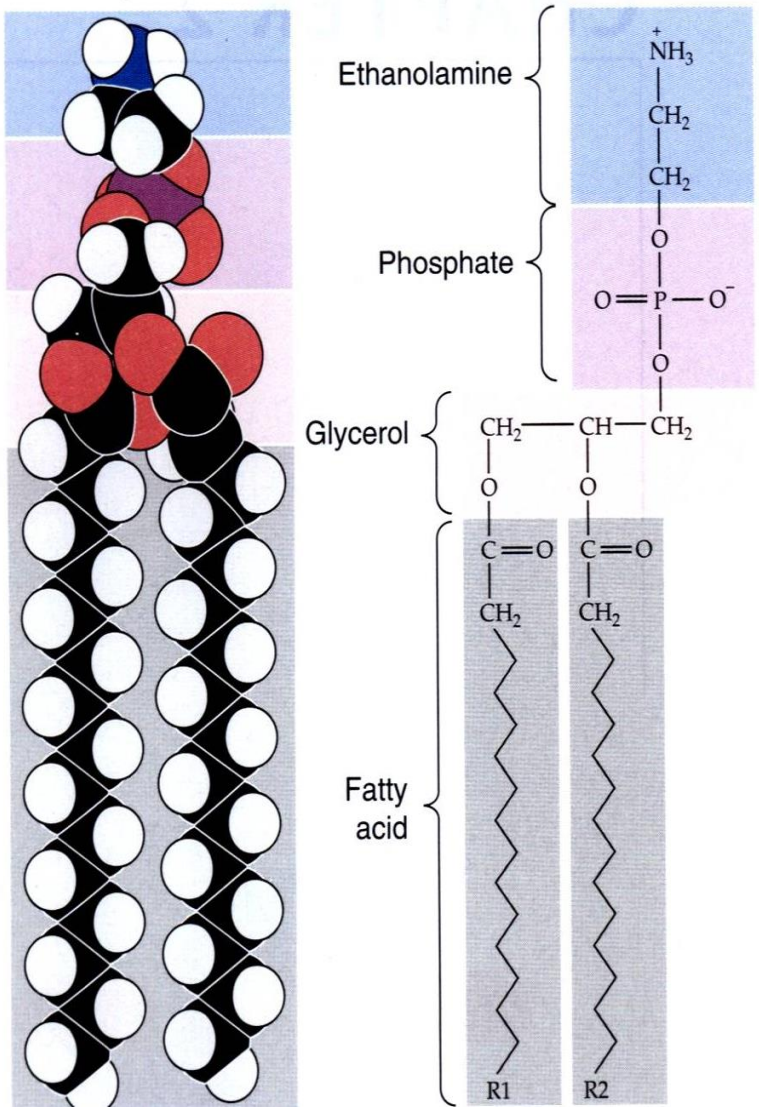
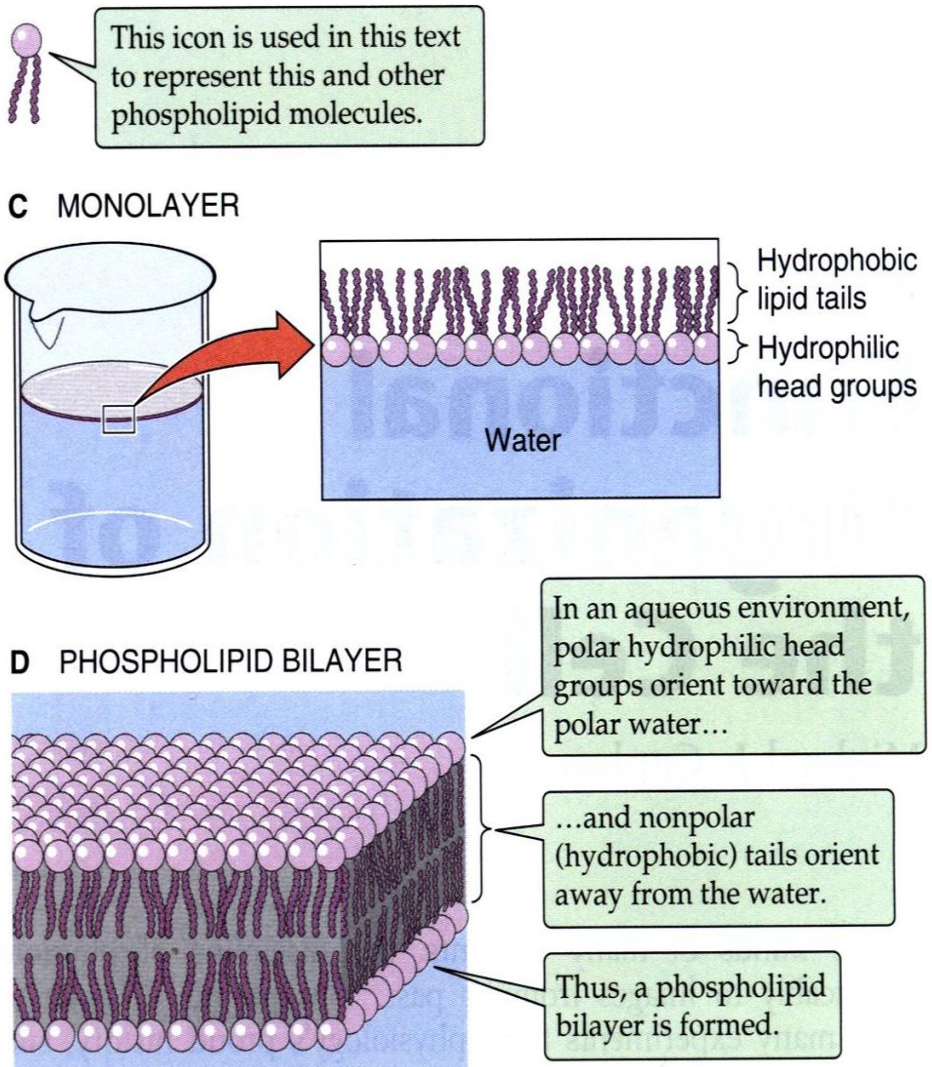
Biological membranes – separation and communication

impermeable for macromolecules, selectively permeable for small molecules



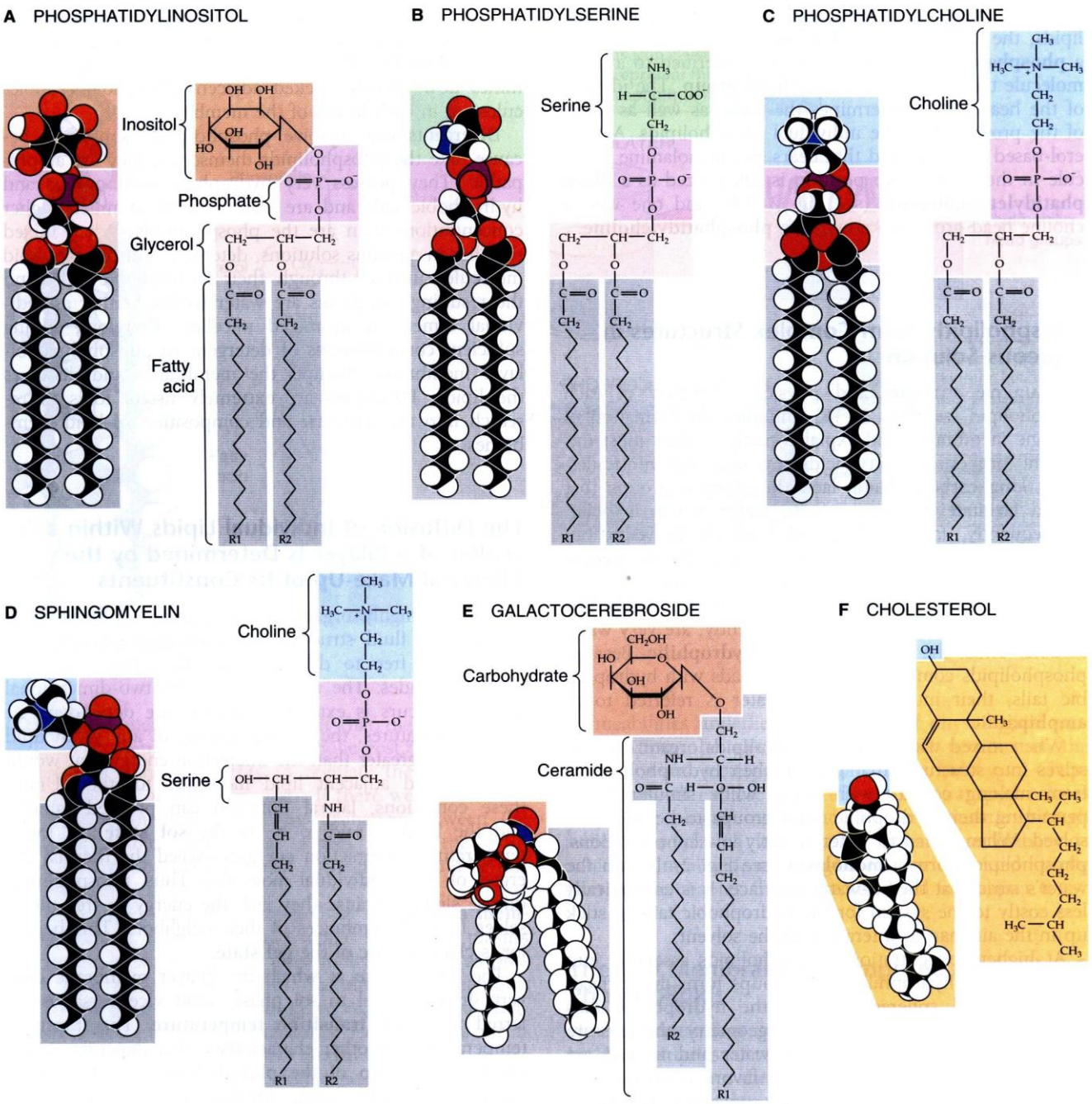


Composition:

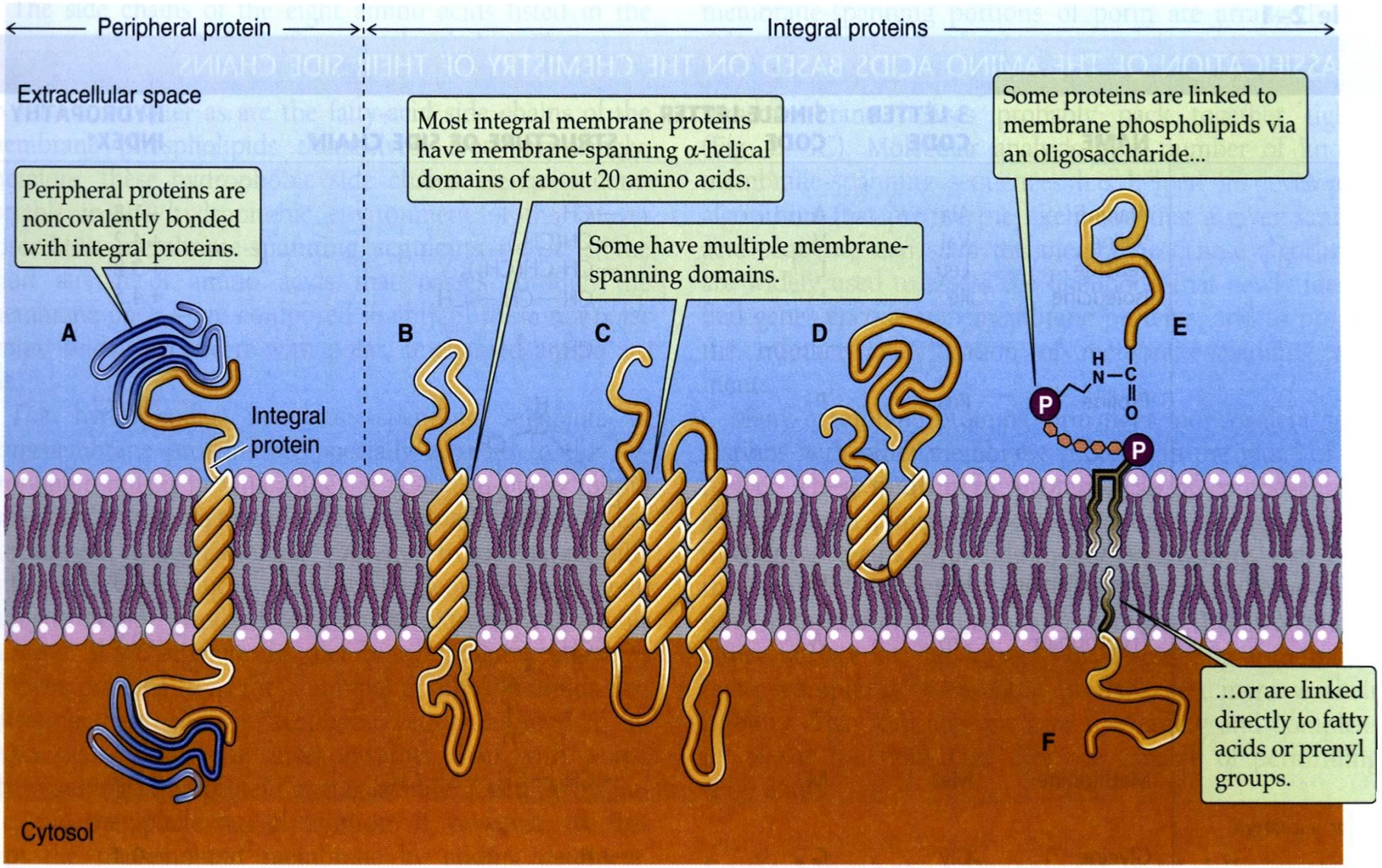
- phospholipids
- cholesterol
- cholesteryl esters
- glycolipids
- proteins

- membrane fluidity

- fatty acids
  - saturated
  - unsaturated



Classes of membrane proteins

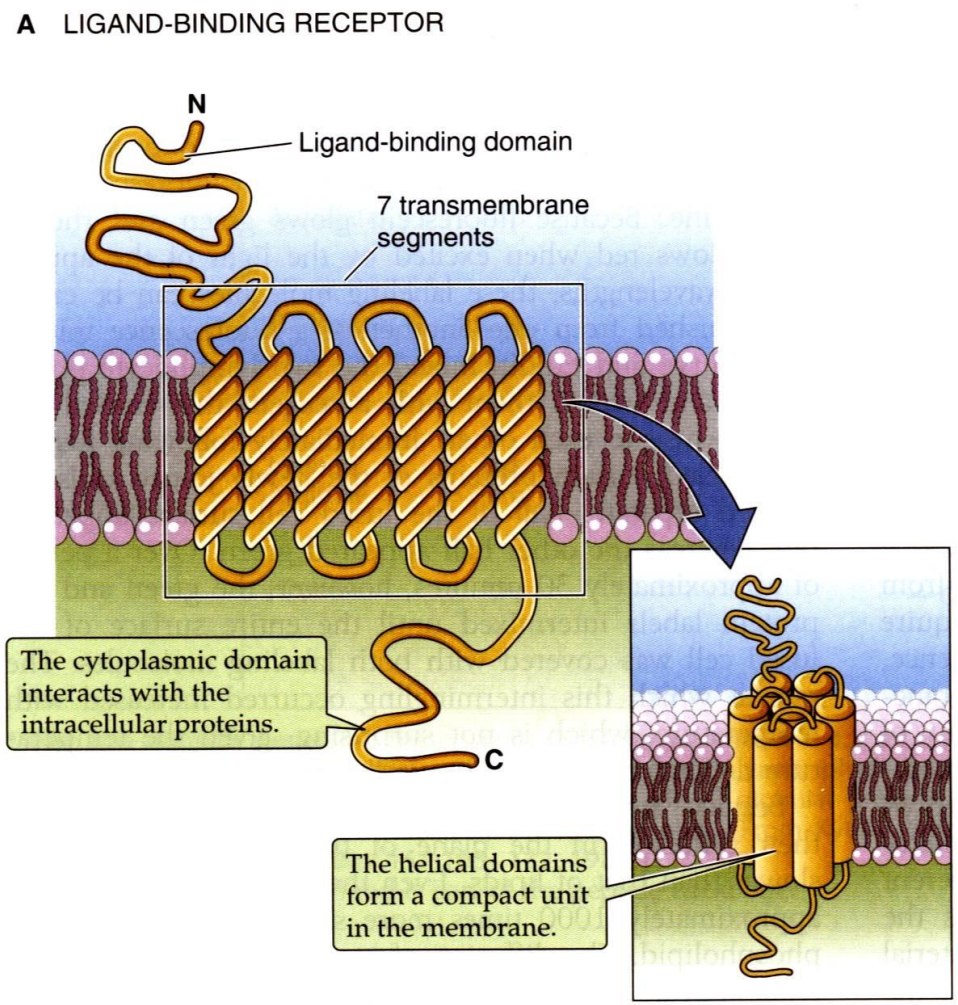


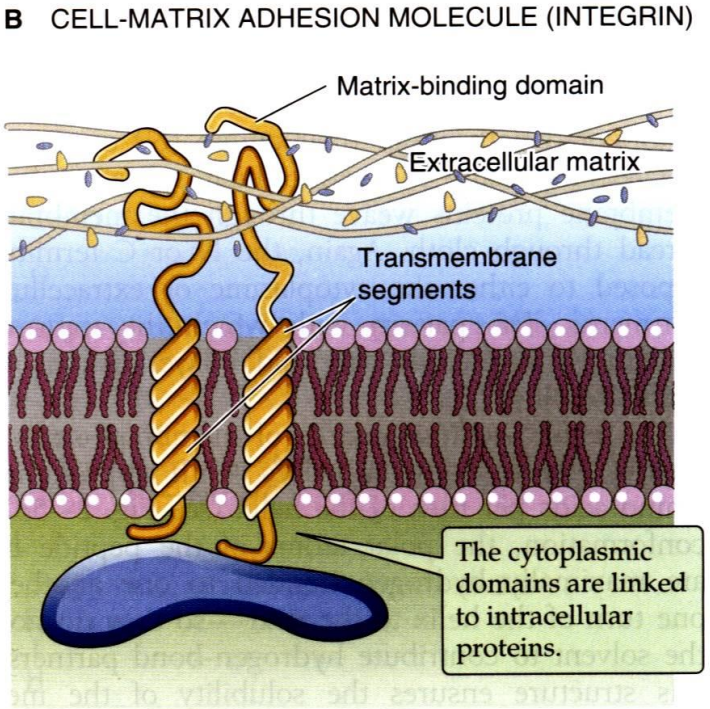
ligand-binding receptors,

adhesion molecules (integrins, cadherins),

transporters (channels, carriers, pumps)

Role of membrane proteins



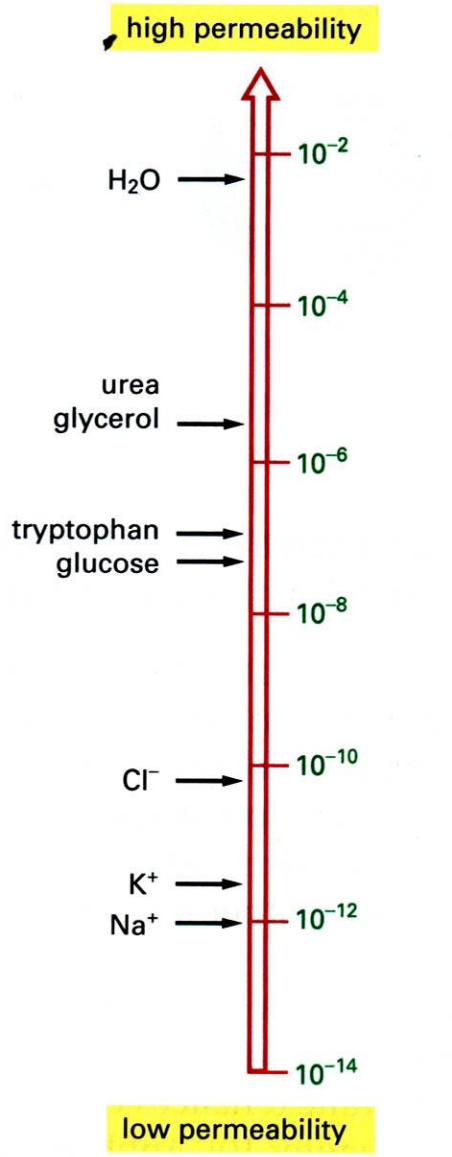


Physiology of membranes

- distribution of solutes is not uniform across the membrane

- steady-state

- the driving force for movement of solutes across the membrane is the ***electrochemical potential difference*** $\Delta\mu$.



Definition of the electrochemical potential:

$$\mu = \mu_o + zF\Psi + RT\ln[X]$$

The difference for the solute X is:

$$\mu_{in} - \mu_{out} = \Delta\mu = zF\Delta\Psi + RT\ln[X]_{in}/[X]_{out}$$

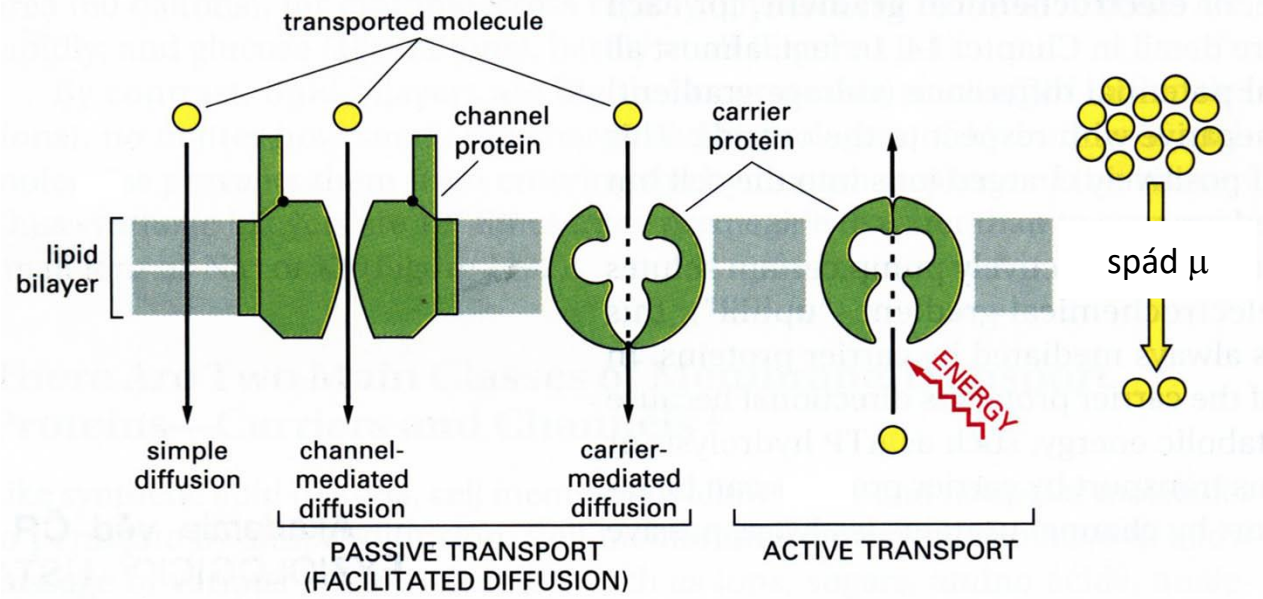
X is at equilibrium when $\Delta\mu = 0$:

$$\Delta\Psi = E_X = -RT/zF \cdot \ln[X]_{in}/[X]_{out}$$

(***Nernst equation***)

E_X, Nernst equilibrium potencial

Transport across biological membranes



Simple diffusion

– depends on partition coefficient water/lipids, diffusion coefficient and membrane thickness

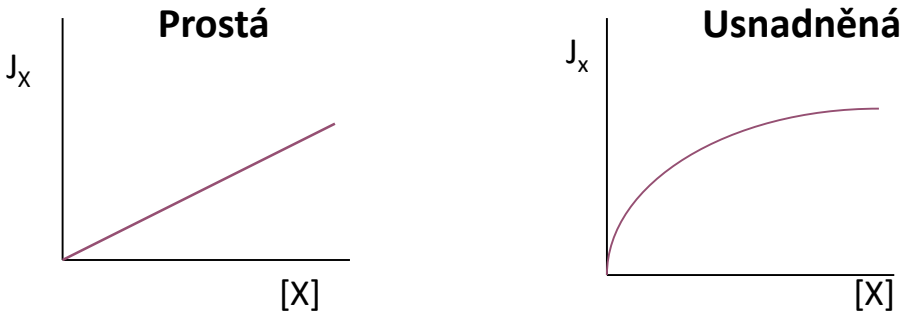
- simplified Fick's First Law of diffusion:

$$J_X = P_X \cdot (X_{out} - X_{in})$$

P_X – permeability coefficient

Facilitated diffusion:

- channels, pores
- carriers
- passive transport

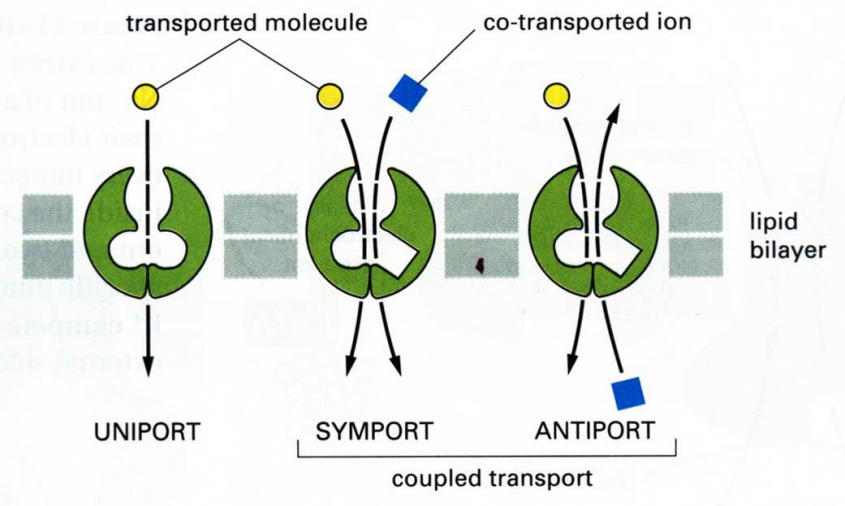


Active transport:

-primary

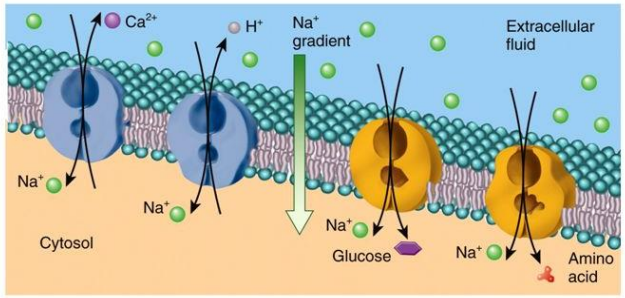
- P-type pumps
- V-type pumps
- F-type pumps
- ABC transporters

- secondary (Na/glucose, Ca/Na)

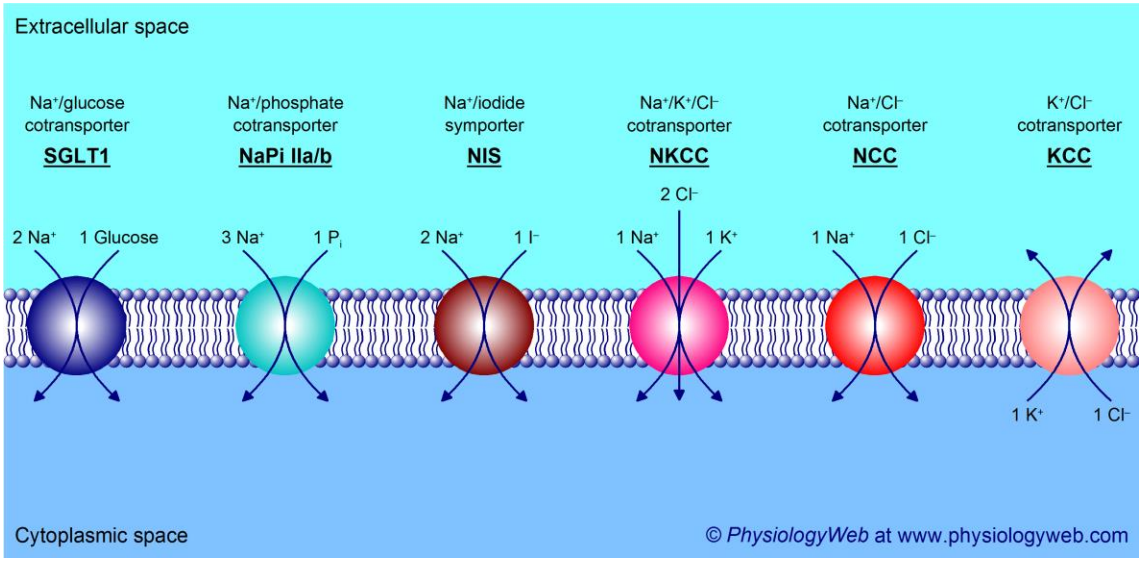


Secondary active transport

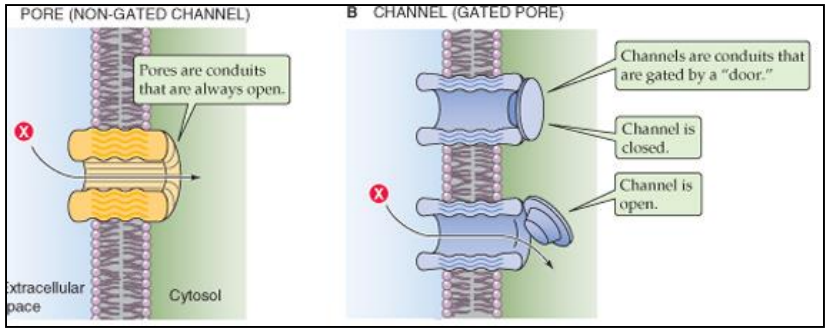
- **Antiporters** carry two substances across the membrane in opposite directions.
- **Symporters** carry two substances across the membrane in the same direction.

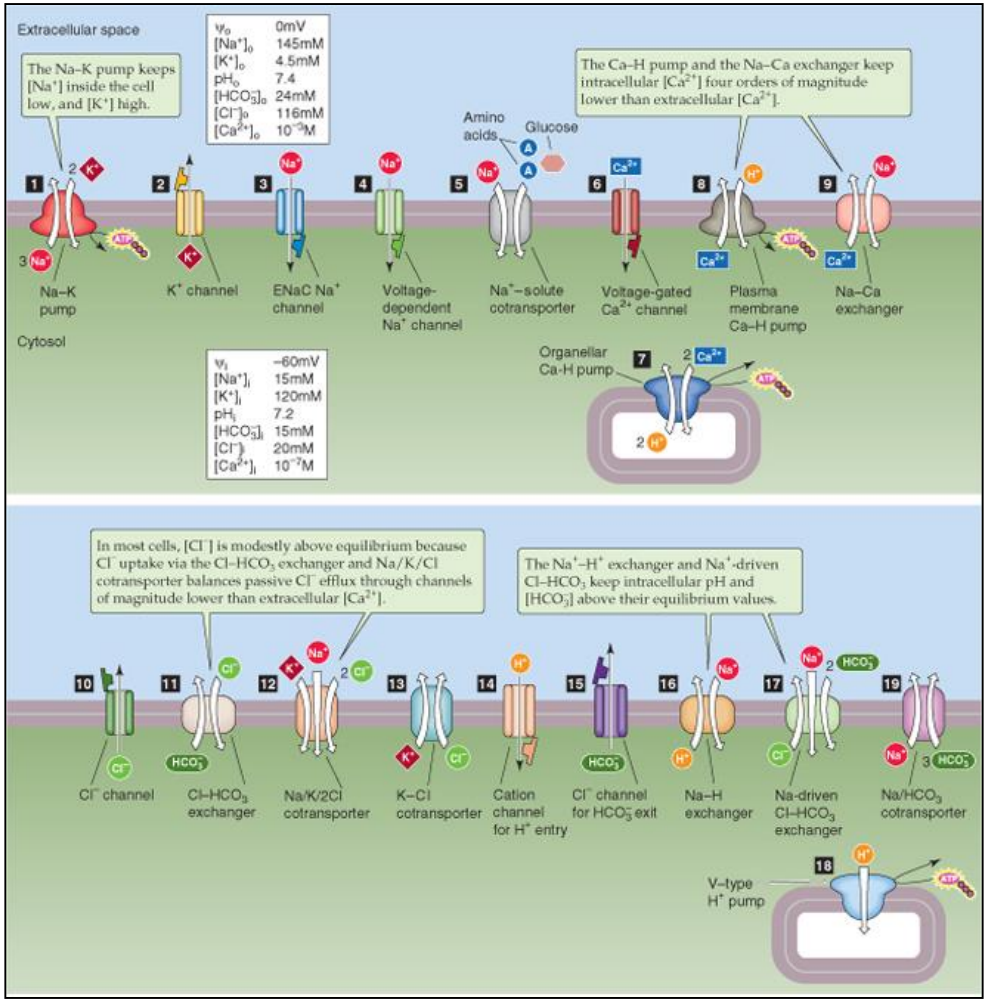


(a) Antiporters (b) Symporters

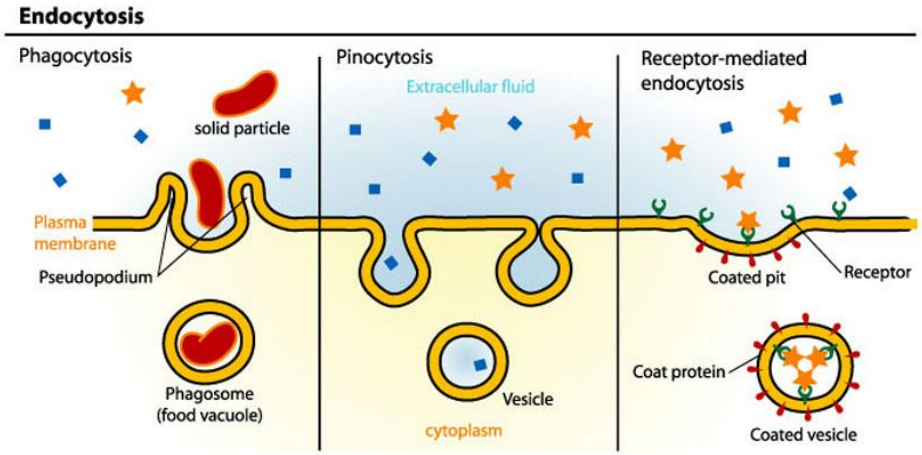


Channels and carriers



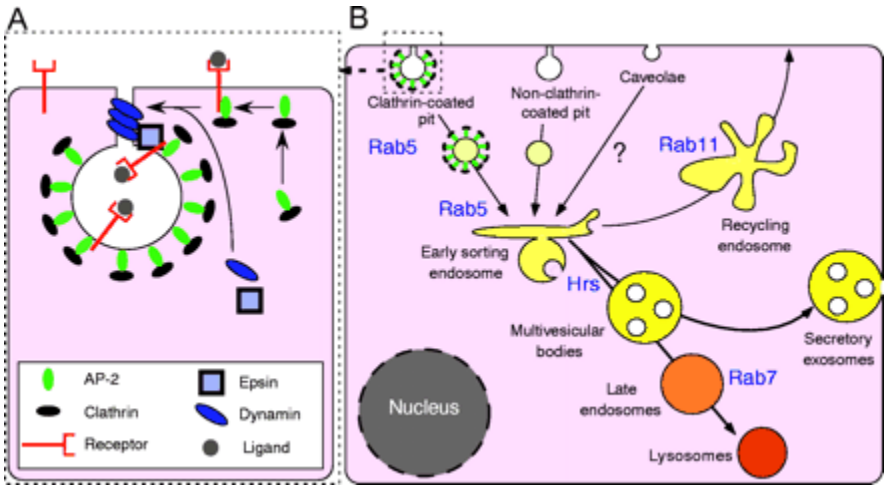


Bulk transport and endosomal sorting



Clatrin-dependent endocytosis

- Assembly protein 2 (AP2) links receptors and clatrin
- Dynamin is required for vesicle fission
- Removing of clatrin coat and fusion of vesicles controlled by the small GTPases Rab



Signal transduction across the membrane

-gap junction (molecules less than 1200 Da, electrical coupling of the cells)

- chemical signals (amines, peptides, proteins, steroids, eicosanoids, amino acids, nucleotides, ions, gases (NO))

-**Interaction with receptors**

- intracellular (steroid receptors, transcription factors)

- membrane

- **IONOTROPIC** (ligand-gated ion channels)

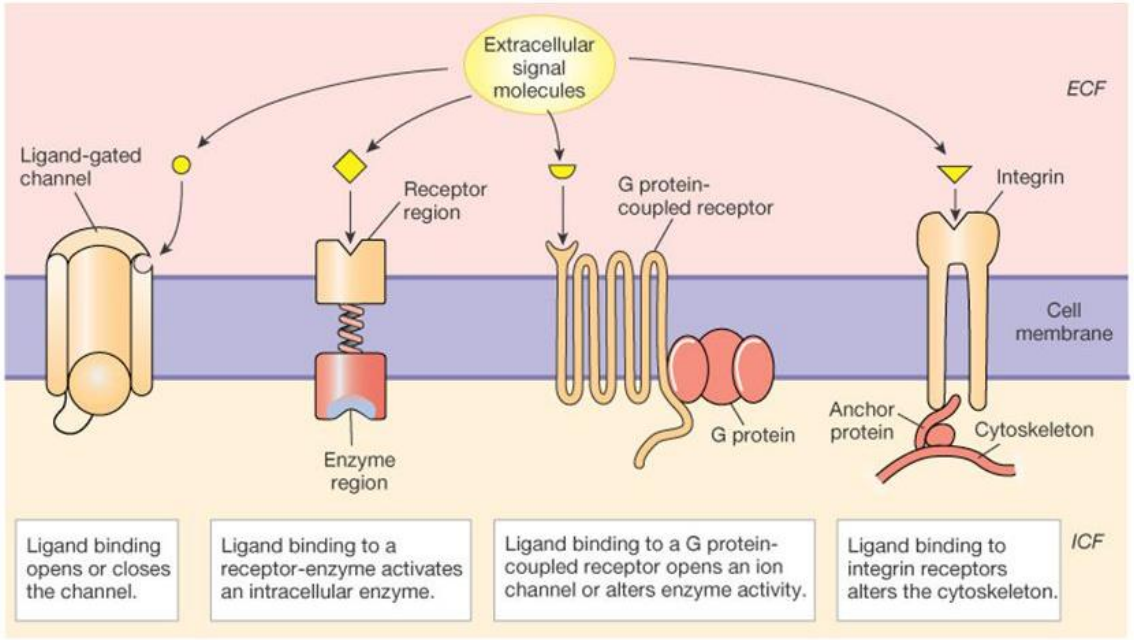
- **CATALYTIC** (guanylyl cyclase, tyrosine kinase, tyrosine phosphatase, and serine/threonine kinase activities)

- **LINKED TO G PROTEINS** (metabotropic)

G-proteins: 7 transmembrane domains, extracellular N-terminus is glycosylated

Activation cycle of heterotrimeric G proteins: ($\alpha+\beta+\gamma$+GDP) inactive complex + activated receptor substitution of GTP for GDP $\longrightarrow$ dissociation of the complex on (α) + ($\beta\gamma$) subunits $\longrightarrow$ activated (α+GTP) subunit stimulates the effector $\longrightarrow$ hydrolysis of GTP terminates the signalling events $\longrightarrow$ dissociation of (α+GDP) from the effector $\longrightarrow$ reassociation with ($\beta\gamma$) subunit.

Classes of membrane receptors



Catalytic receptors

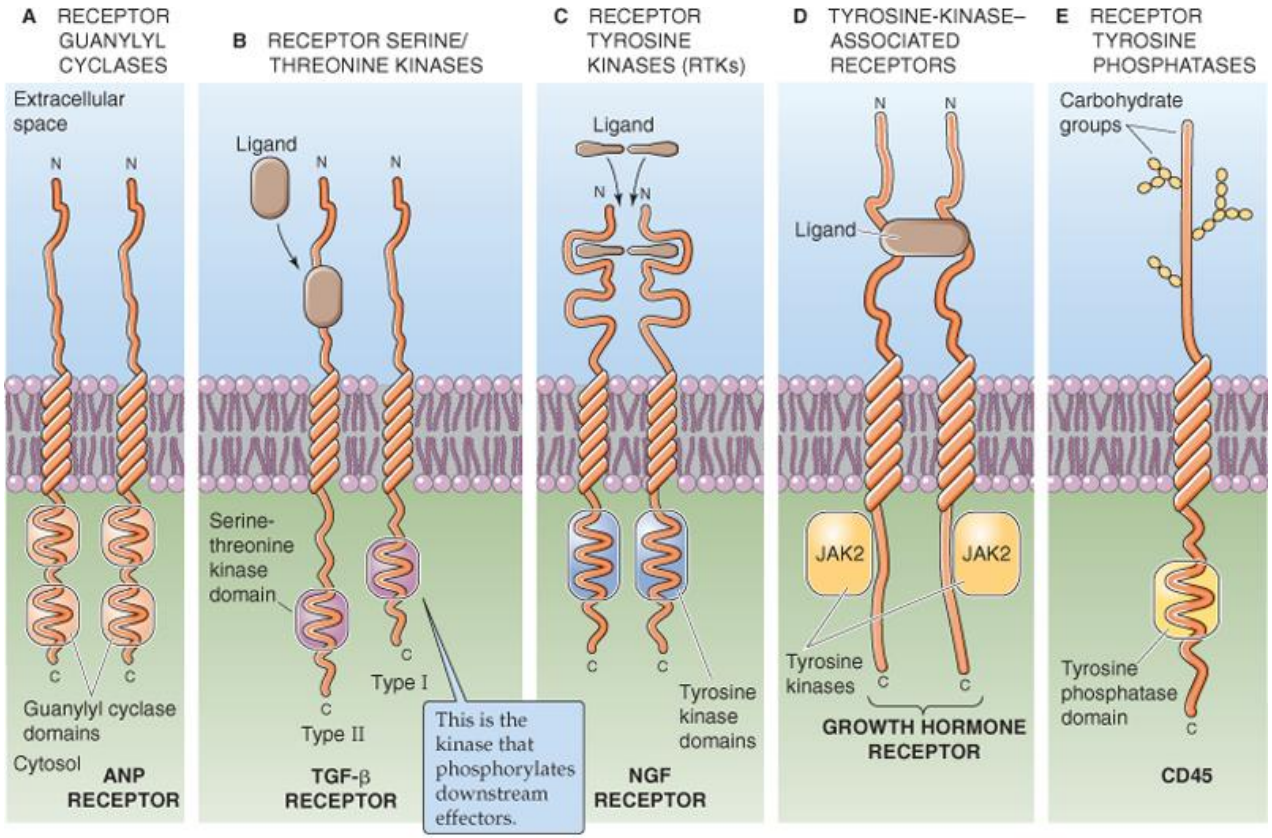
A: antrial natriuretic peptid – cGMP-dependentní kinase (PKG)

B: inhibins and activins, growth factors. Type I receptors do not bind the ligands but propagate the signal downstream

C: insulin, EGF, IGF-1, ligand binding induces the formation of receptor dimers or tetramers (insulin, IGF-1)

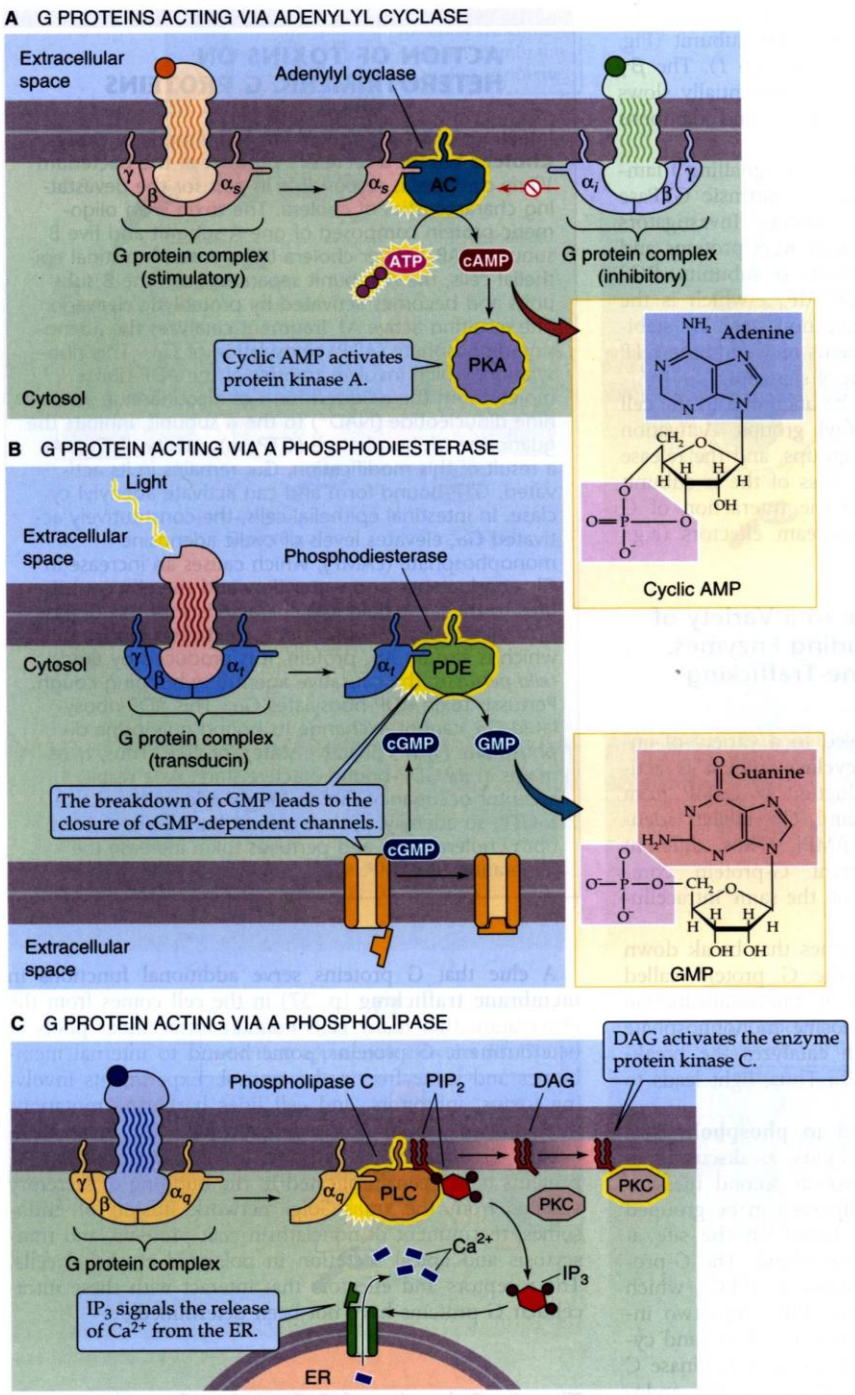
D: ligand binding activates loosely associated tyrosinkinases (Src, JAK). Prolactin, erythropoietin, interferon, growth factors, cytokines, etc.

E: receptors that are required for lymphocyte activation



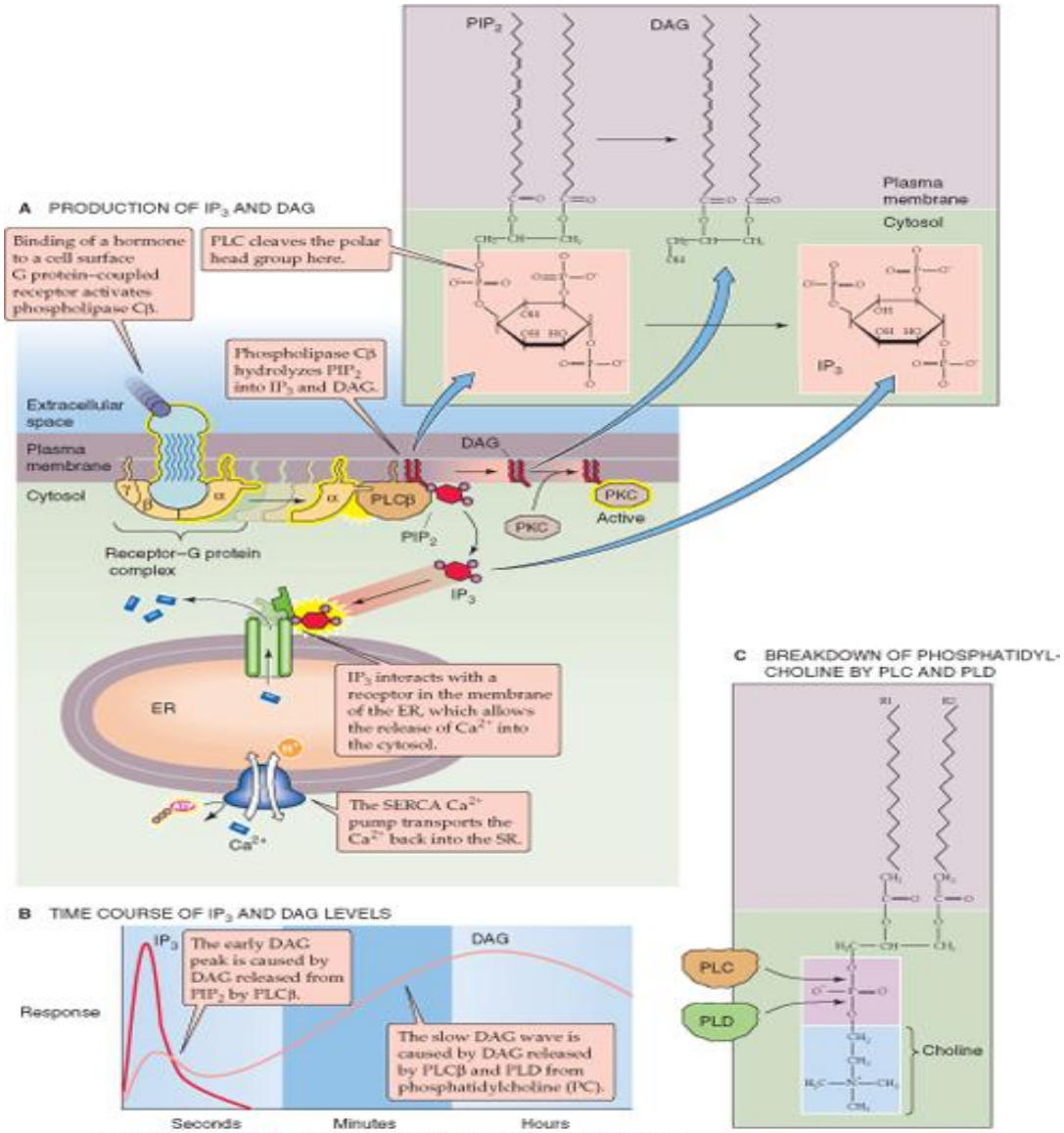
Downstream effects of activated G protein α subunit

- adenylyl cyclase (Gs-cholera toxin, Gi-pertussis toxin)
- phosphodiesterase (phototransduction)
- phospholipase PLCβ (IP3, SERCA, DAG, PKC)
- phospholipase A2 (via MAPkinases, eicosanoids)
  - prostaglandin pathway
  - leukotriene pathway
  - epoxygenase pathway

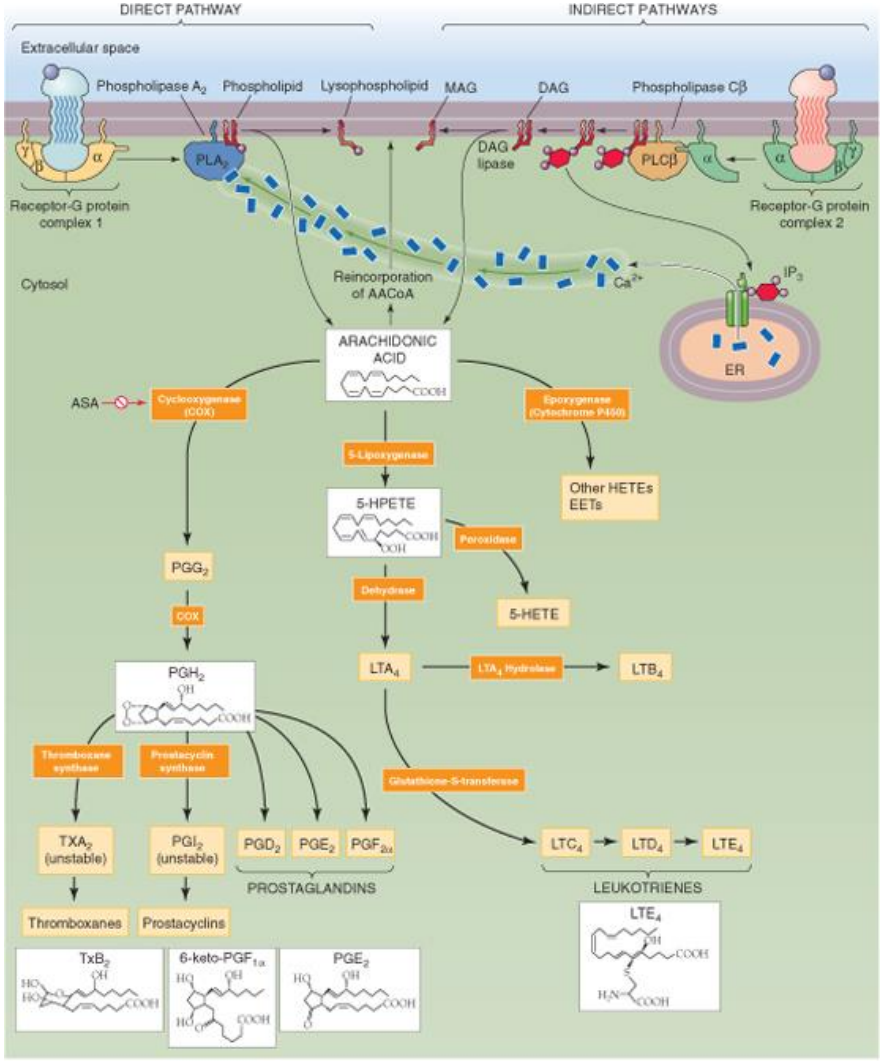


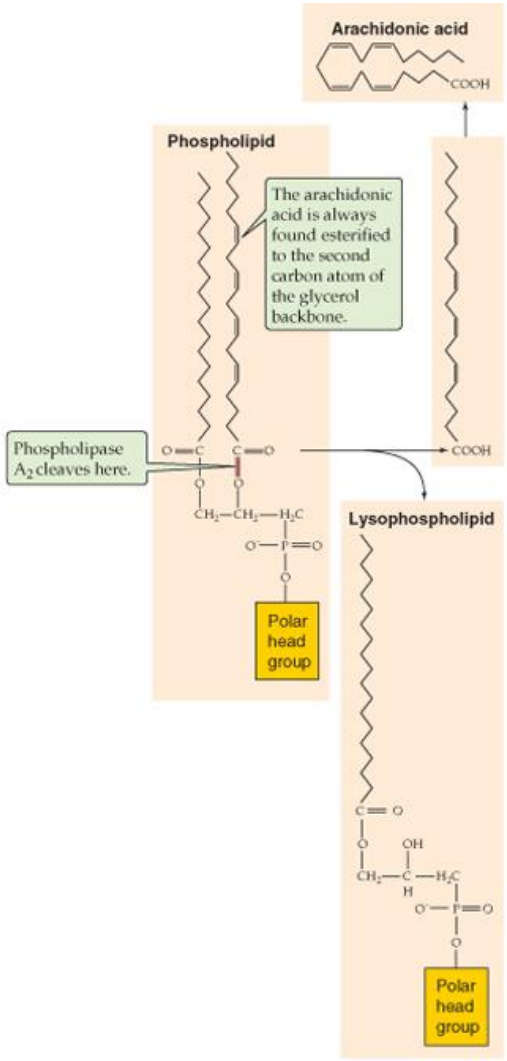
Phospholipases PLC and PLD

- Ca activates calmodulin-dependent kinases (CaM kinases)
- Ca activates soluble and inactive proteinkinase C (PKC)
- activated PKC binds to diacylglycerol (translocation into membrane)



Phospholipase A2 and synthesis of eicosanoids





Intracellular receptors