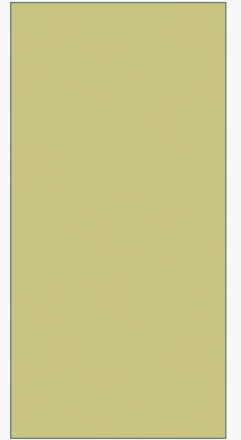


PHOSPHOLIPIDS OF
CLINICAL SIGNIFICANCE



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

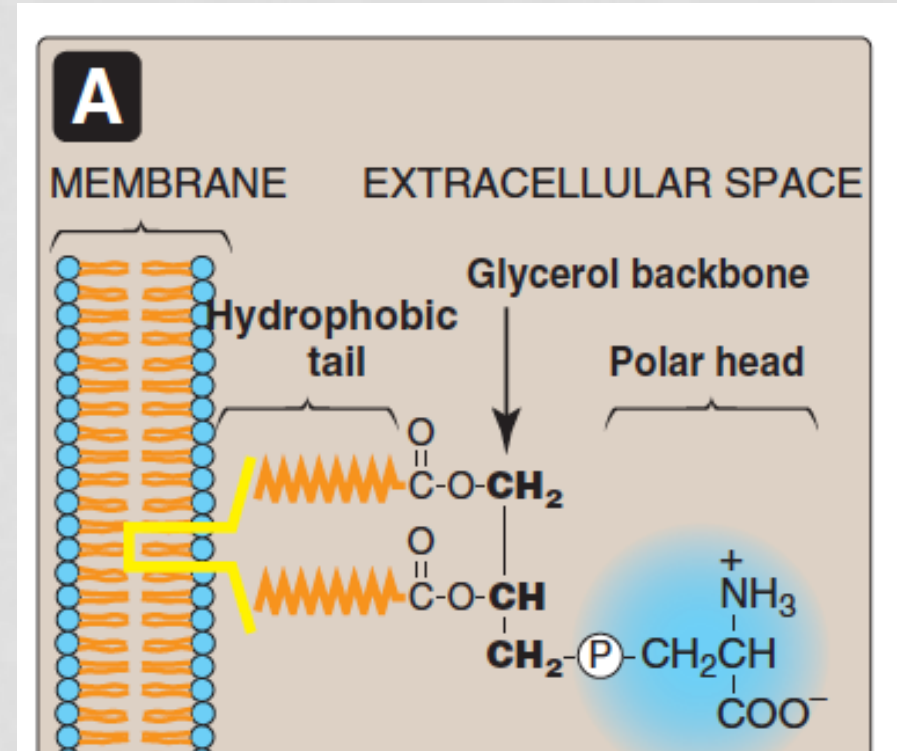
- **Phospholipids** are polar, ionic compounds that contain an alcohol group attached either to:
 - Diacylglycerol or
 - Sphingosine
- Major lipids of cell membranes

Two classes:

- **Glycerophospholipids**
- **Sphingophospholipids**

PHOSPHOLIPIDS

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

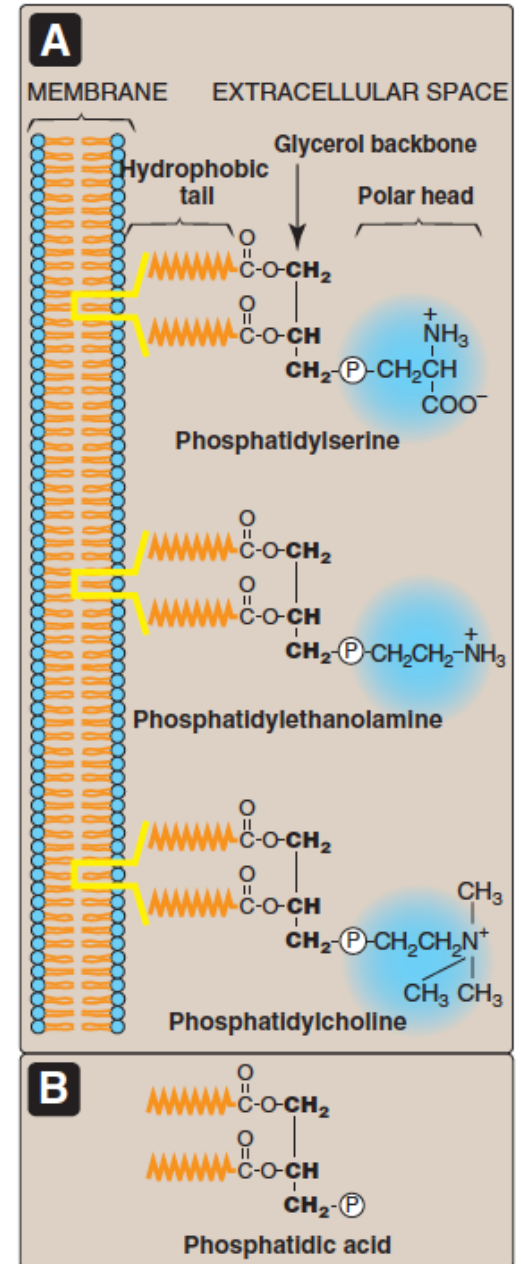


FUNCTIONS OF PHOSPHOLIPIDS

- 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

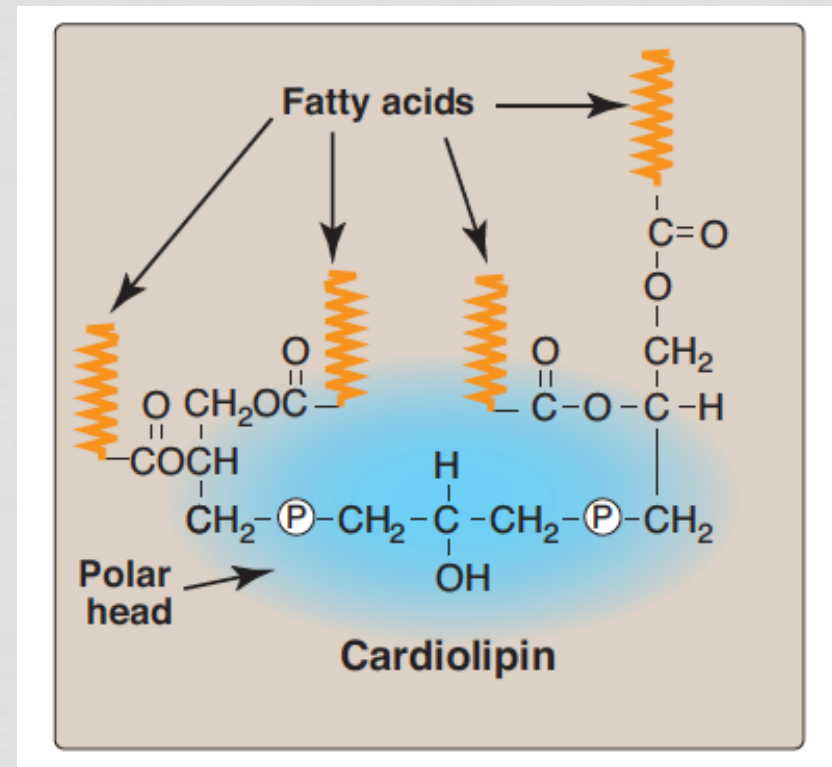
Phospholipids are derived from PA such as:

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

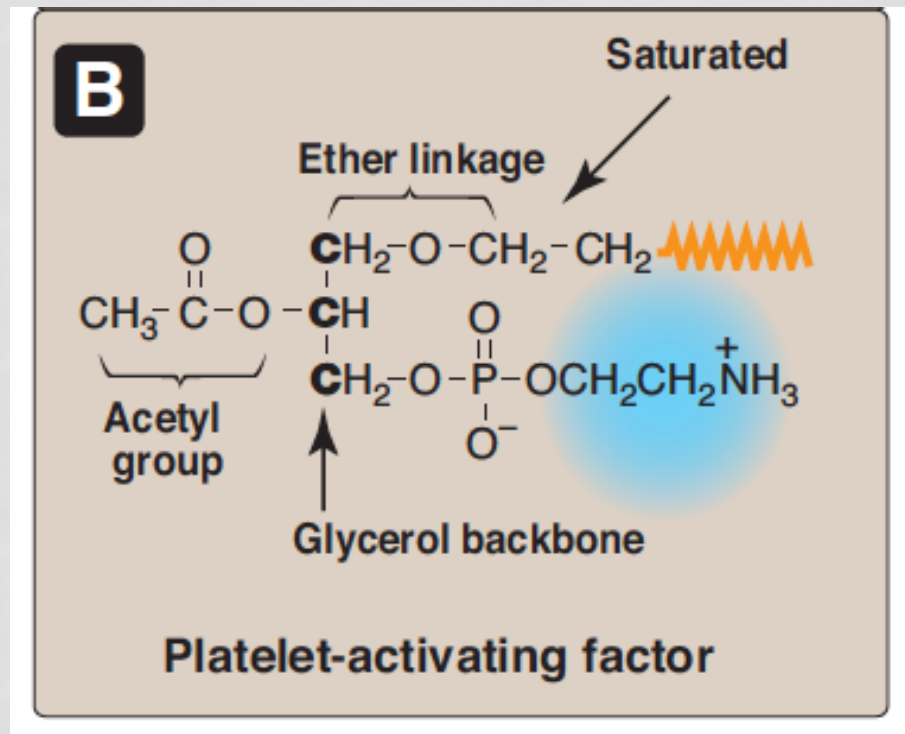
- Two molecules of **PA** joined to an additional molecule of **glycerol** through **PO₄** groups
- In the inner mitochondrial membrane
- **Function**: maintenance of respiratory complexes of electron transport chain



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**)

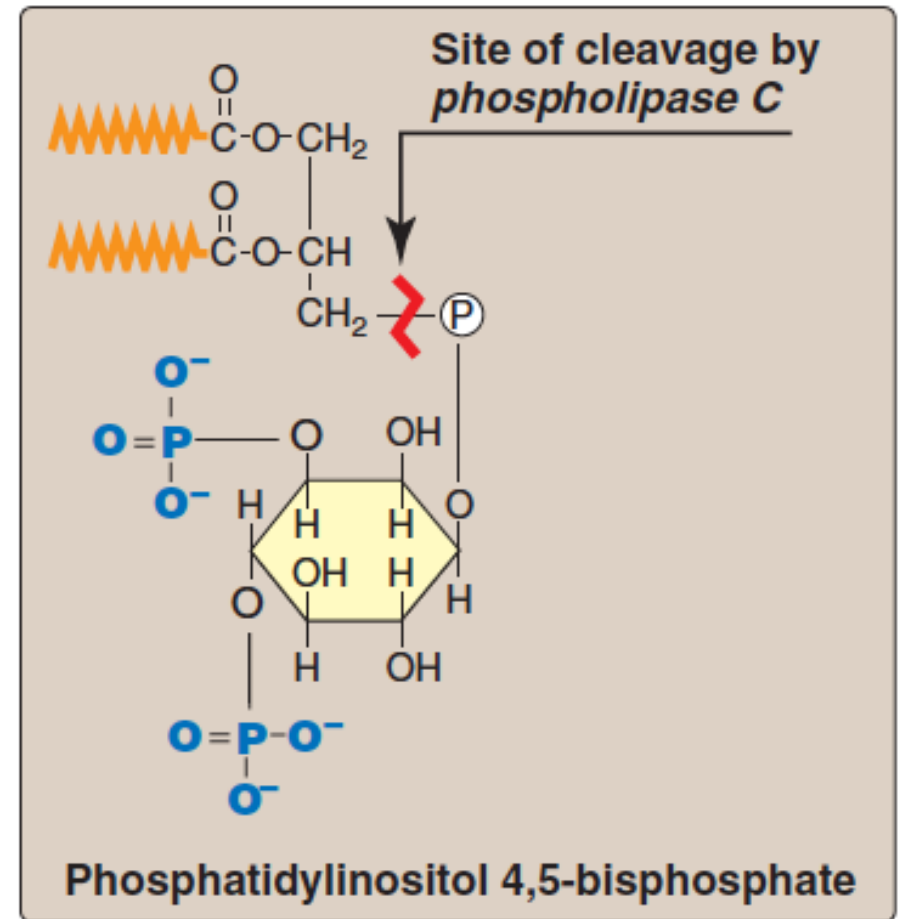
ROLE OF PC IN LUNG SURFACTANT

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



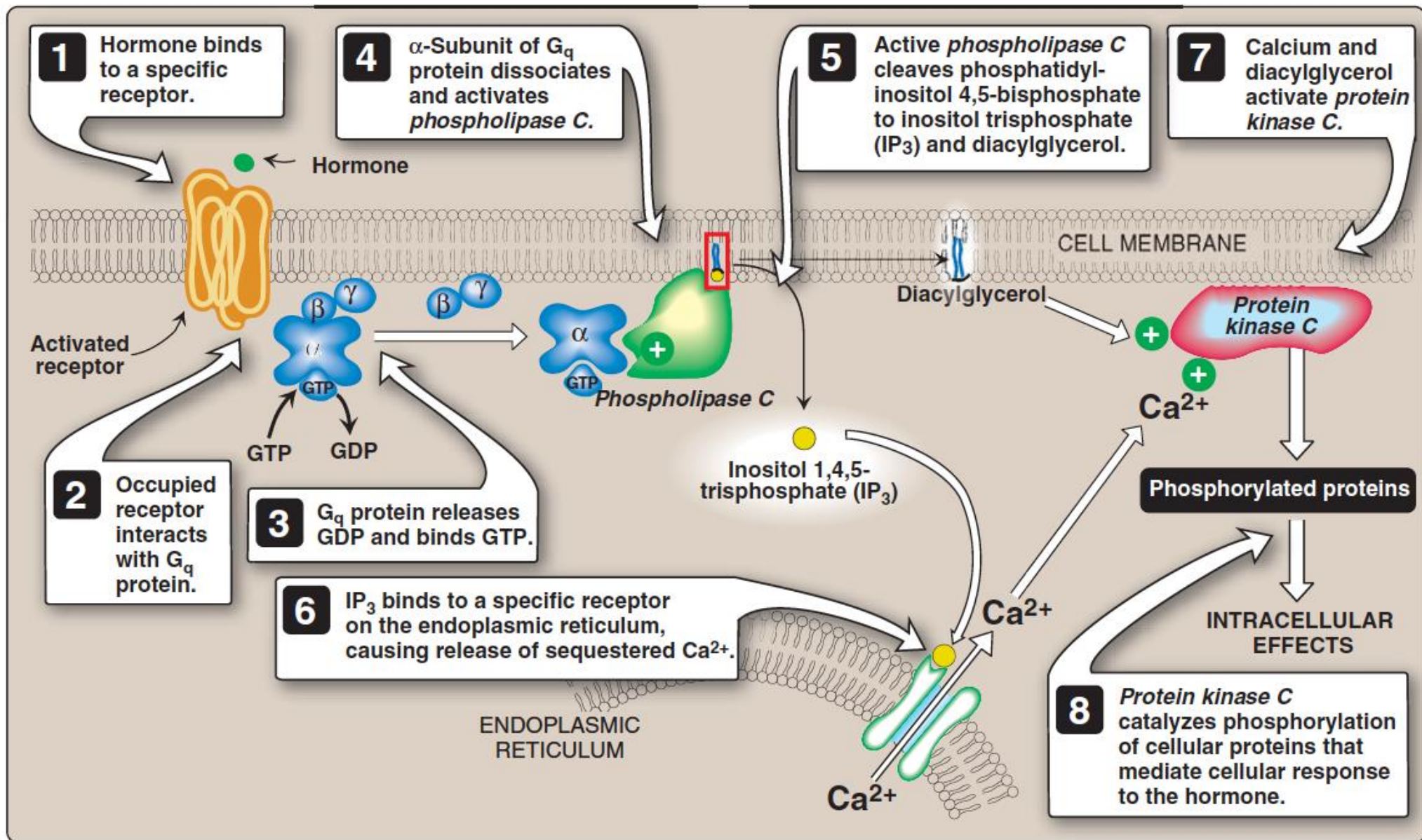


Figure 17.8

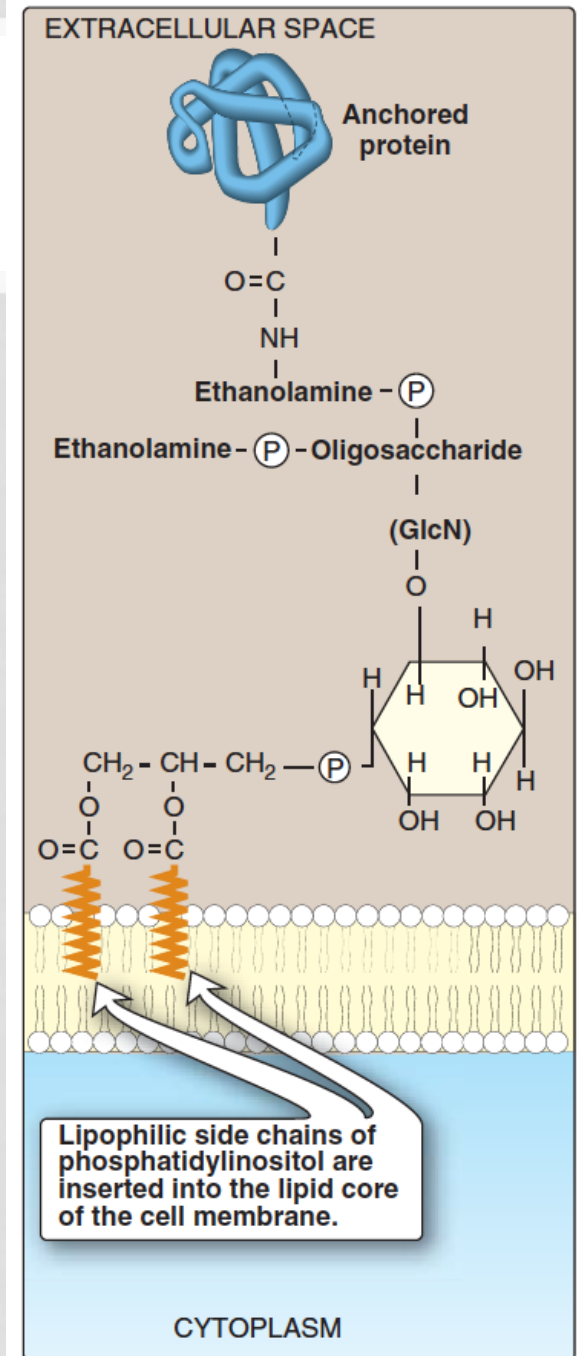
Role of inositol trisphosphate and diacylglycerol in intracellular signaling.

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**

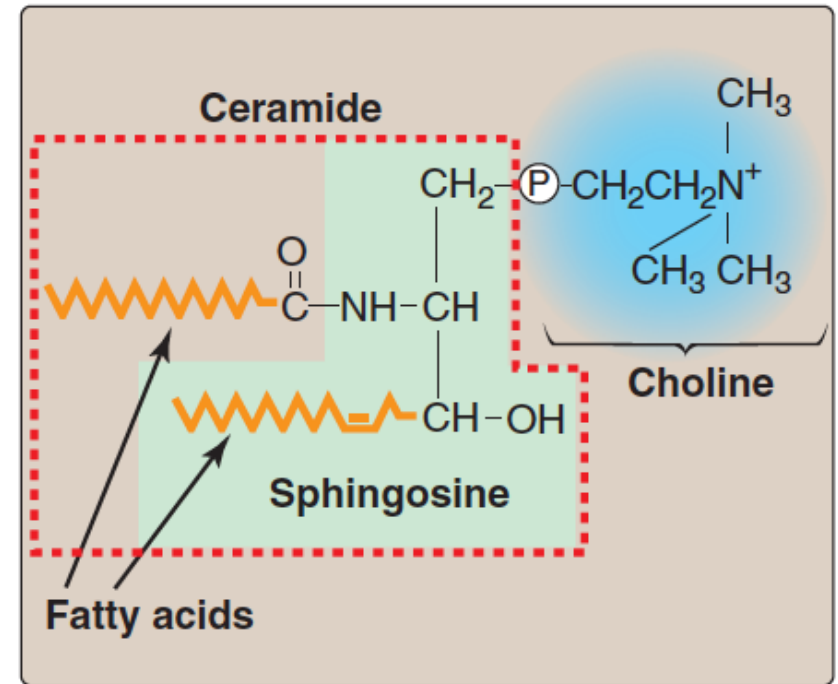


Figure 17.4

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

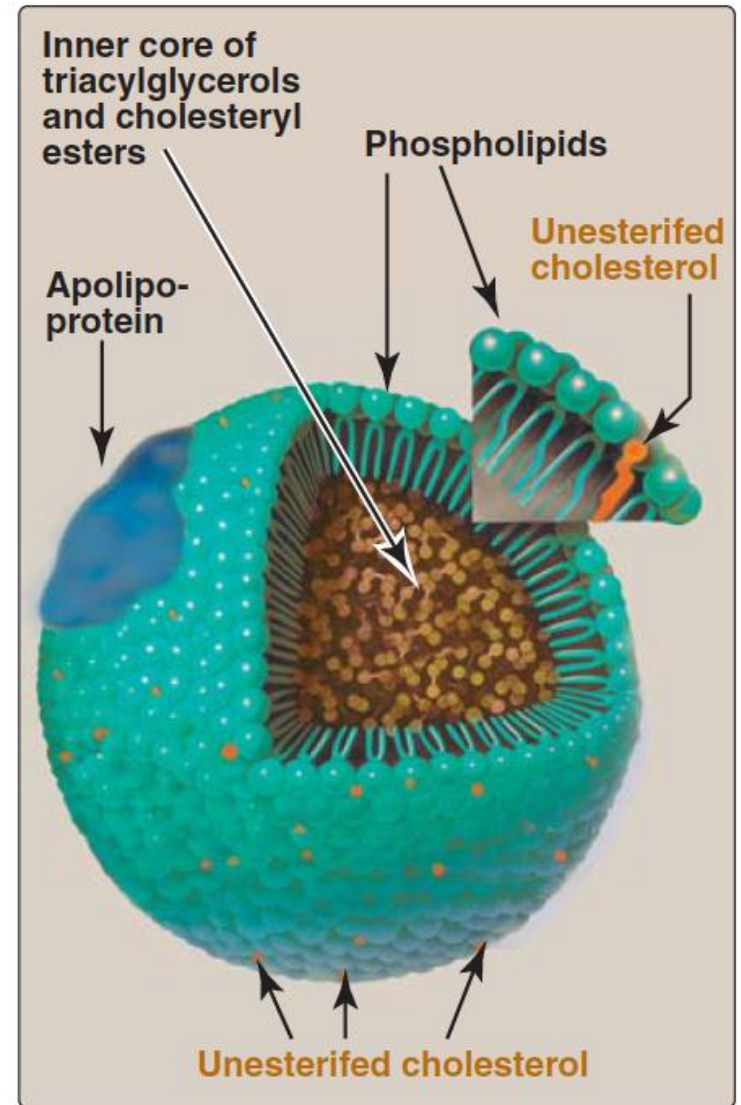


Figure 18.14
Structure of a typical lipoprotein particle.

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

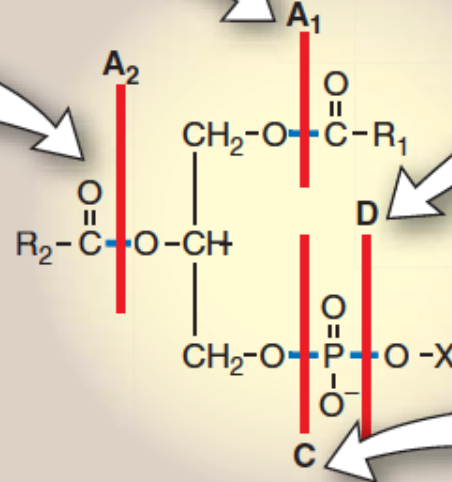
- *Phospholipase A₂* is present in many mammalian tissues and pancreatic juice. It is also present in snake and bee venoms.
- *Phospholipase A₂*, acting on phosphatidylinositol, releases arachidonic acid (the precursor of the prostaglandins).
- Pancreatic secretions are especially rich in the *phospholipase A₂* proenzyme, which is activated by *trypsin* and requires bile salts for activity.
- *Phospholipase A₂* is inhibited by glucocorticoids (for example, cortisol).

PHOSPHOLIPASE A_1

- *Phospholipase A₁* 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 phospholipids
- 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.