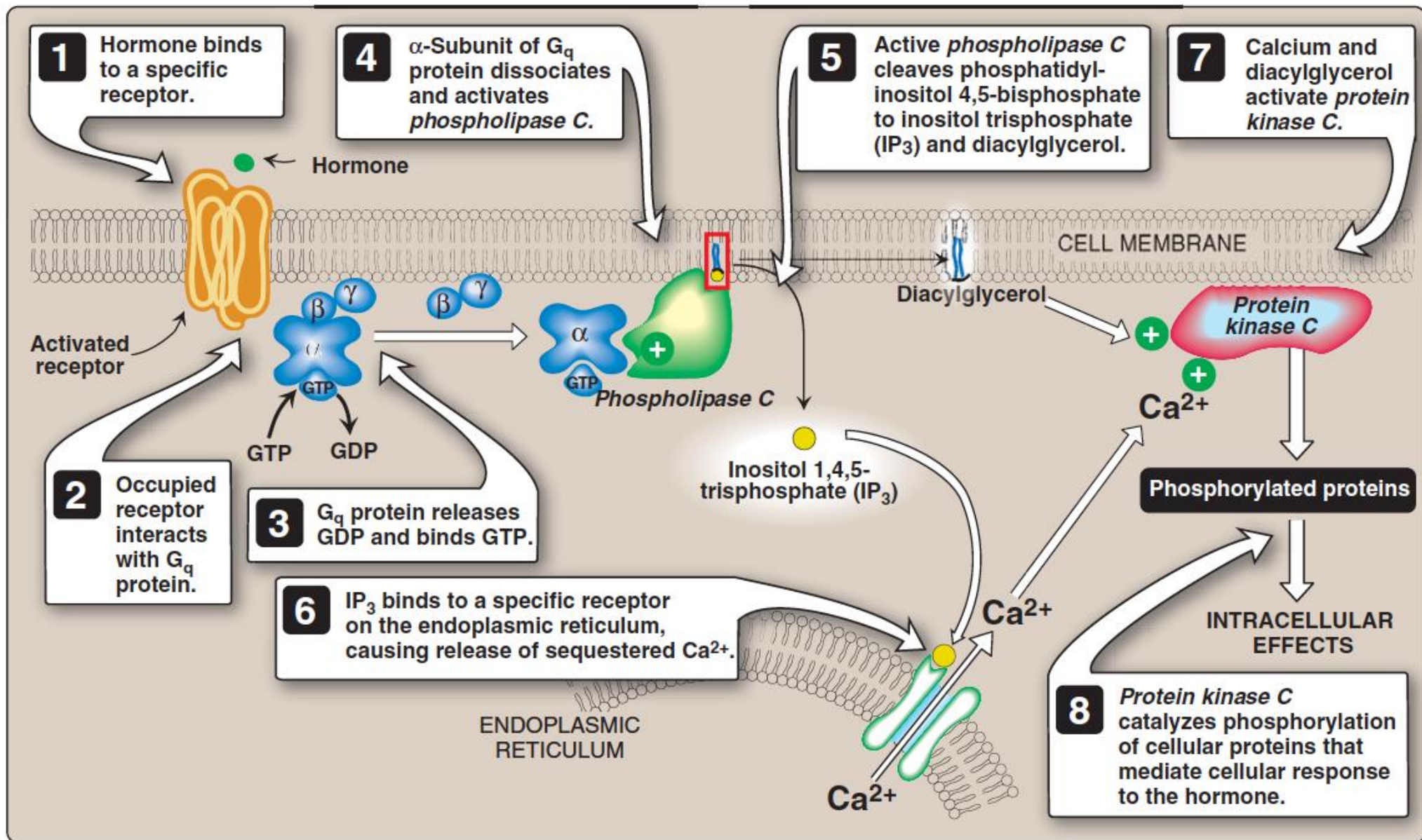


Figure 17.8

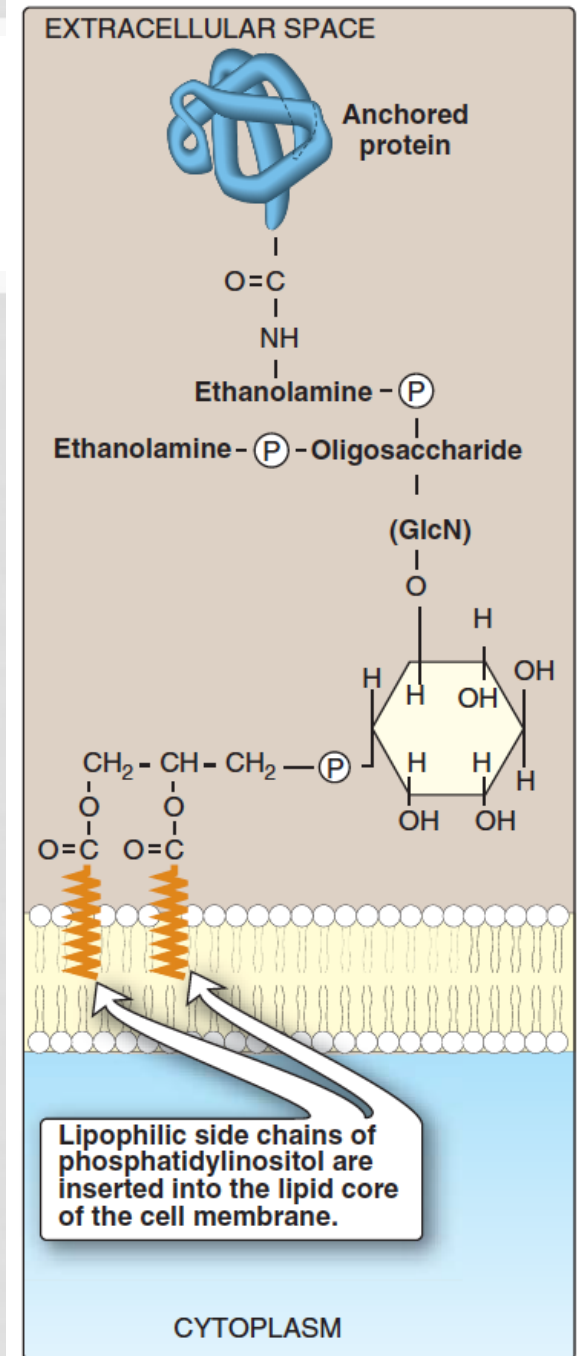
Role of inositol trisphosphate and diacylglycerol in intracellular signaling.

ROLE OF PI IN MEMBRANE PROTEIN ANCHORING

- Anchoring of proteins to membranes through carbohydrate-PI bridge

Examples:

- Alkaline phosphatase (on the surface of small intestine)
- Acetylcholine esterase (on postsynaptic membrane of neurons)
- Anchoring proteins can be cleaved by phospholipase C enzyme



SPHINGOPHOSPHOLIPIDS

- A long-chain fatty acid attached to sphingosine
- Example: Sphingomyelin
- An important component of myelin that protects and insulates nerve fibers

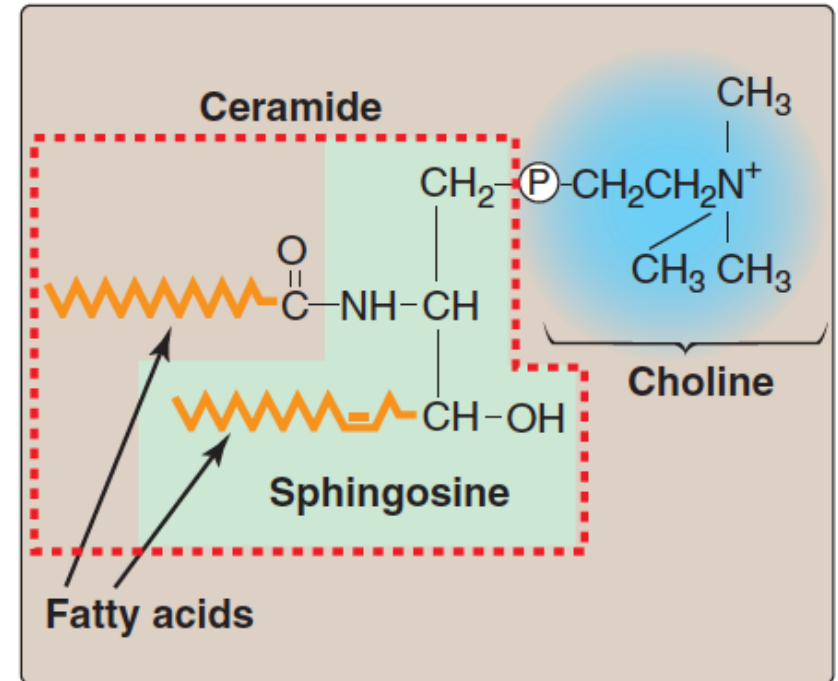


Figure 17.4

Structure of sphingomyelin, showing sphingosine (in green box) and ceramide components (in dashed box).

PHOSPHOLIPIDS IN LIPOPROTEIN PARTICLES

- The outer core of lipoprotein particles is hydrophilic
- Contains phospholipids and free cholesterol
- Allows transport of core lipids in aqueous plasma

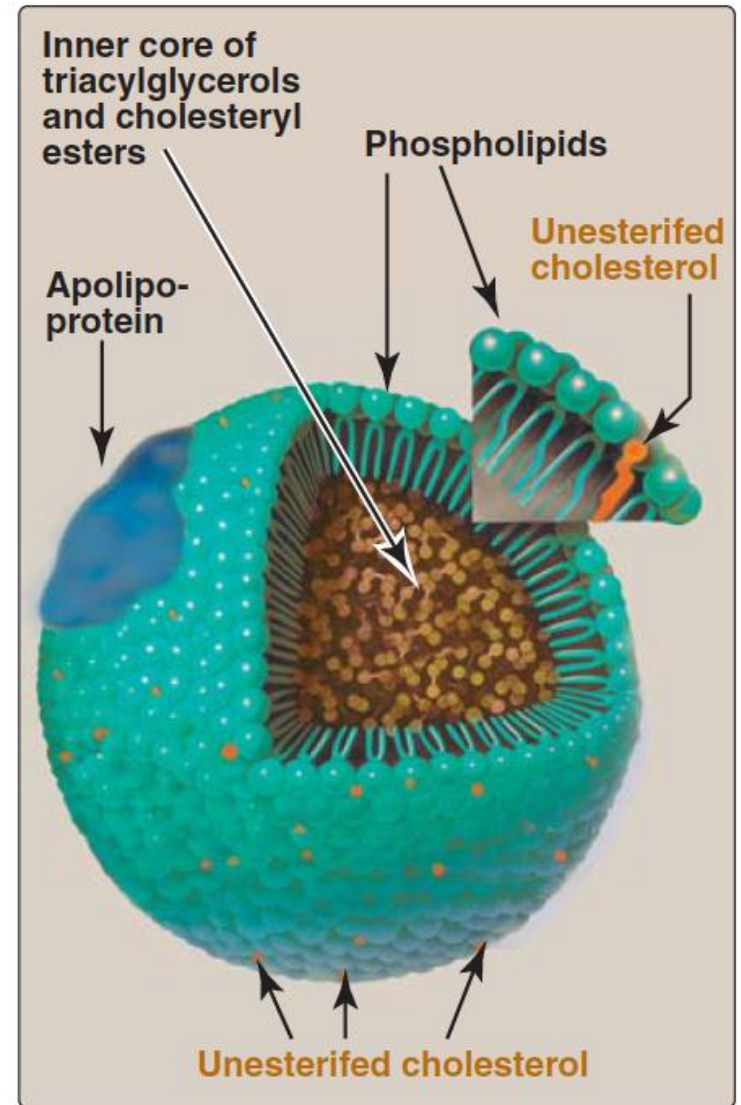


Figure 18.14
Structure of a typical lipoprotein particle.

PHOSPHOLIPASES

- Phospholipids are degraded by phospholipase enzymes
- Present in all tissues including pancreatic juice
- Glycerophospholipids are degraded by:
 - Phospholipase A1, A2, C, D
- Sphingophospholipids are degraded by:
 - Sphingomyelinase

FUNCTIONS OF PHOSPHOLIPASES

- Digestion of phospholipids by pancreatic juice
- Important for remodeling of phospholipids
- Production of second messengers
- Pathogenic bacteria produce phospholipases to dissolve cell membranes and spread infection

PHOSPHOLIPASE A_2

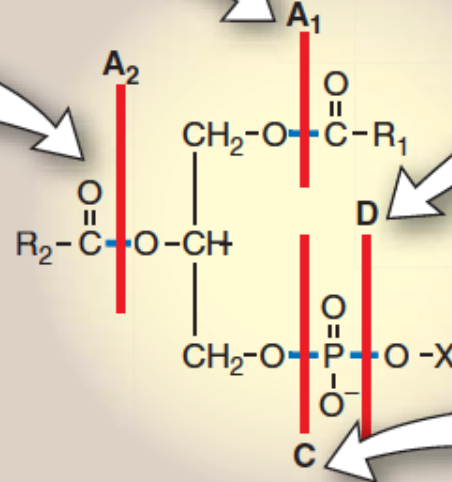
- *Phospholipase A_2* is present in many mammalian tissues and pancreatic juice. It is also present in snake and bee venoms.
- *Phospholipase A_2* , acting on phosphatidylinositol, releases arachidonic acid (the precursor of the prostaglandins).
- Pancreatic secretions are especially rich in the *phospholipase A_2* proenzyme, which is activated by *trypsin* and requires bile salts for activity.
- *Phospholipase A_2* is inhibited by glucocorticoids (for example, cortisol).

PHOSPHOLIPASE A_1

- *Phospholipase A_1* is present in many mammalian tissues.

PHOSPHOLIPASE D

- *Phospholipase D* is found primarily in plant tissue.



PHOSPHOLIPASE C

- *Phospholipase C* is found in liver lysosomes and the α -toxin of clostridia and other bacilli.
- Membrane-bound *phospholipase C* is activated by the PIP₂ system and, thus, plays a role in producing second messengers.

Figure 17.11

Degradation of glycerophospholipids by *phospholipases*.

TAKE HOME MESSAGE

- Phospholipids are complex lipids that perform important physiological functions in the body
- Membrane-bound phospholipids are involved in cell signaling, protein anchoring and myelin protective functions
- Nonmembrane-bound phospholipids function as lung surfactant and as detergent in the bile
- Phospholipases are enzymes that degrade phospholipases
- They are important for remodeling of phospholipids

REFERENCES

- Lippincott's Illustrated Reviews, Biochemistry, 6th Edition, Denise R. Ferrier, Lippincott Williams & Wilkins, USA, pp 201-207.