BIOLOGICAL MEMBRANES

- **Biological membranes are supramolecular structures composed of lipids and proteins that define cellular content of external environment and can perform some functions.**

Functions:

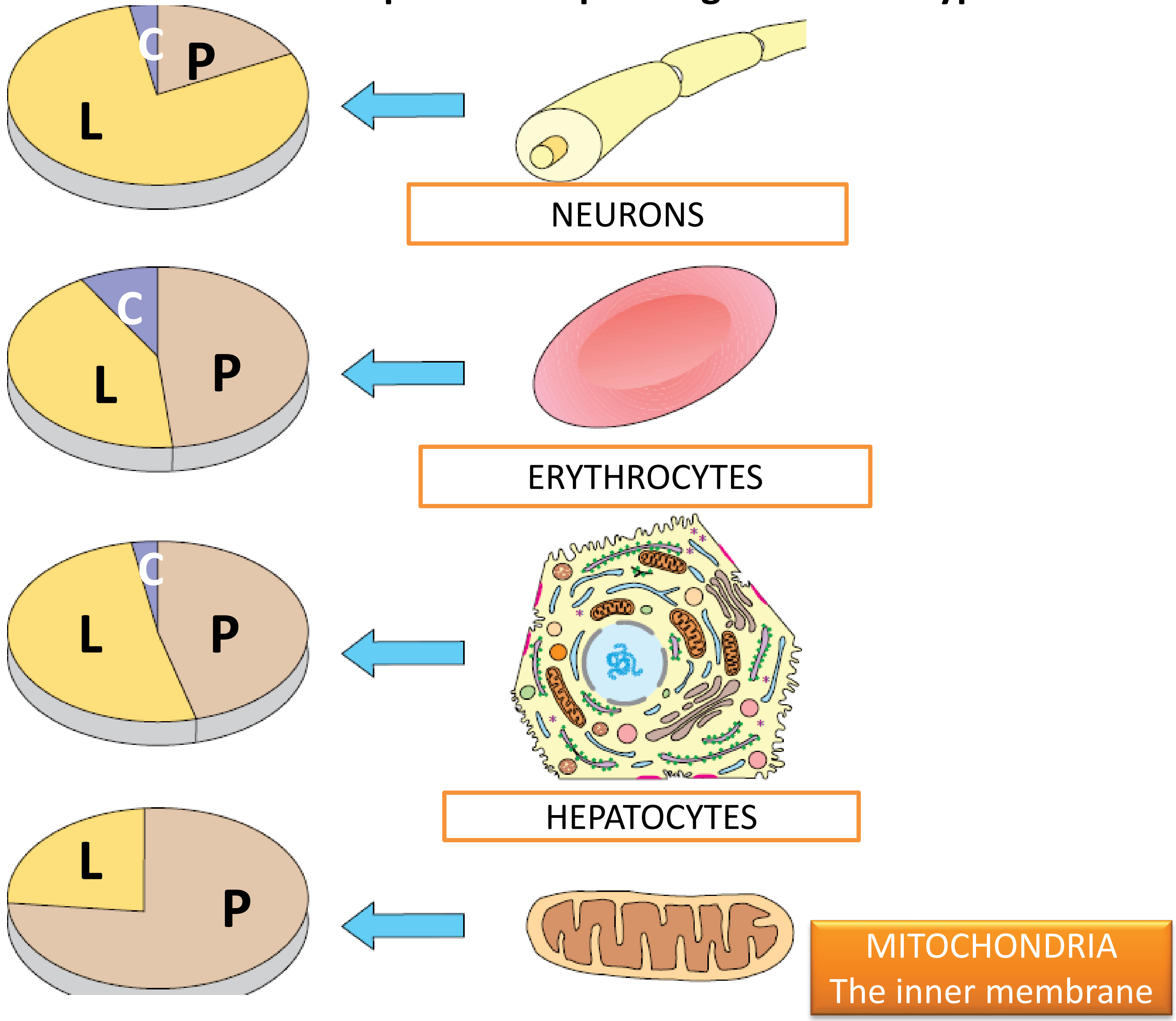
- Compartmentalisation - delimitation of the specialized cell organelles content of the cytosol
- Selective permeability of different compounds
- Organization of biochemical reactions
- Receiving external signals and their transduction
- Transport of solutions, ions
- Provides intercellular interactions
- Energy transformations

Chemical composition

- Lipids 30-50%
- Cholesterol 20% (e.g. erythrocytes 25%)
- Proteins 30-50%
- Carbohydrates 5-15%

Their amount varies depending on the type of membrane

Examples of the membrane composition depending on the cell type



Lipids

- Phospholipids
  - Glycerophospholipids
  - Sphingophospholipids
- Glycolipids
- Cholesterol

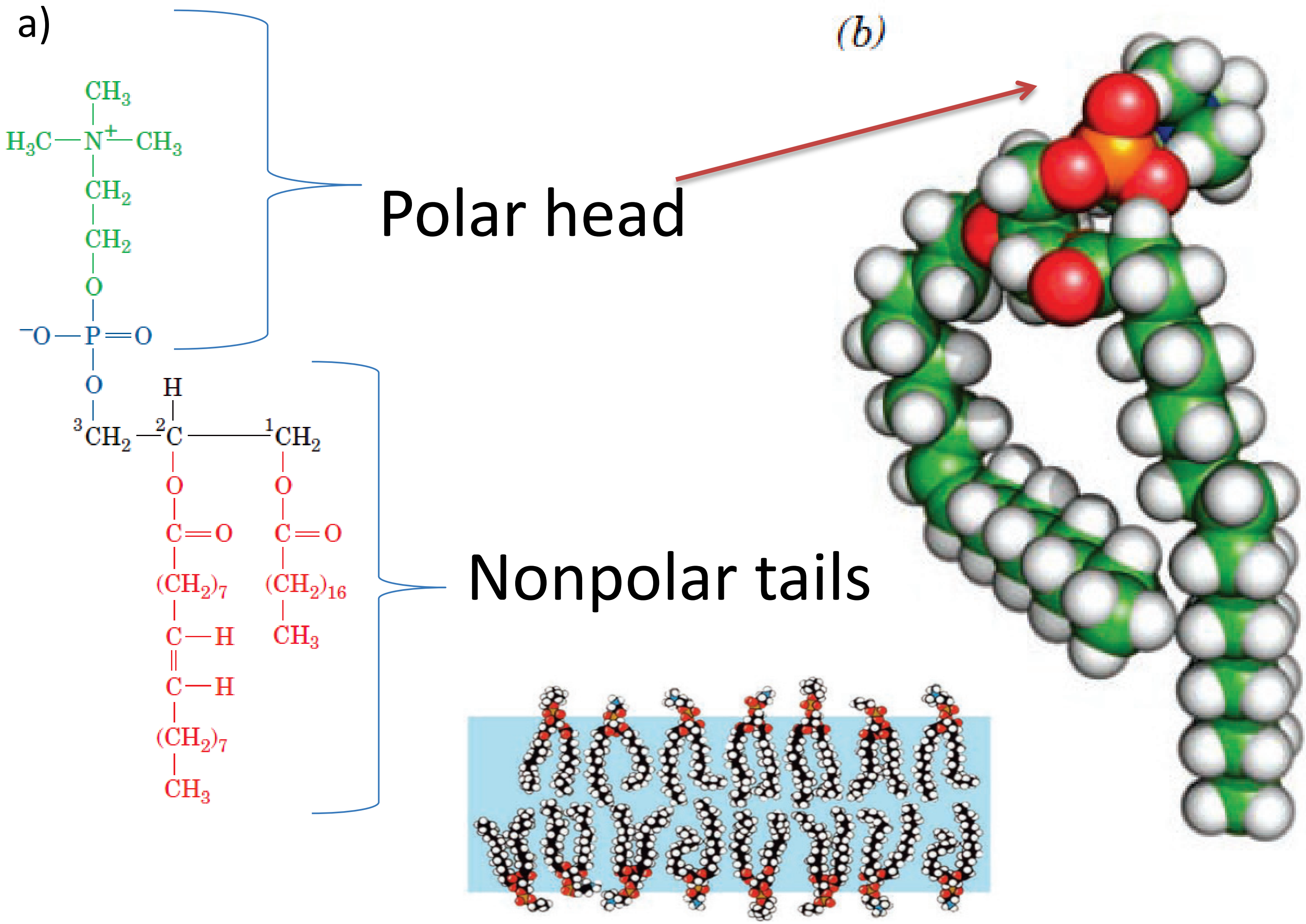
Glycerophospholipids

- Phosphatidylcholine (lecithins)
- Phosphatidylethanolamines (cephalins)
- Phosphatidylserine
- phosphatidyl inositol
- Cardiolipin

Role:

- ✓ lipid bilayer formation
- ✓ covalently bind some proteins
- ✓ can serve as a source of second messenger in signal transduction of some hormones
- ✓ can signal apoptosis

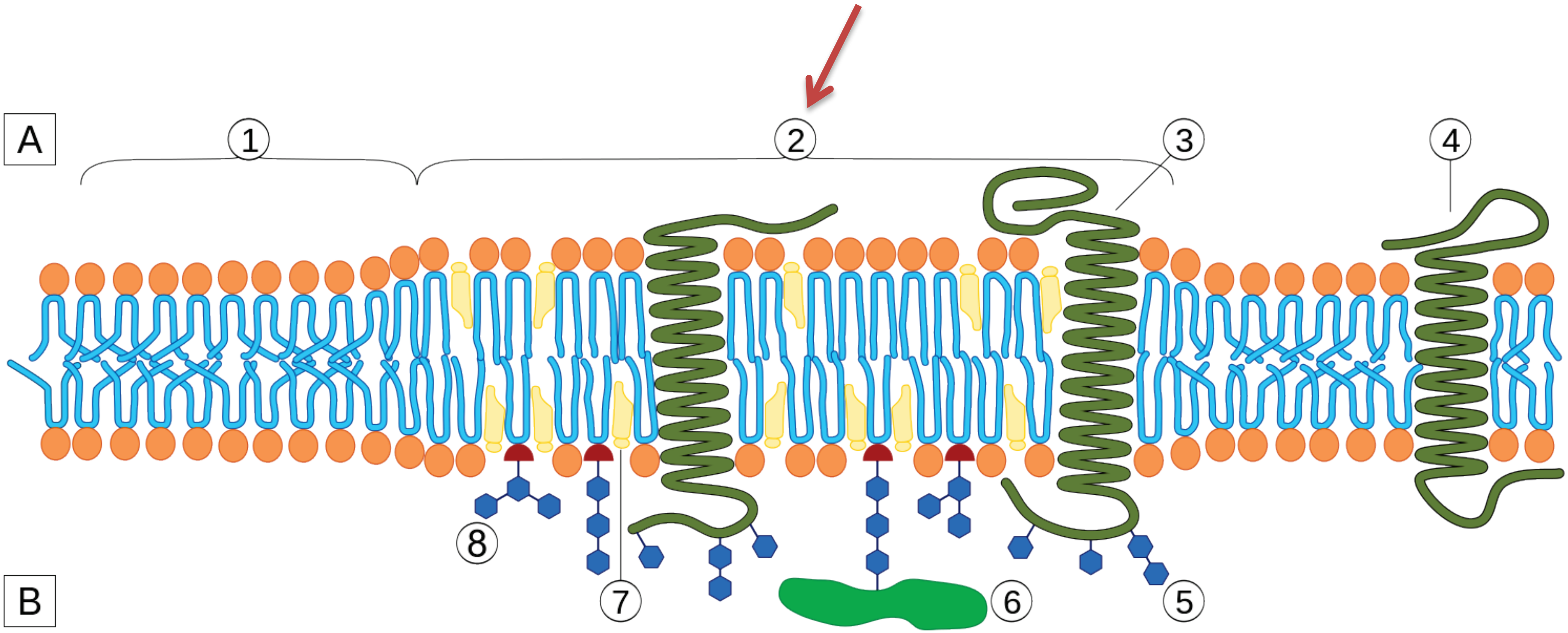
Amphiphilic property of phospholipids and lipid bilayer formation:



Sphingophospholipids

- Sphingomyelins 10-20%
- Are part of the myelin sheath of axons acting as electrical insulators
- Participates in numerous signaling pathways by releasing diacylglycerols (DAG) and ceramide
- Are involved in apoptosis by releasing ceramide
- Form lipid pontoons - rigid lipid combination associated with proteins

Lipid pontoon



Glycolipids

- Cerebrosides
  - galactocerebrosides
  - glucocerebrosides
- Ganglioside

Galactocerebrosides

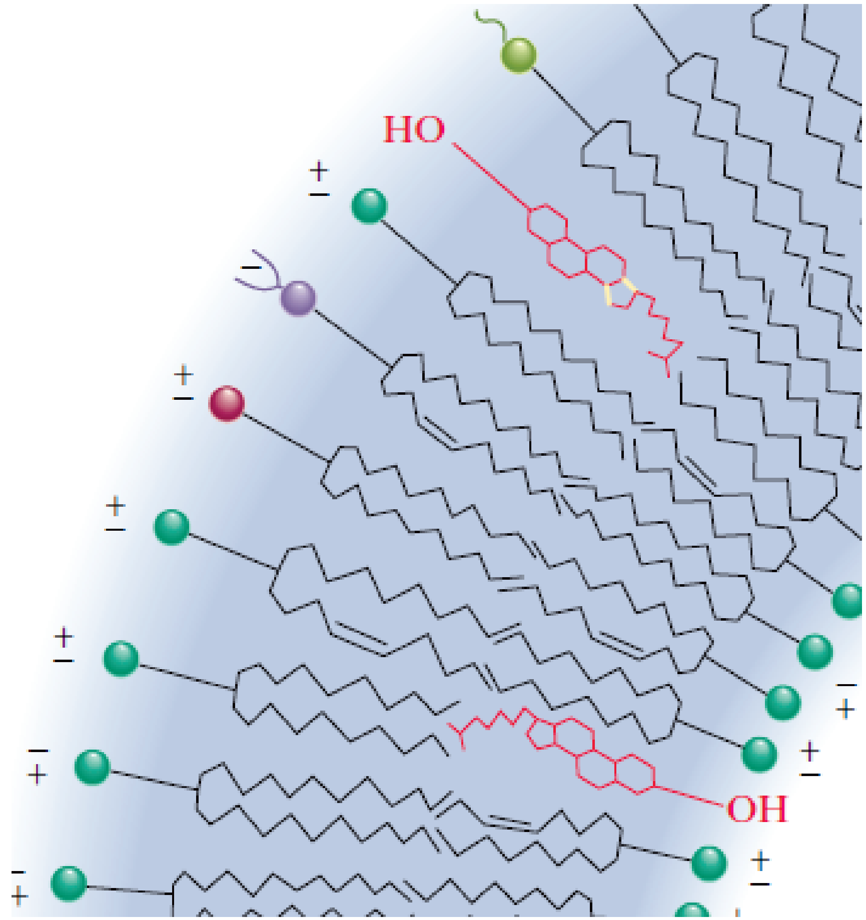
- The main components of nerve cell membranes, especially in the brain
- 2% in the gray matter and 12% in the white matter of the brain
- The myelin sheath, oligodendrocytes
- Have an important role in the lipid pontoons organization due to the high degree of intermolecular hydrogen bonding
- In the combination with cholesterol form sites of proteins binding, receptors

Glucocerebrosides

- Predominates in erythrocyte membranes, in the spleen, skin, nervous tissue cells membranes
- Have the common functions of glycolipids

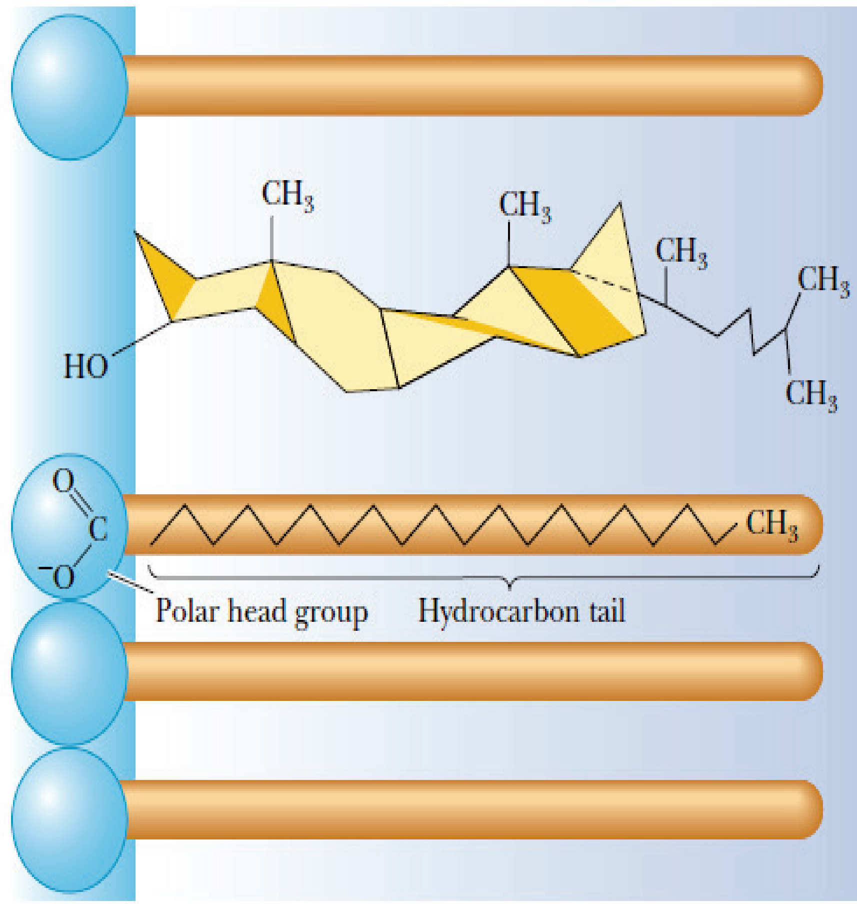
The location of cholesterol in membrane

- Due to its rigidity, cholesterol is located among the non-polar hydrocarbon tails of the fatty acids, mainly unsaturated

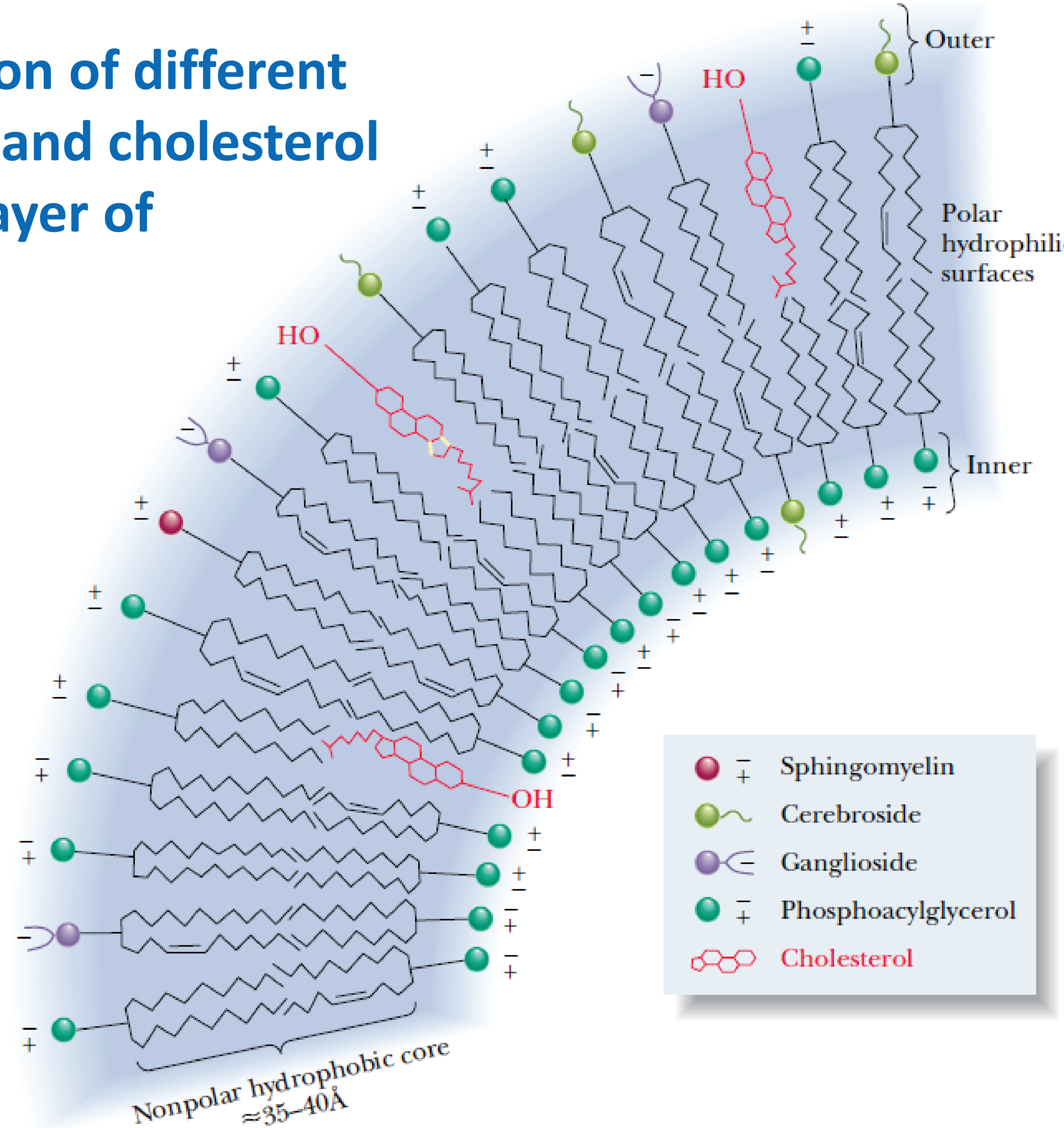


The role of cholesterol in membranes

- Raises the degree of order and rigidity
- Stabilizes the tails of saturated fatty acid keeping them upright, due to Van der Waals interactions
- As a result membranes become rigid, shock-resistant



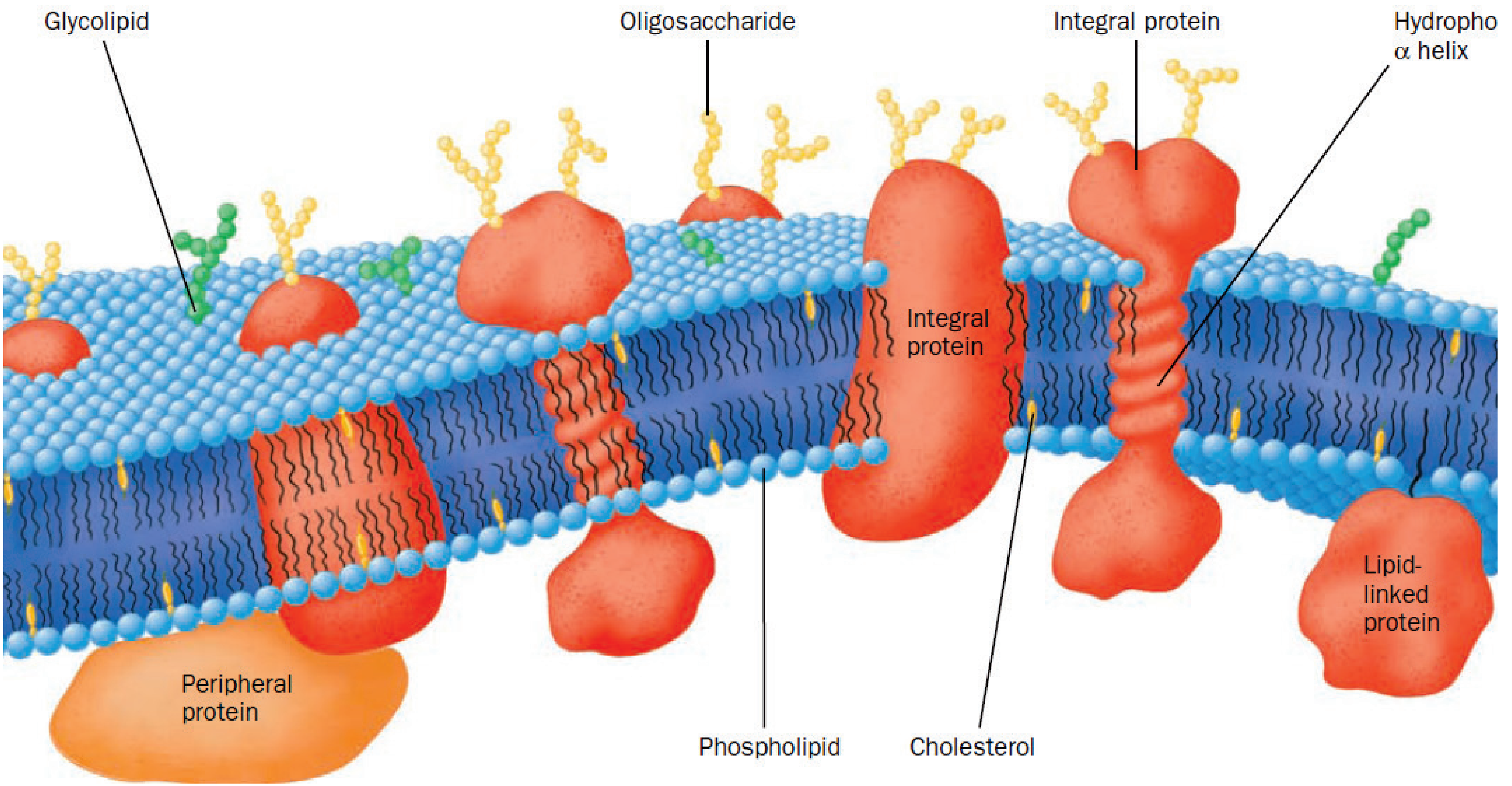
The organization of different types of lipids and cholesterol in the lipid bilayer of membranes:



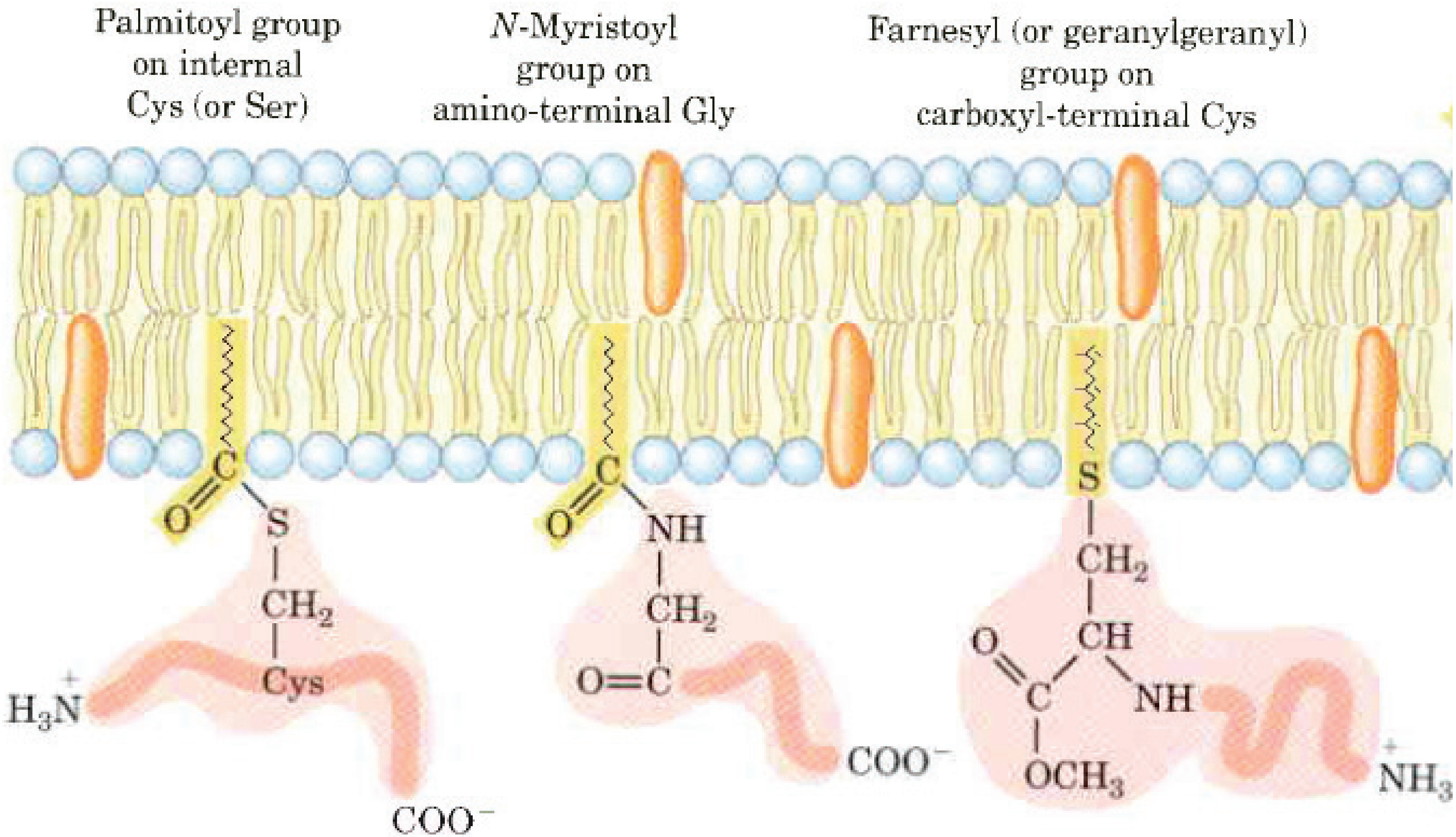
Proteins

- Can be located in the peripheral lipid bilayer or integrated in it;
- Peripheral proteins bind to the polar lipids by ionic bonds or by polar interactions
- They can be easily separated by detergents
- Integral proteins are strongly linked by many hydrophobic interactions due to their of α-helices or β-structures
- Some proteins are covalently linked to the lipid bilayer

Organization of membrane proteins



Membrane proteins covalently bound with fatty acids

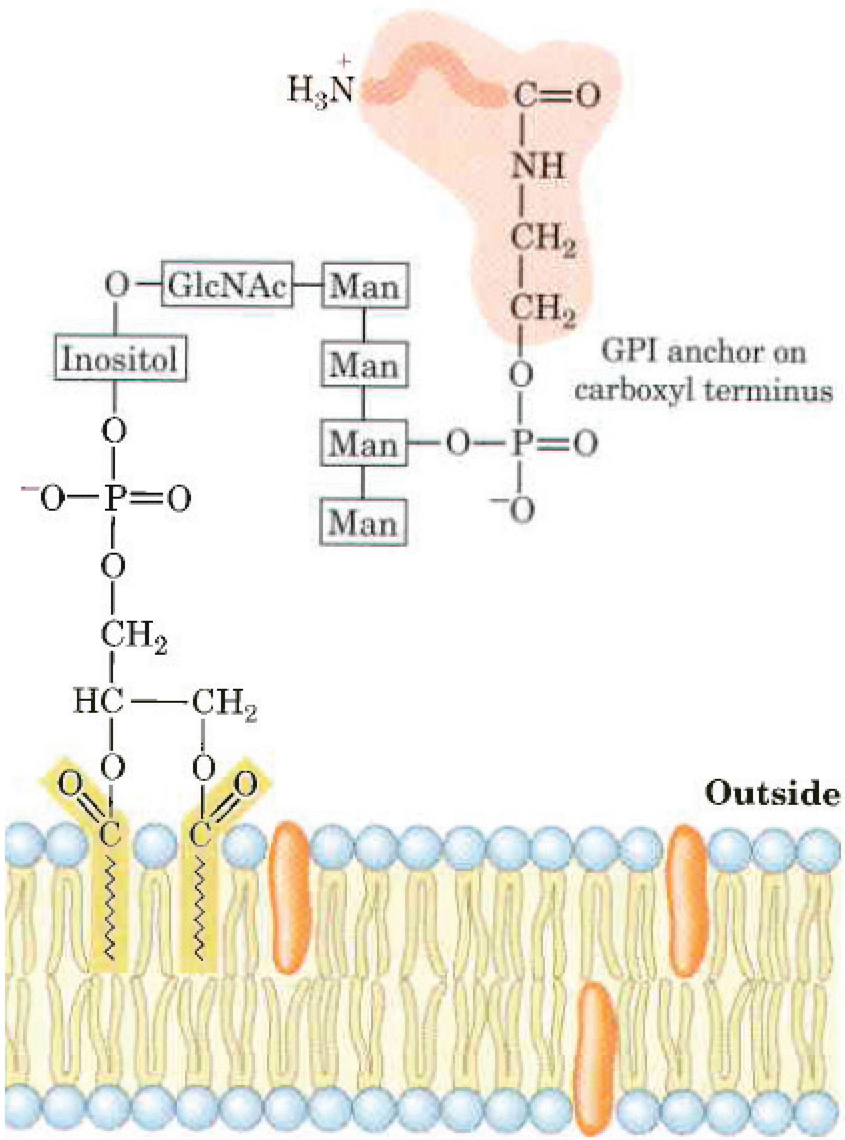


Glycosylphosphatidylinisotol (GPI) anchored proteins

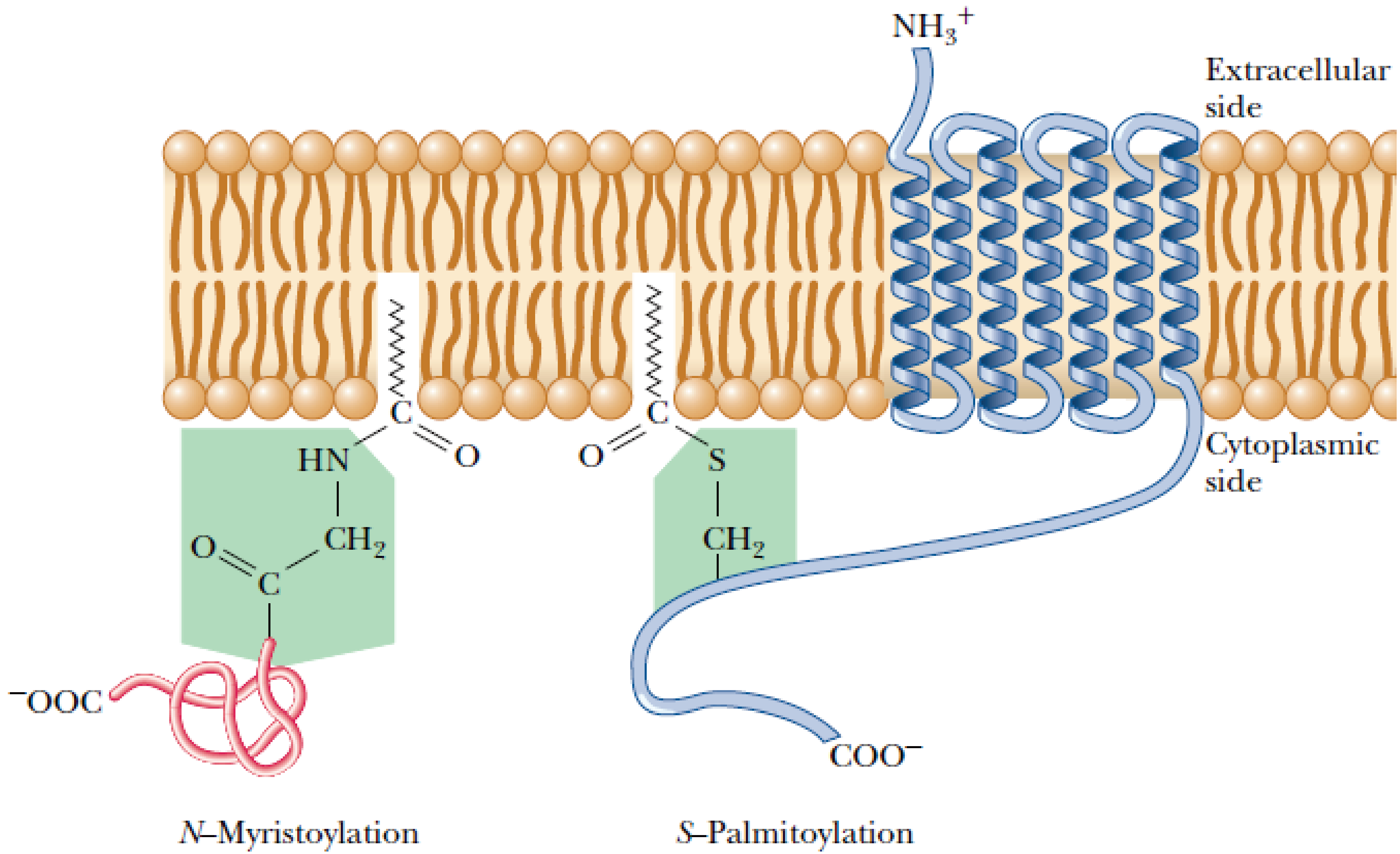
GPI-anchored proteins are linked at their carboxy-terminus through a phosphodiester linkage to phosphoethanolamine attached to a trimannosyl-nonacetylated glucosamine (Man_3-GlcN) core. The reducing end of GlcN is linked via another phosphodiester linkage to phosphatidylinositol (PI)

Functions

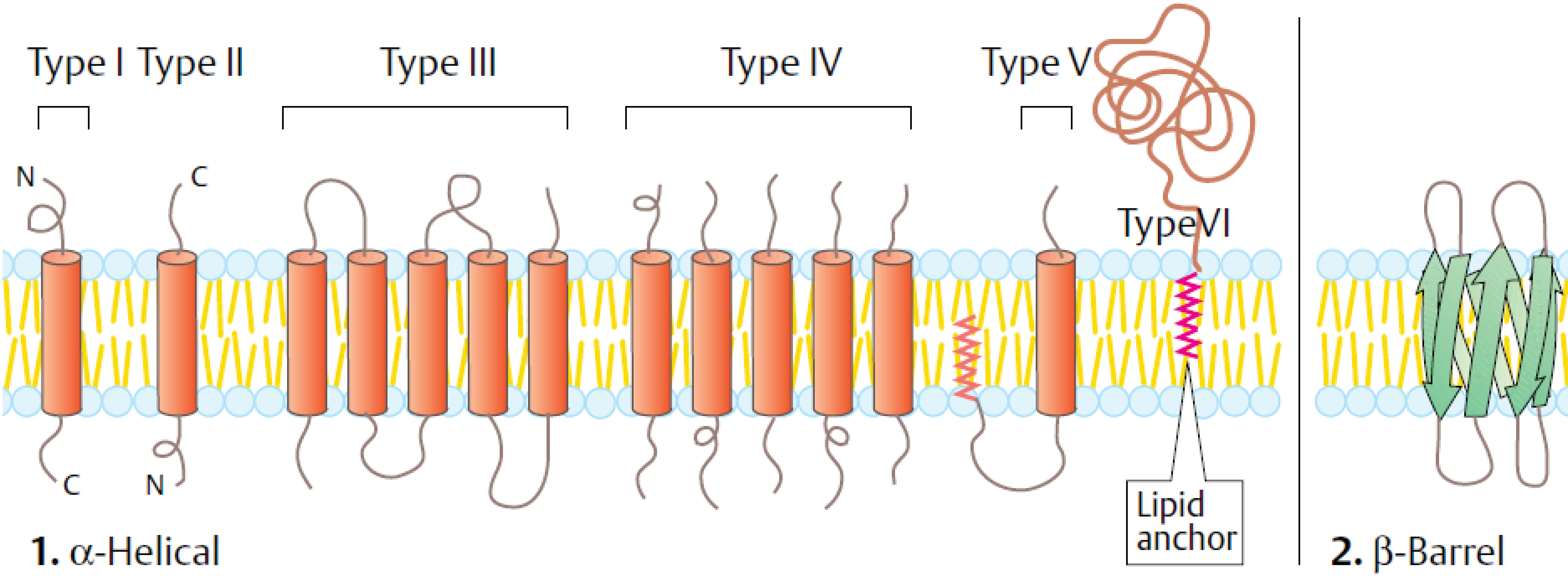
GPI anchored proteins are involved in membrane protein transportation, cell adhesion, cell wall synthesis, and cell surface protection. Some GPI anchored proteins are antigens, others inhibit tumor invasion and metastasis. In mammalian cells, GPI anchored proteins are concentrated in lipid rafts that are involved in receptor-mediated signal transduction pathways and membrane trafficking.



Membrane protein covalently bound with fatty acids



Structural classification of transmembrane proteins:



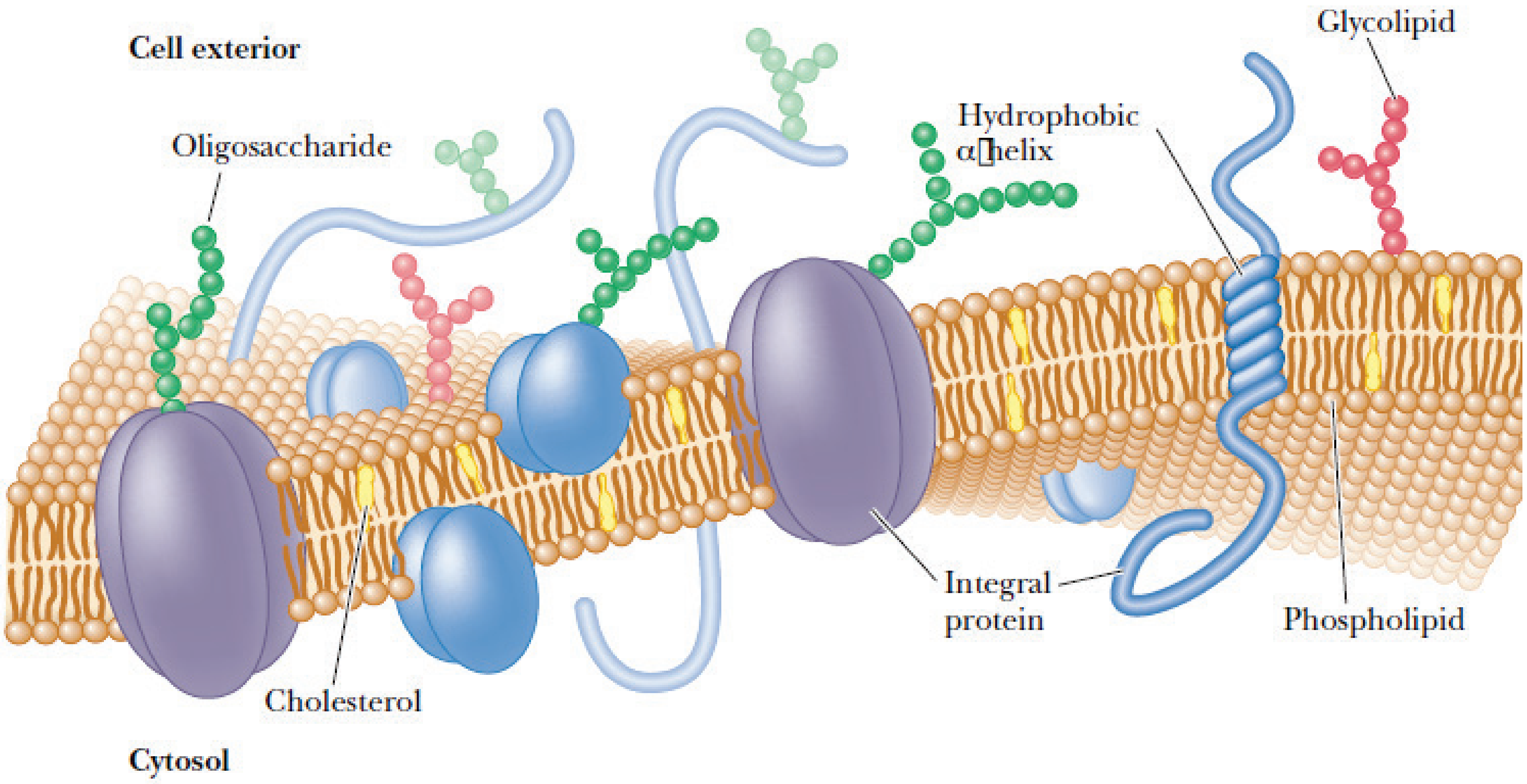
The role of membrane proteins:

- protein carriers
- protein receptors

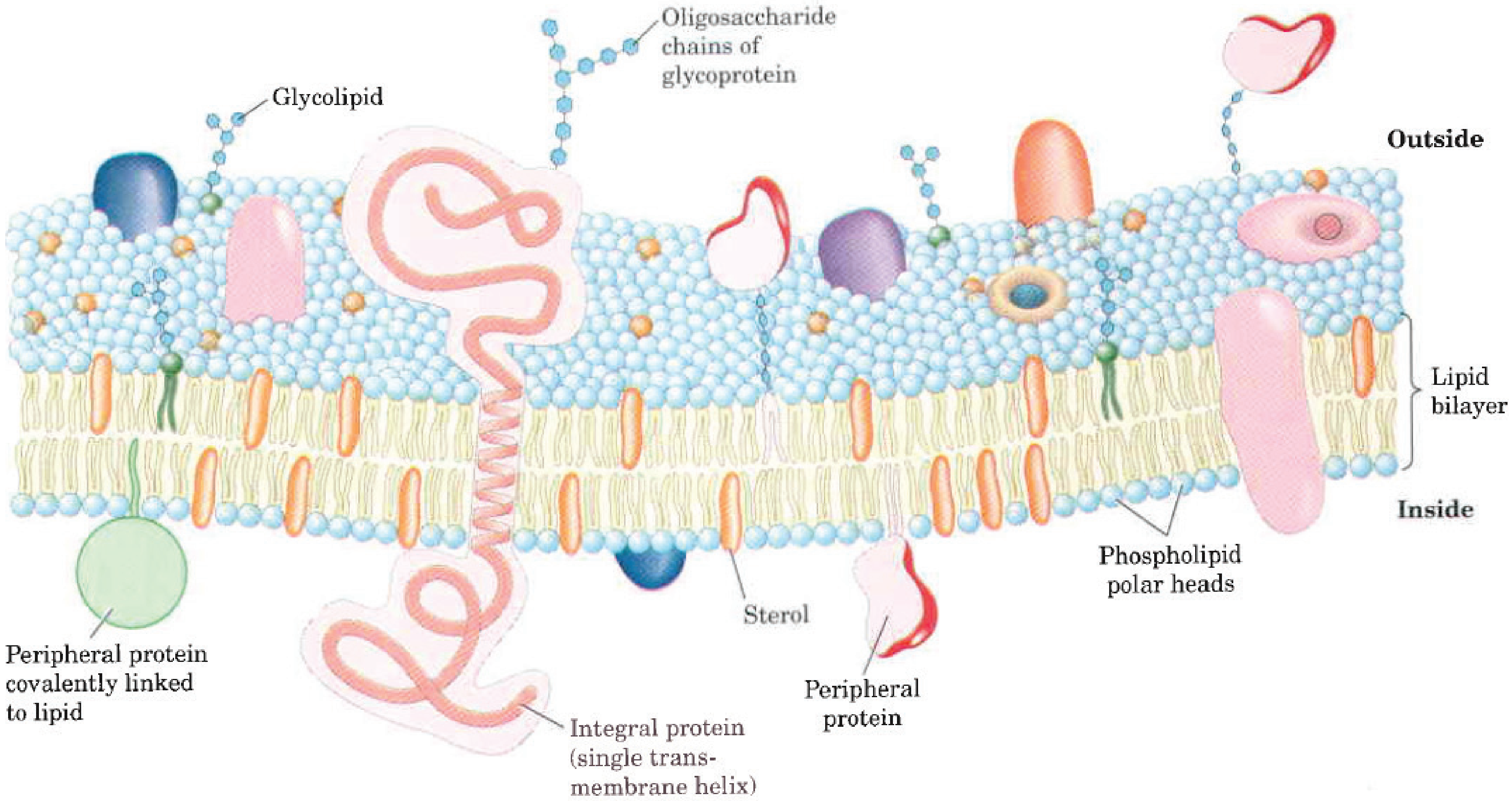
Structural-functional organization of the membranes

- It is described by **fluid-mosaic model**
- Membrane components are closely associated with each other without interacting chemically
- The model describes the membrane as a lipid bilayer with integrated proteins

Fluid-mosaic model of the cell membrane



Fluid-mosaic model of the cell membrane

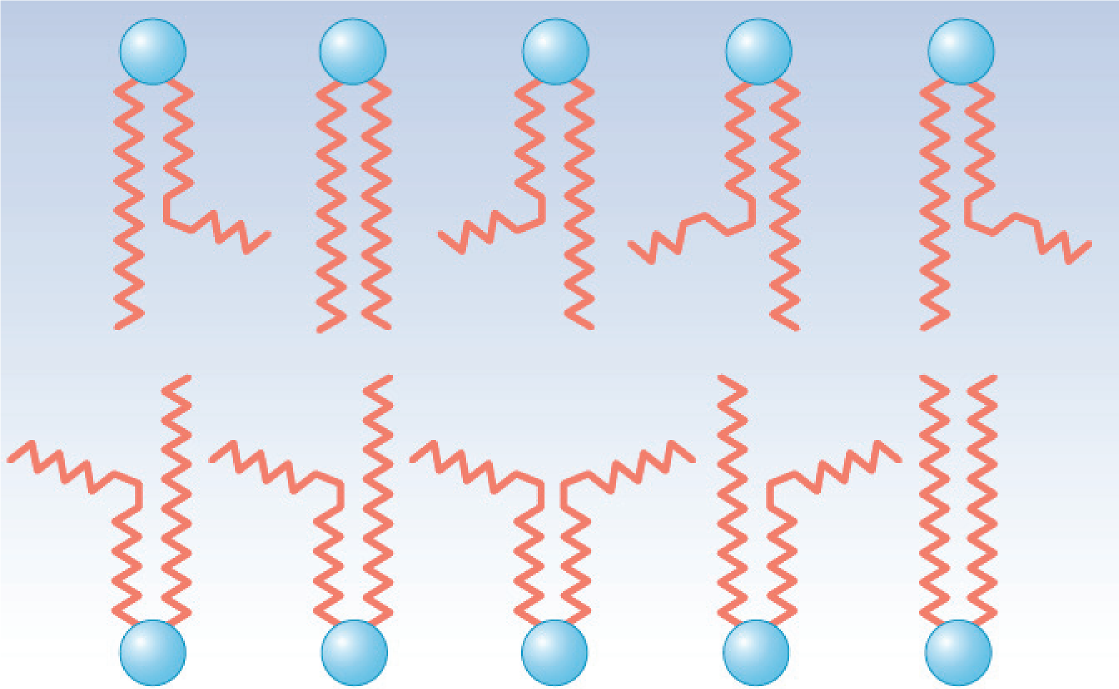


The properties of biological membranes:

- **Fluidity**
- **Motility**
- **Selective permeability**
- **Asymmetry**
- **Self-assembling**
- **Autorepair**

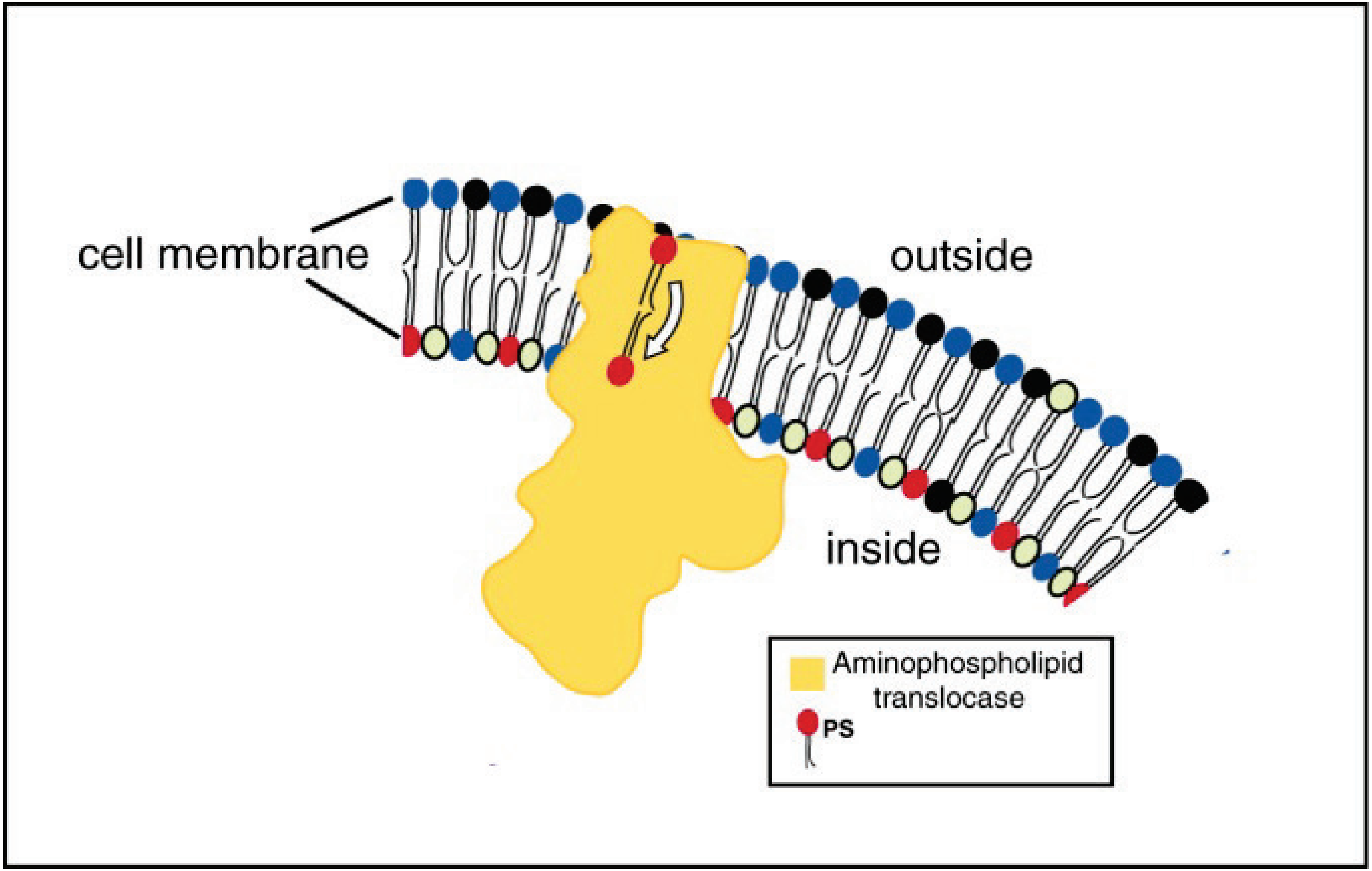
The importance of unsaturated fatty acids in fluid-crystalline organization of the membrane

Saturated fatty acids press in on each other, making a dense and fairly rigid membrane. **Unsaturated fatty acids,** due to the "kinks" in their tails, push adjacent phospholipids molecules away, which helps maintain fluidity in the membrane.



The asymmetric distribution phospholipids in membrane

- Lipids are distributed asymmetrically on both sides of the lipid bilayer
- Asymmetry, it is an effect, a reply to various factors, which the membrane contacts with
- Asymmetry is ensured by some enzymes - **membrane lipid transporters (LT)**
- We distinguish at least three groups of LT: **aminophospholipid translocases (flippases), floppases and phospholipid scramblases**


cell membrane
outside
inside
Aminophospholipid translocase
PS

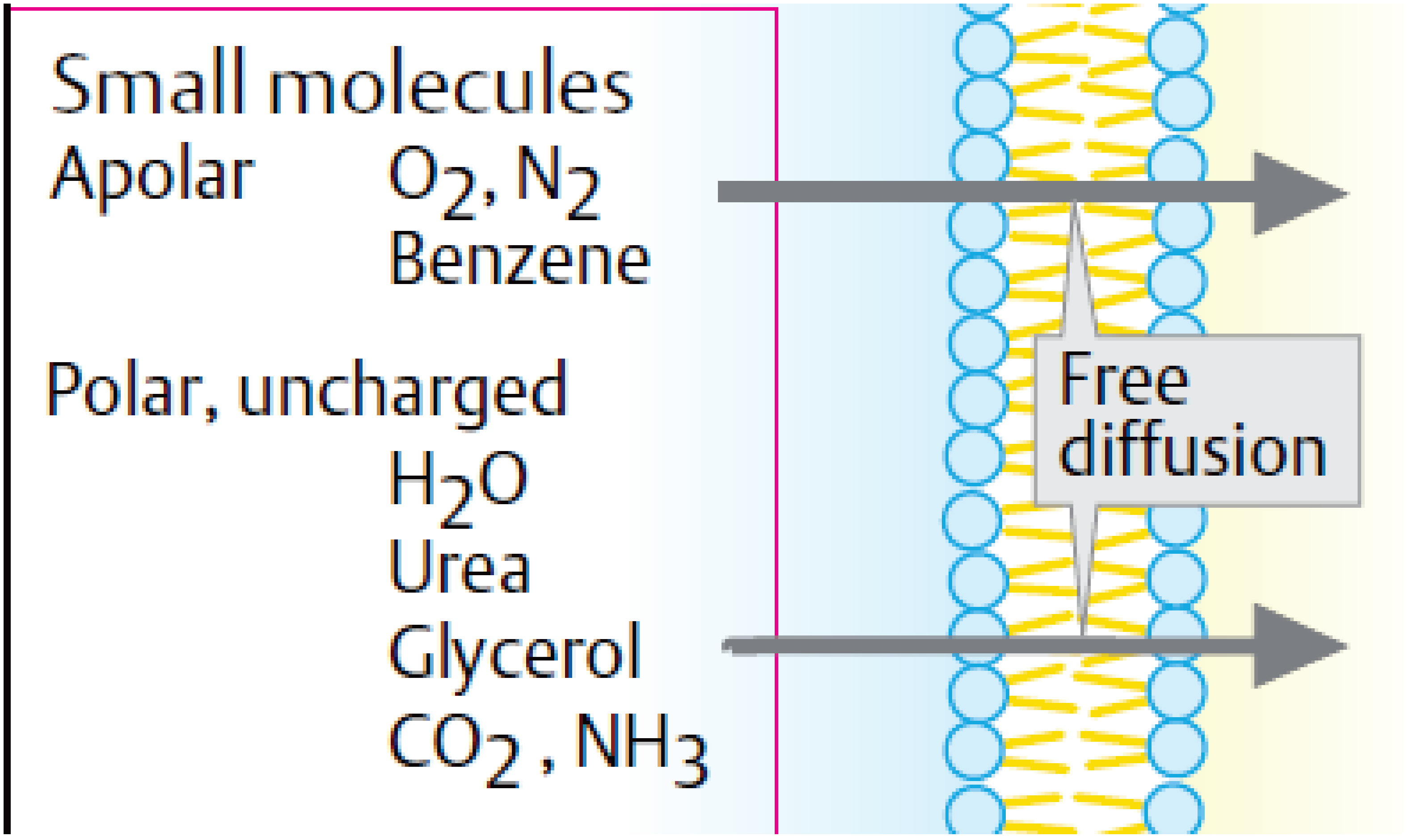
Diversity and structural and functional specificity of membranes

- Cytoplasmic membrane
- Simple membranes of cell organelles
- Double membranes of the organelles
- Specialized membranes for protection, transport, electricity generation, transformation of different types of energy, membranes involved in the oxidation and synthesis of various compounds

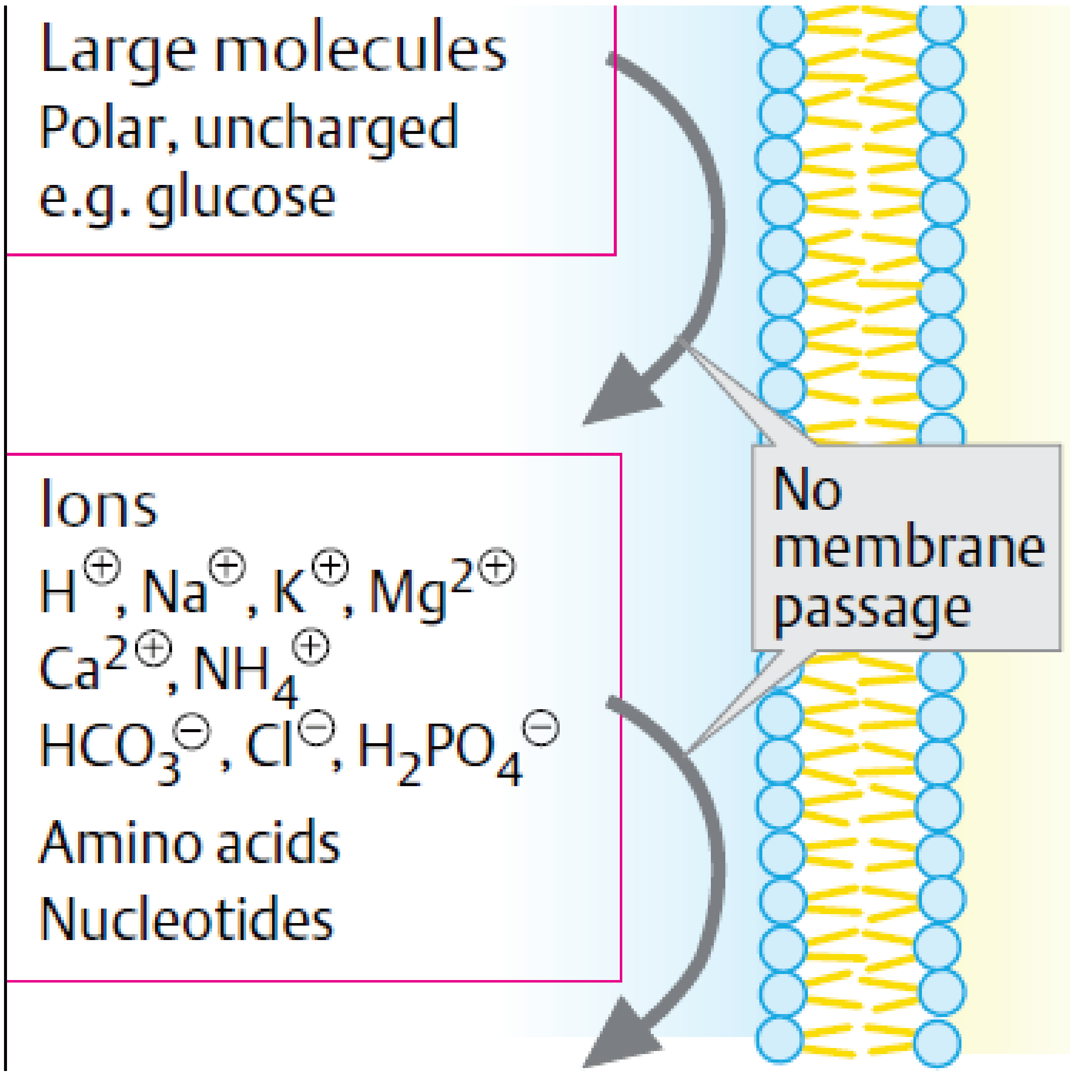
Membrane transport

- membrane transport ensures selective penetration of different compounds in the cell
- can be provided by diffusion, channels or transporters.
- Defects in membrane transport is associated with some diseases as cystic fibrosis, renal disease, neurological disorders, drug resistance, early senescence

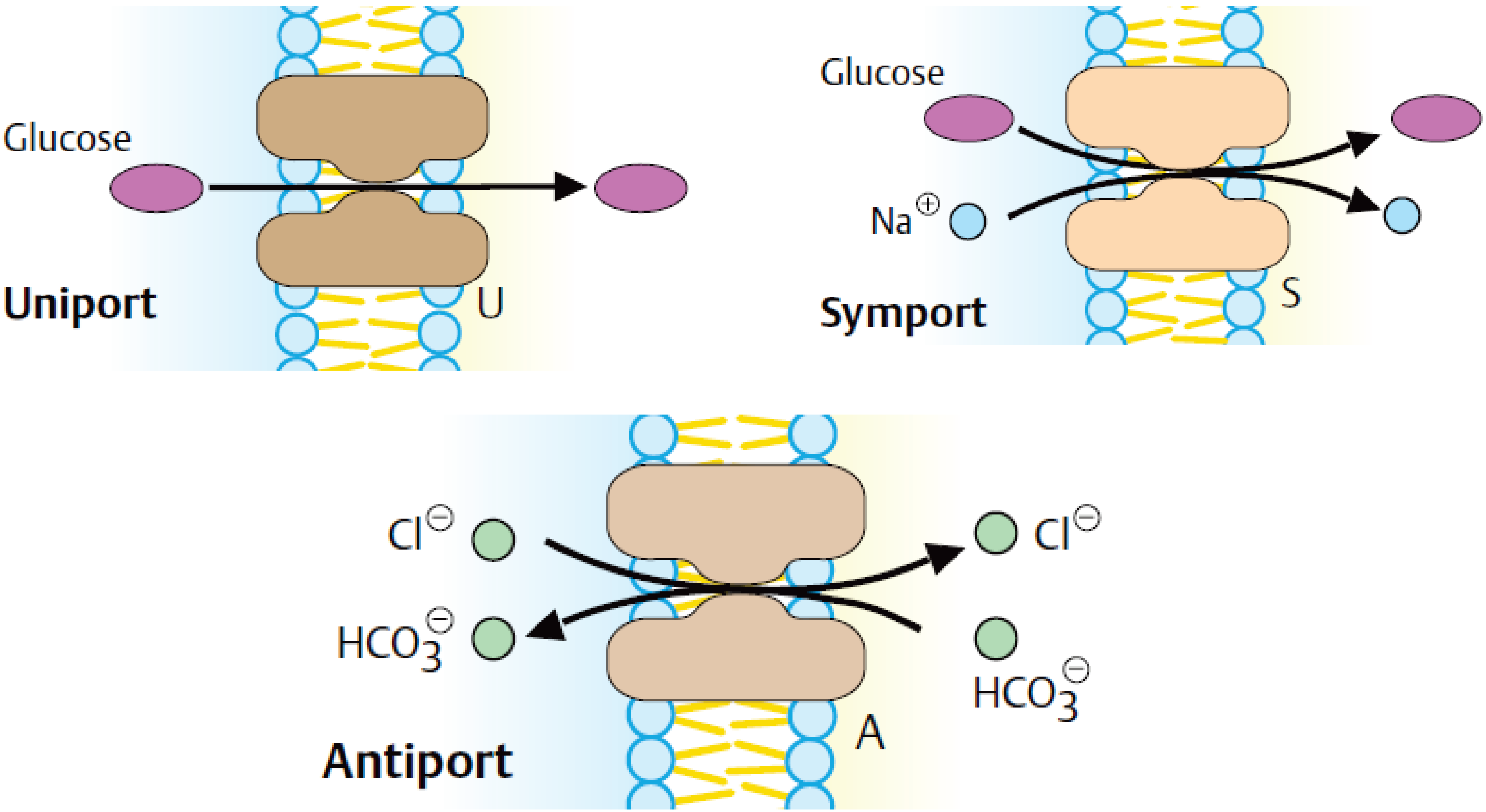
Permeable molecules



Impermeable molecules



Types of transport



Membrane channels

There are two types of channels:

alpha-channels and

beta-channels

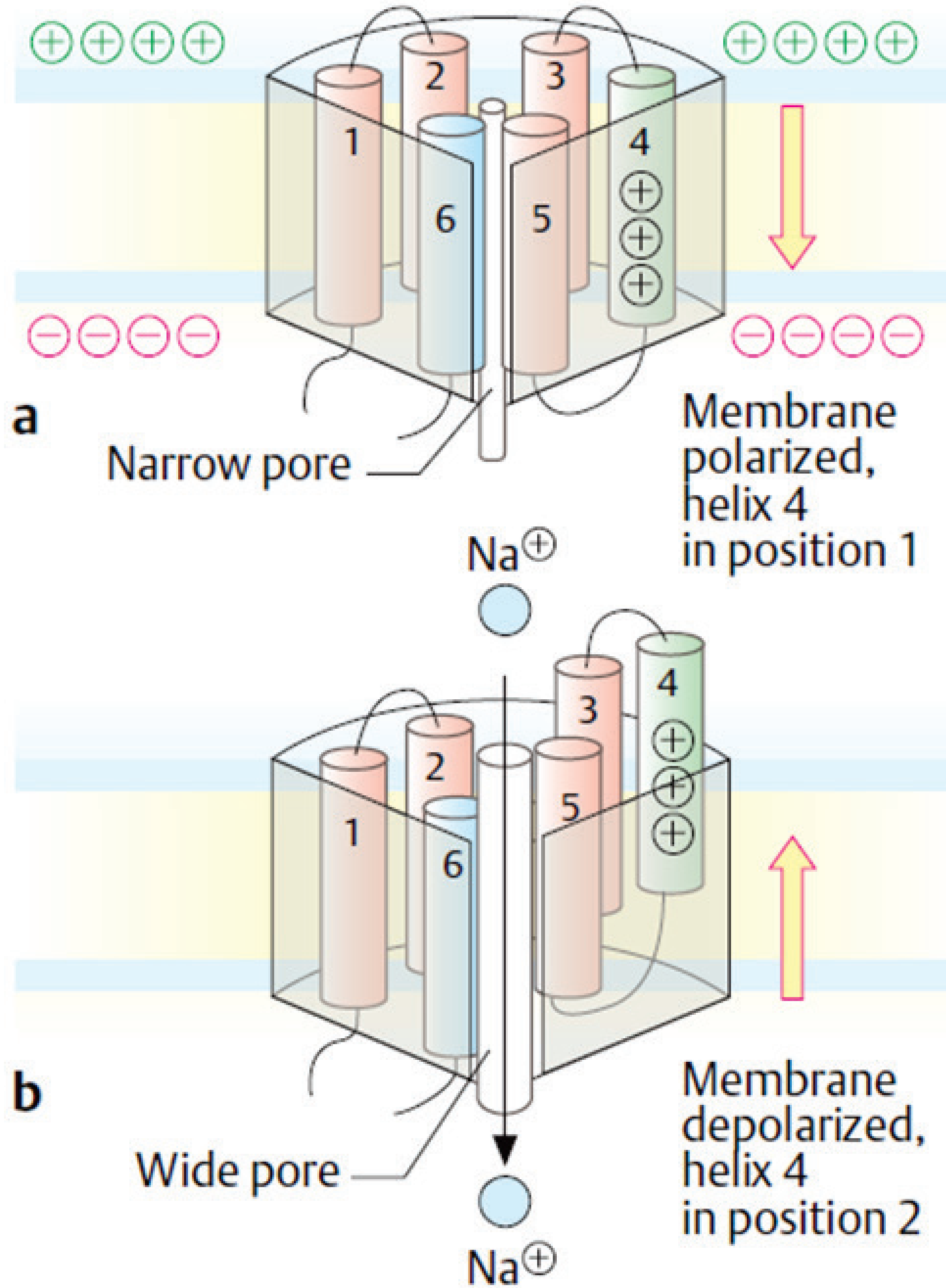
Alpha-channels

- are homo- or hetero- oligomeric proteins containing alpha-helical transmembrane segments.
- Membrane alpha channels include:
  - **voltage-gated channels specific for Na, K, Ca, Cl ions ;**
  - **aquaporins**
  - **agonist or ligand-gated channels**
  - **cAMP-dependent channels**

Voltage-gated Na^+ channels

- Play a decisive role in the conduction of electrical impulses in the nervous system
- These channels open when the membrane potential in their environment reverses.
- Due to the high equilibrium potential for Na^+, an inflow of Na^+ ions takes place, resulting in local **depolarization of the membrane, which** propagates by activation of neighboring voltage-dependent Na^+ channels.
- A spreading depolarization wave of this type is known as an **action potential.**
- **Externally directed** K^+ channels are involved in the repolarization of the membrane.

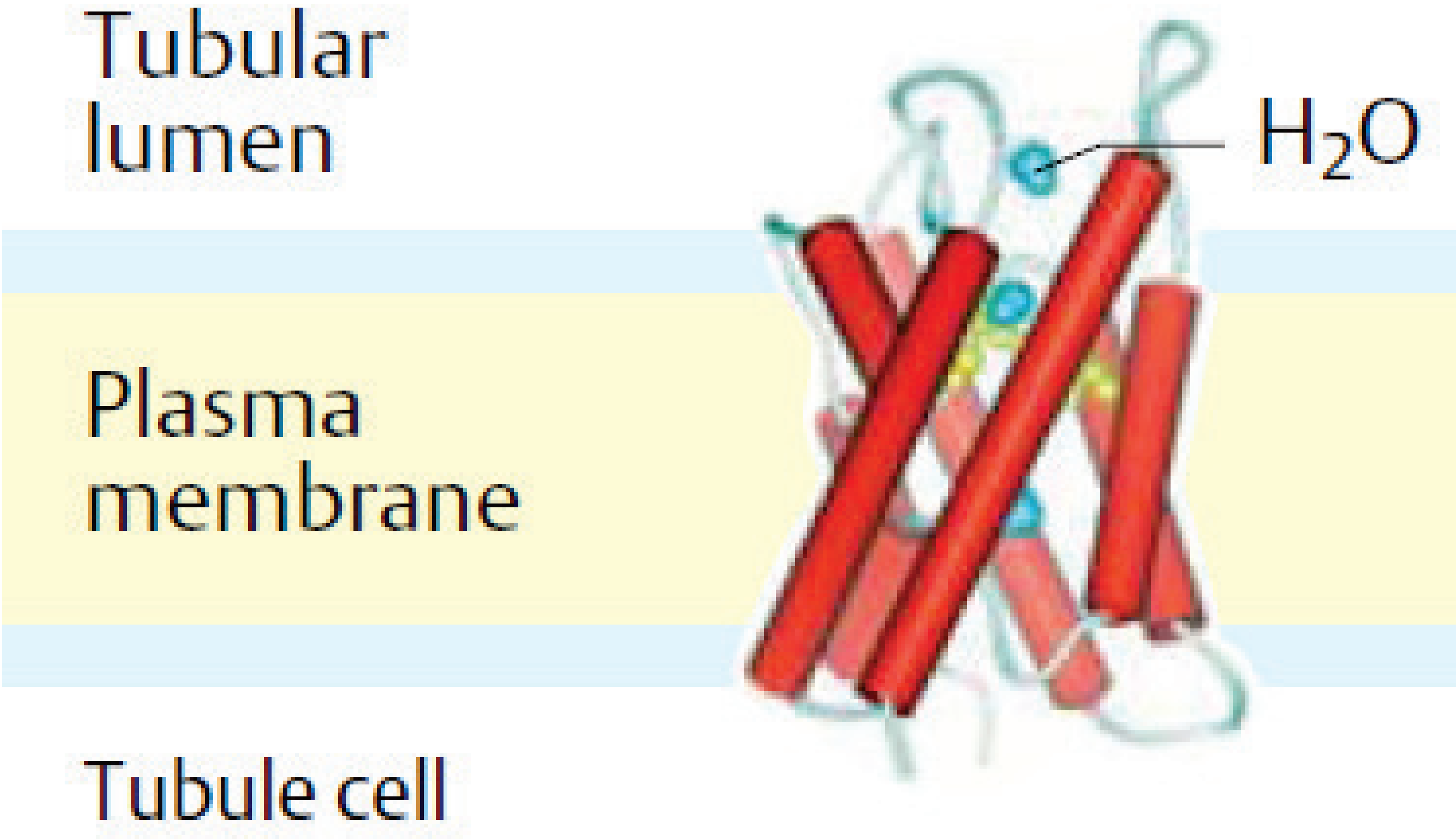
Structure and mechanism of functioning of a voltage-gated channel for Na+ ions



Aquaporin-1

- Aquaporins help water to pass through biological membranes.
- They form hydrophilic pores that allow H2O molecules, but not hydrated ions or larger molecules, to pass through.
- Aquaporins are particularly important in the kidney, where they promote the reuptake of water.
- Aquaporin-2 in the renal collecting ducts is regulated by **antidiuretic hormone (ADH, vasopressin),** which via cAMP leads to shifting of the channels from the ER into the plasma membrane.
- Aquaporin-1, shown here, occurs in the proximal tubule and in Henle's loop. It contains eight transmembrane helices with different lengths and orientations.

Aquaporins type 1 in kidney



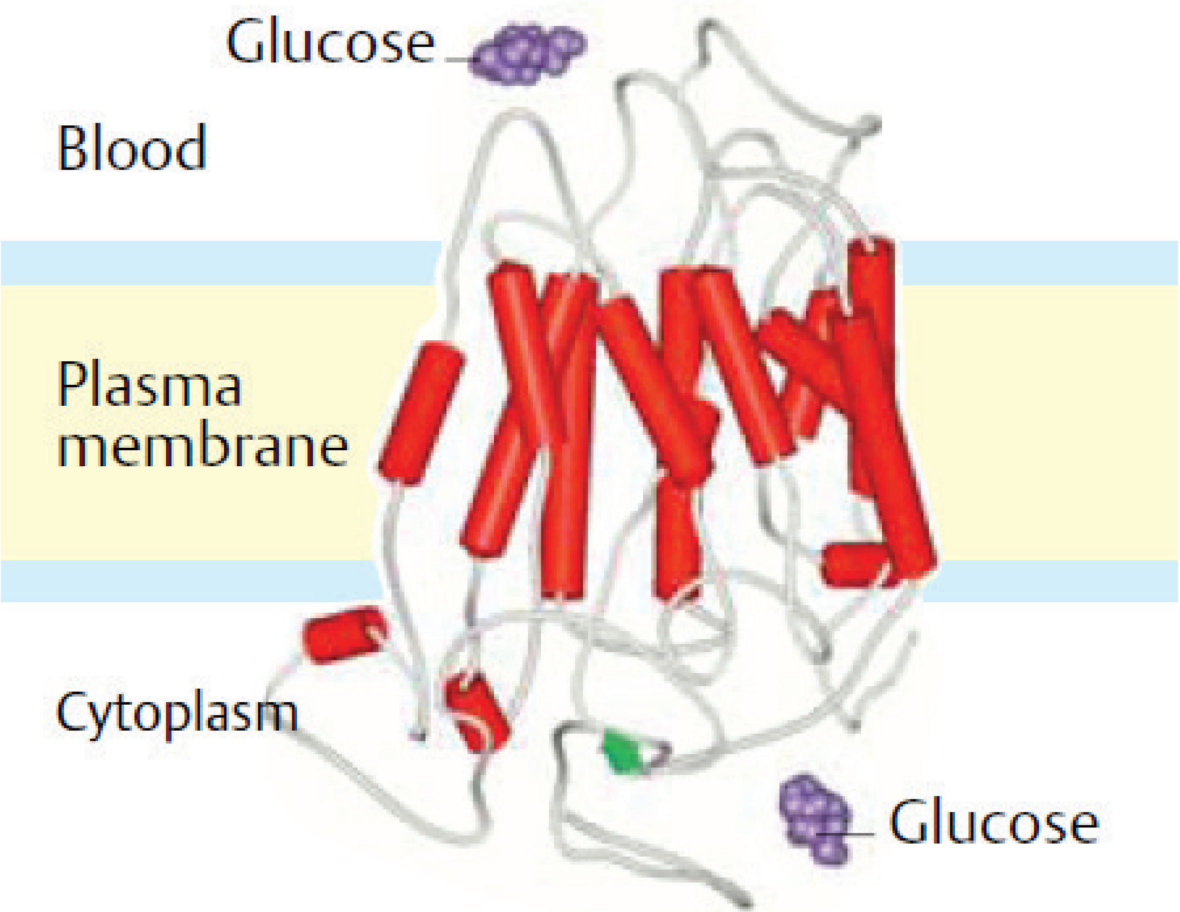
The beta channels or porins

- are proteins comprising the transmembrane sequences of the beta-structure forming a cylinder with a diameter of 0.6 - 3 nm
- Such channels are present more in the outer mitochondrial membrane, in membranes of bacteria
- Allow the passage of different types molecules – from inorganic ion to the proteins.

Membrane transporters

- It presents a very diverse group of transmembrane proteins with different structure, specificity and function
- They have a very high degree of structural specificity and even stereospecificity for the transporting molecules
- For example, the transporter for D-glucose in the erythrocytes has a 10-fold lower affinity for D-galactose and 1000-fold lower for the L-glucose.

Glucose transporter GLUT1

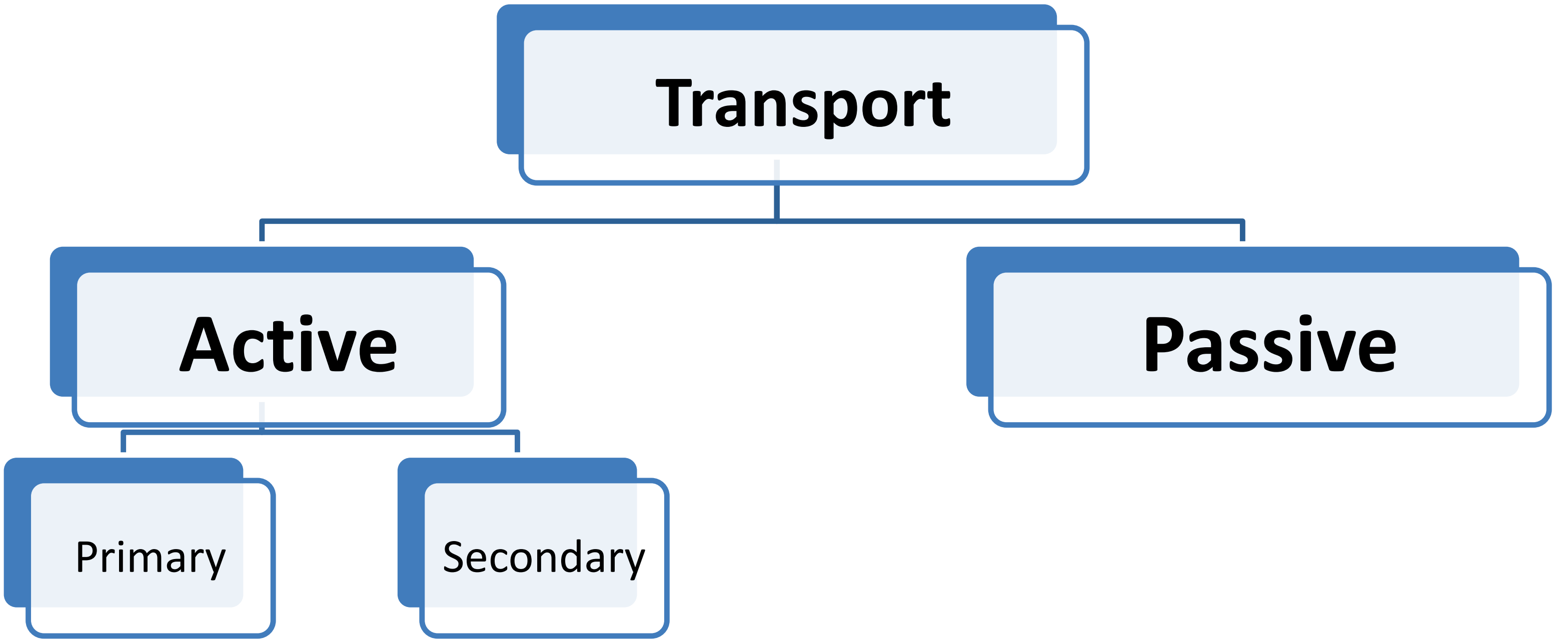


4 stages are distinguished in the functioning of transporters:

1. Recognition of the specific molecule
2. Specific binding and translocation of the molecule through the membrane
3. Releasing the molecule into the cytosol
4. Regeneration of the transporter to its original state

Depending on the additional requirements for the transporters functioning, are distinguished:

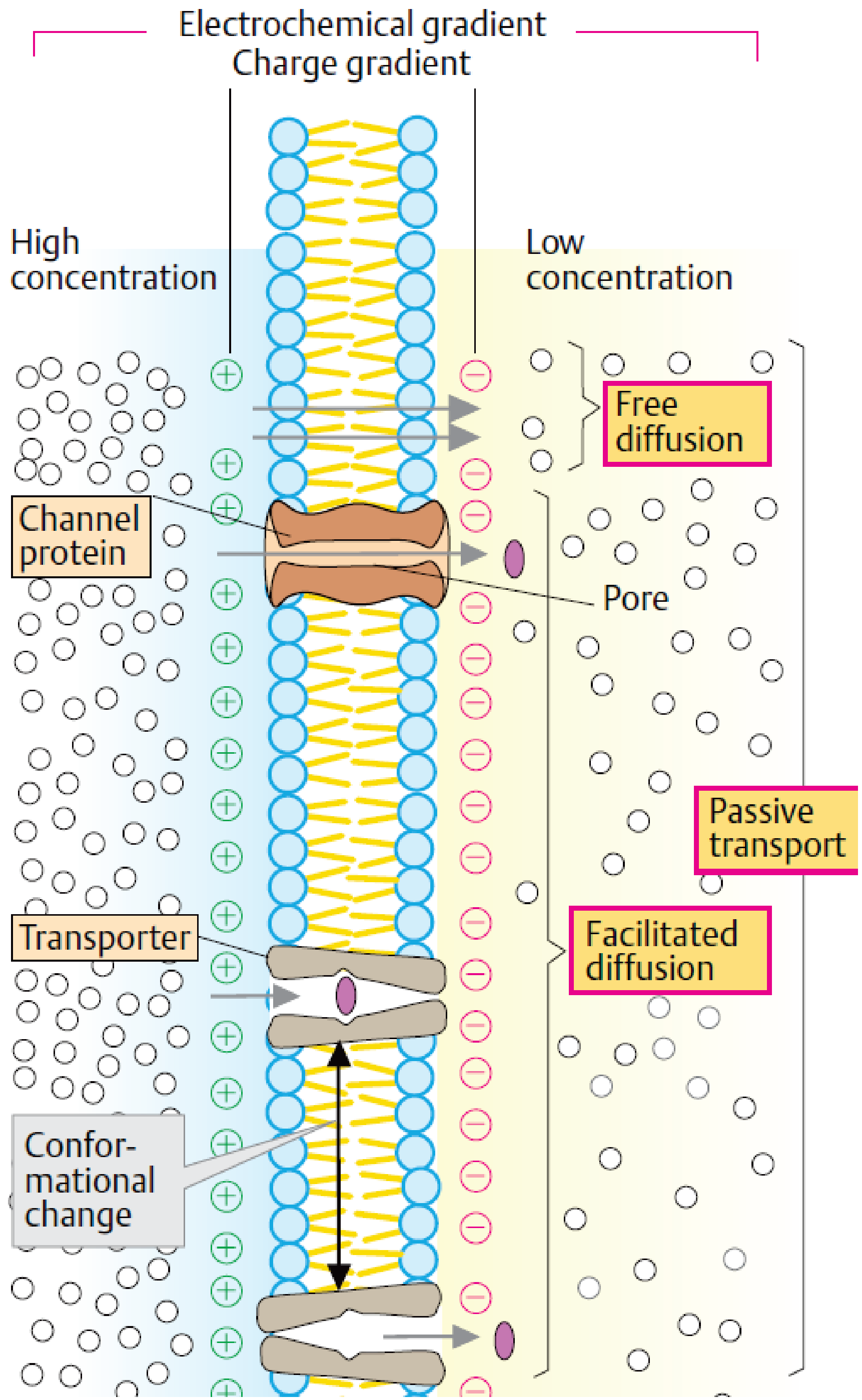
- **Passive transporters** - don’t use energy
- **Active transporters** - require energy



Passive transport

- The transporters are protein molecules containing 400-600 amino acid residues.
- Their polypeptide chains forme 2-24 alpha-helix transmembrane sequences.
- Passive transporters carry inorganic ions, monosaccharides, amino acids, various metabolites

PASSIVE TRANSPORT



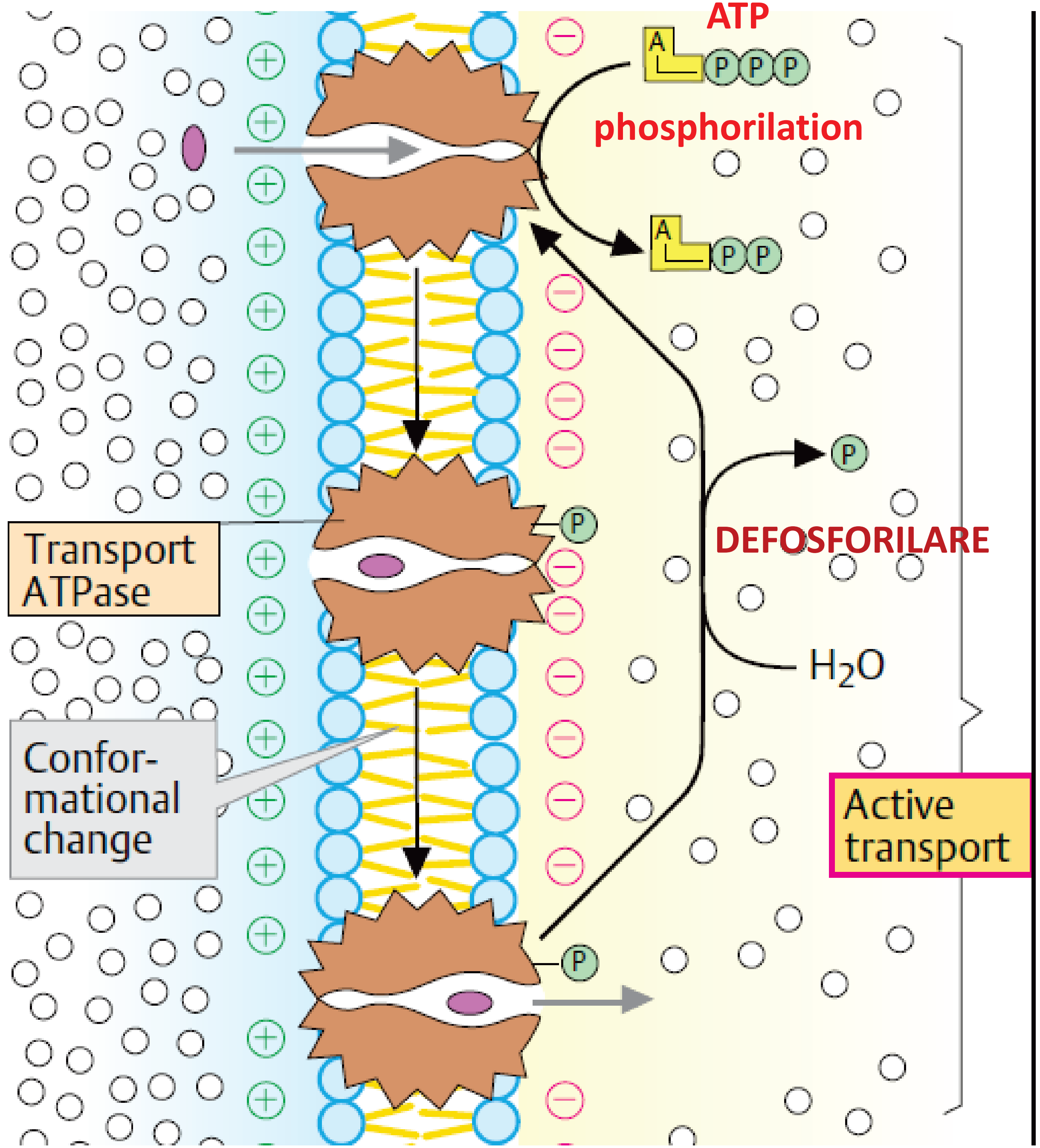
Examples of passive transporters :

- glucose transportes GLUT1-GLUT5
- Passive antiport transporters of Cl^- and HCO_3^- anions in erythrocytes and kidneys (anion exchange proteins).
- Internal mitochondrial membrane transporters:
  - antiporters for ADP and ATP;
  - simporters for phosphate and H^+;
  - glutamate-aspartate antiporters .

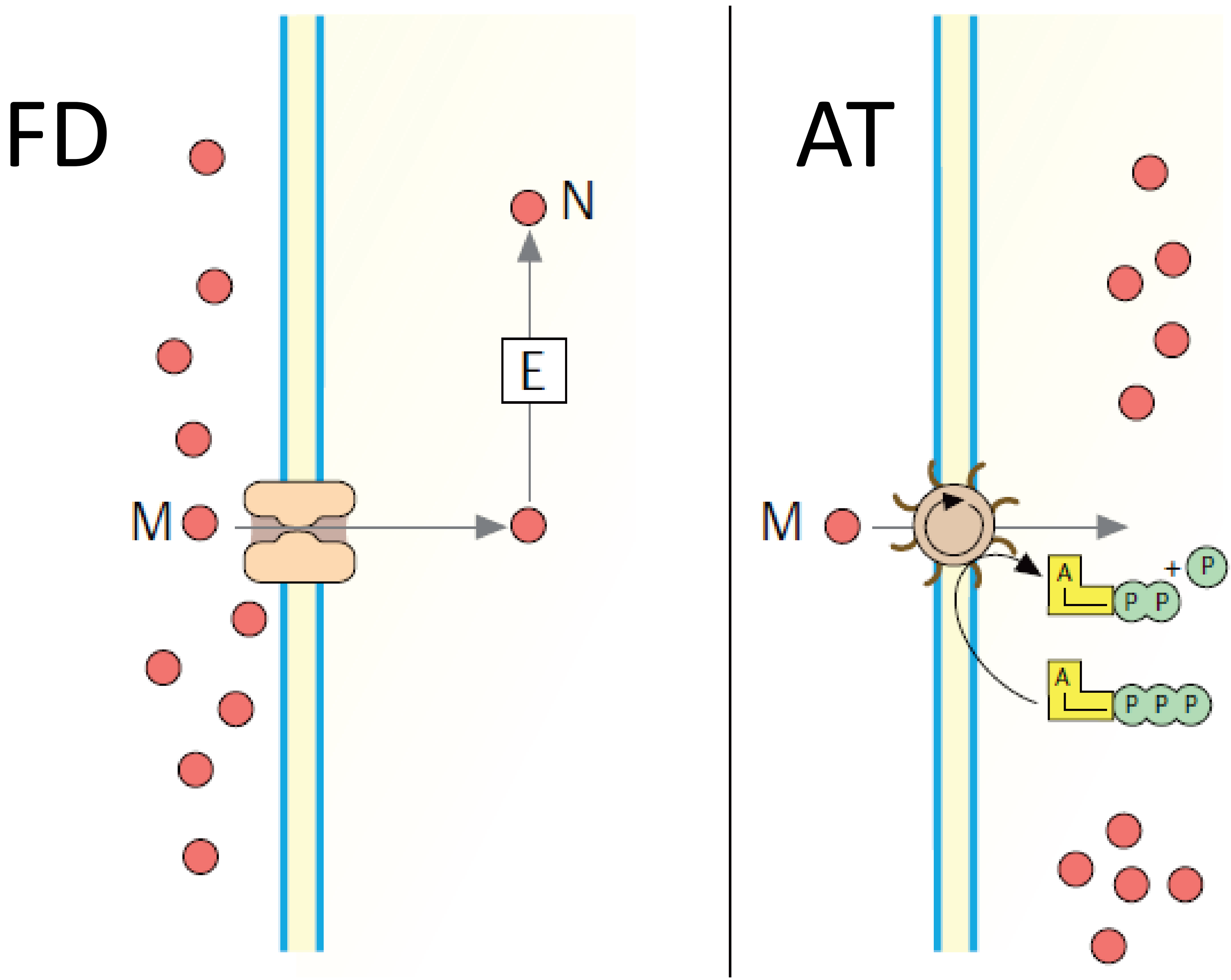
Active transport

- Active transporters catalyze the molecules translocation against the concentration gradient and require energy consumption
- There are **primary and secondary active transporters,** and respectively **primary and secondary active transport.**

ACTIVE TRANSPORT



MECHANISM OF FACILITATED DIFFUSION (FD) (PASSIVE) AND ACTIVE TRANSPORT (AT)



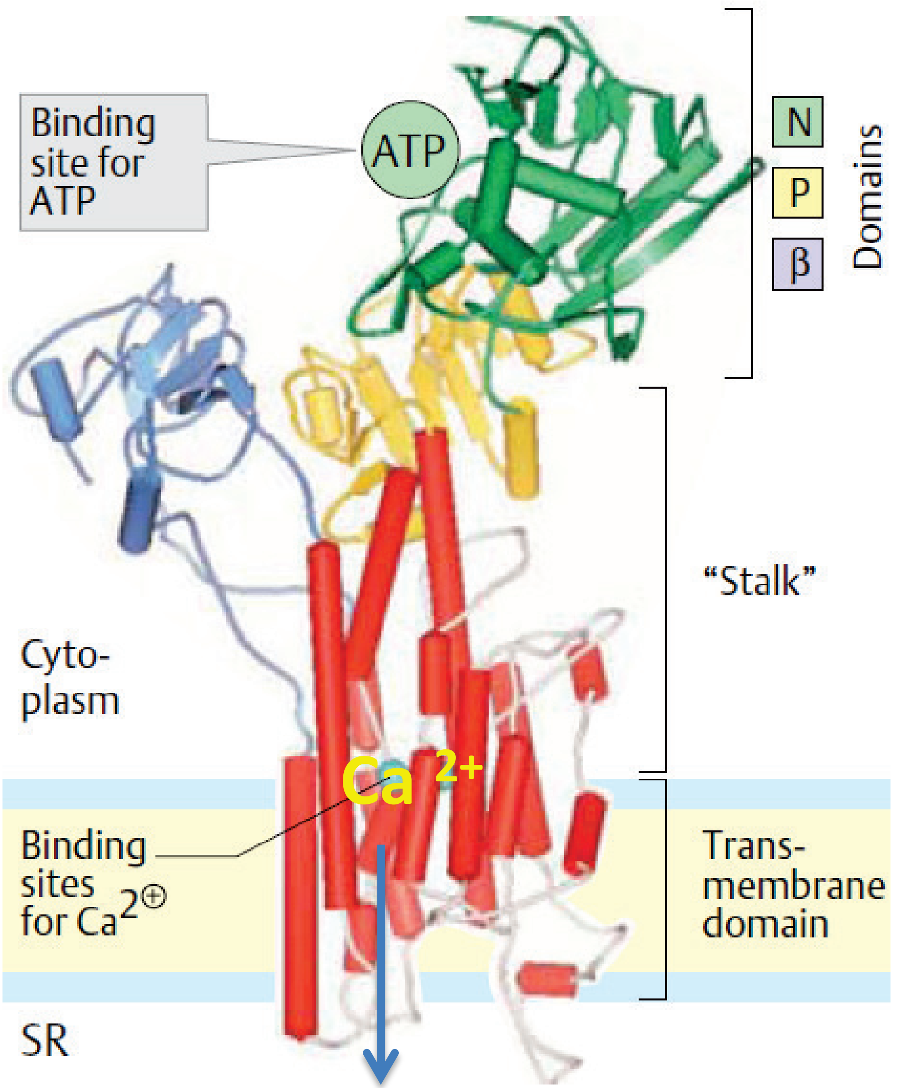
The primary active transporters (PAT)

- Primary active transport utilizes energy in form of ATP to transport molecules across a membrane against their concentration gradient. The transported substrate is not phosphorylated.
- These type of transporters refer to ATP-ases.
- There are considered four classes of ATP-dependent ion pumps:
  - P-class pumps
  - F-class pumps
  - V-class pumps
  - ABC superfamily (ATP-binding cassette)
- The P-, F- and V-classes only transport ions, while the ABC superfamily also transports small molecules.

Types of primary active transporters (TPA):

- **Type P** - transports Na^+, K^+, Ca^{2+} ions, comprises more than 300 members.
- **Type V** transporters are H^+ pumps, responsible for the acidification of the content of lysosomes, endosomes, secretory and Golgi vesicles.
- **Type F** - are present in the membranes of mitochondria, chloroplasts and bacteria. Participate in the translocation of H^+ with consumption of ATP.
- **ABC superfamily** transporters transport small molecules using ATP.

The structure of the sarcoplasmic Ca^{2+} -ATP-ase pump

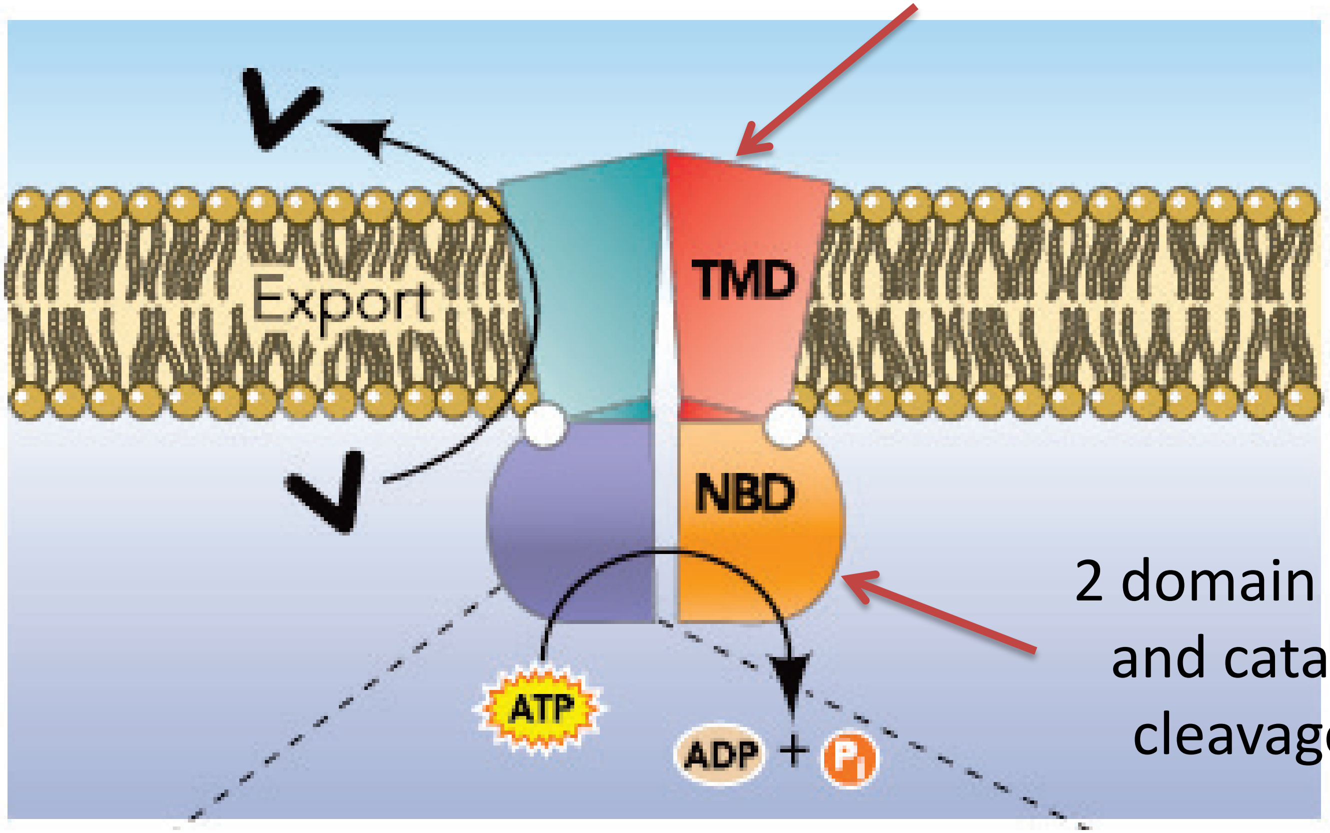


ABC transporters

- ABC transporters catalyze the influx or efflux of various phospholipids, long chain acyl-CoA, bile salts, cholesterol, peptides.
- The normal function of human ABC transporters is to remove cytotoxic compounds and drugs from the cell
- These transporters have a very important medical role.
- Many of them are involved in selective transport of various exogenous compounds, toxins and drugs.
- Some ABC transporters are responsible for the phenomenon of drug resistance, particularly in chemotherapy.

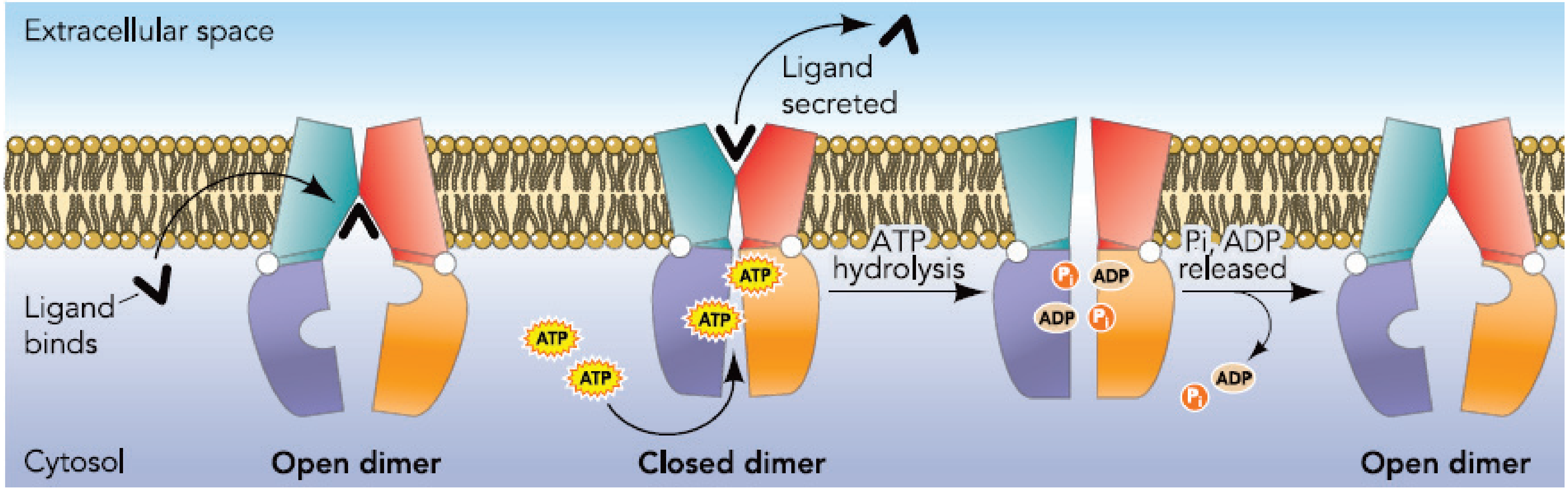
The structure of a typical ABC transporter

2 transmembrane domains
linking the ligand



2 domain that binds
and catalyzes the
cleavage of ATP

The mechanism of ABC transporters functioning



The mechanism of ABC transporters

- Two transmembrane domains (TMDs) form the ligand binding sites and provide specificity, and two nucleotide binding domains NBDs bind and hydrolyze ATP to drive the translocation of the bound ligand.
- The NBDs, but not the TMDs, are homologous throughout the family and have several characteristic motifs including the Walker A and B motifs common to many nucleotide binding proteins and others like the ABC signature, stacking aromatic D, H, and Q loops, which are unique to the family.

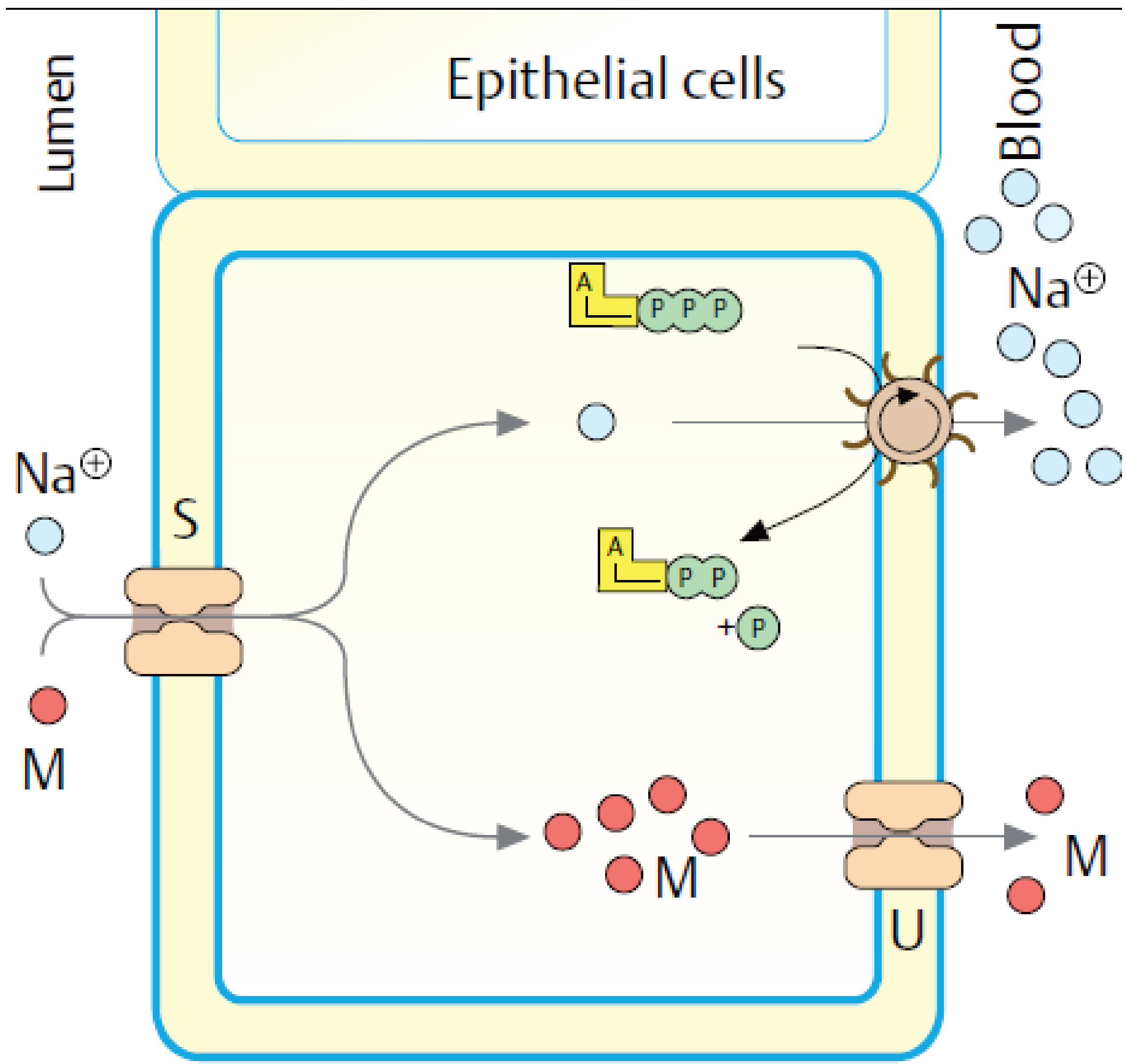
The normal function of some human ABC transporters

- is to secrete from cells cytotoxic compounds (dietary cytotoxics and therapeutic drugs).
- These transporters (P-glycoprotein, BCRP, and MRP1) are highly expressed in the gut, liver and kidneys where they restrict the bioavailability of administered drugs.

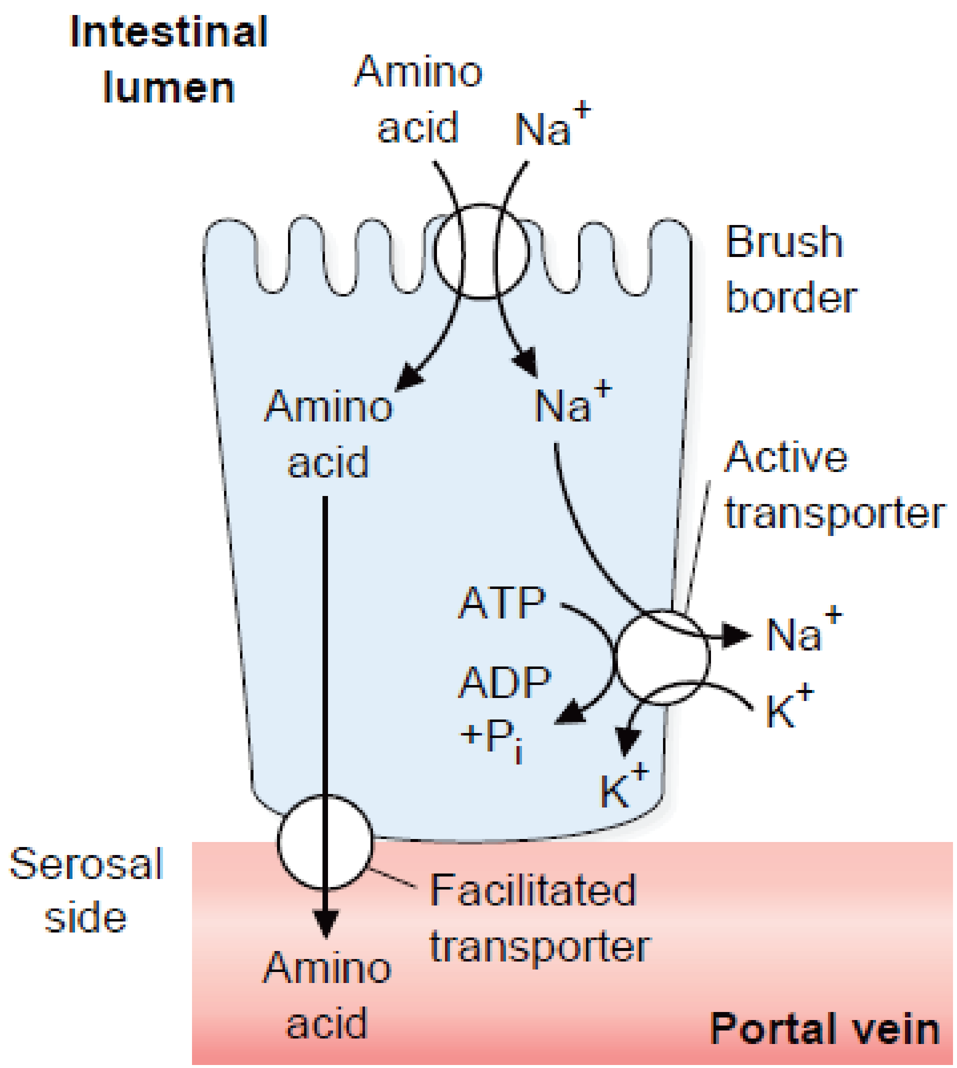
Secundary active transporters (SAT)

- ATP does not require ATP directly.
- Are Na^+ - dependent transporters (SSAT - sodium-dependent secondary active transporters). Over 400 representatives.
- SAT transport monosaccharides, amino acids, ions and other micromoles by simport with Na^+.
- SAT use as a source of energy the electrochemical gradient created by Na^+; then the accumulated excess of intracellular Na^+ is pumped by Na^+ / K^+ -ATP-ase, hence the name of secondary active transporters.
- SAT use the energy of ATP indirectly, because ATP is used only for the maintenance of Na^+ gradient, not for phosphorylation and activation of the transporter

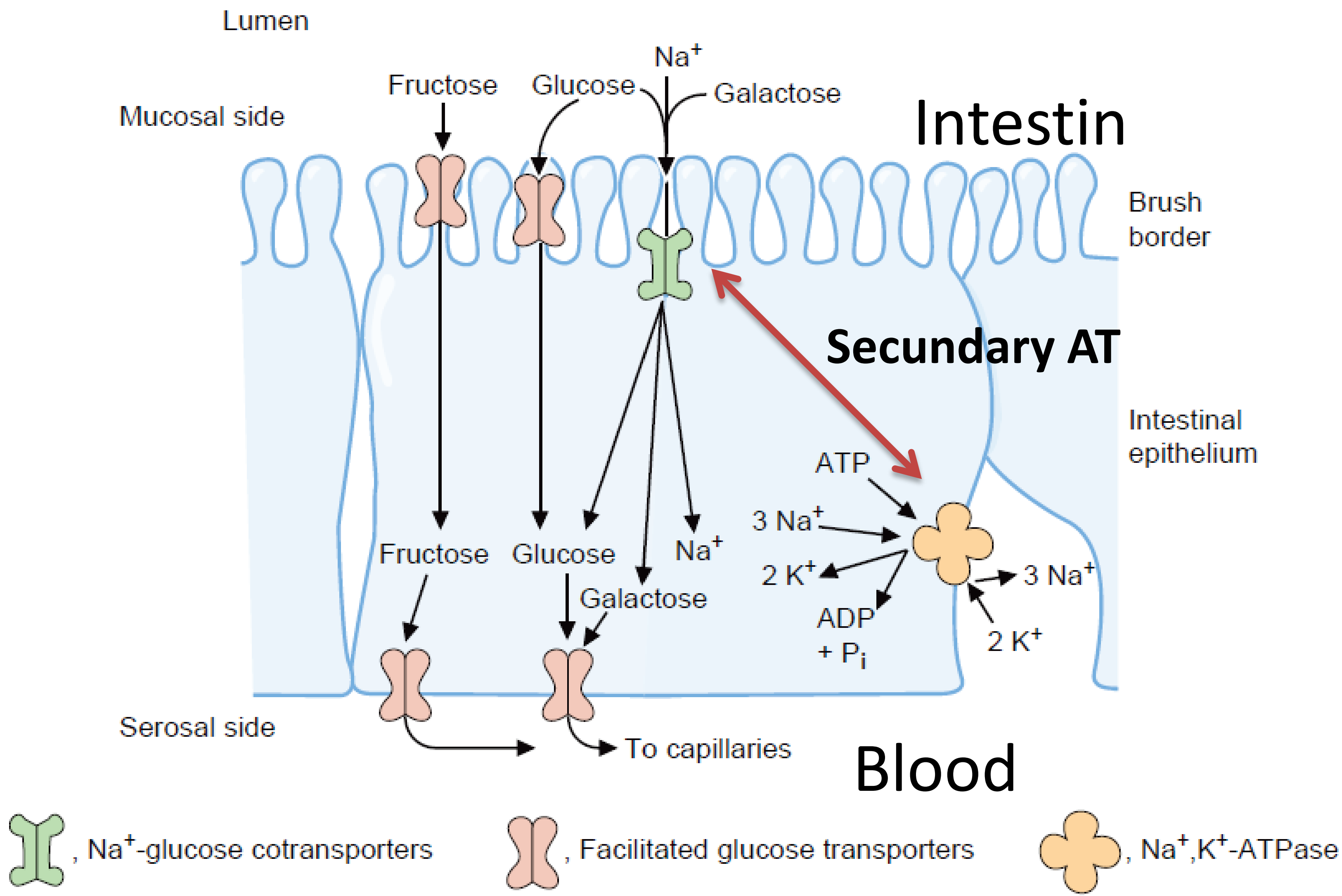
Secondary active transport mechanism



Amino acid absorption in the intestine by the secondary active transport (simport with Na^+ ions)



Different types of transport in the absorption of monosaccharides



Examples of diseases caused by genetic mutations of the transport protein

- **Nephrogenic diabetes insipidus -** mutations in some channel proteins - aquaporin 2 AQP2 12q13
- **Generalized epilepsy with febrile seizures -** alpha subunit of neuronal sodium channel type 1 SCN1A
- **Periodic Hypokalemic Paralysis - calcium channel voltage-dependent L-type subunit α -1 S CACNA1S 1q32**
- **Osteopetrosis -** Chlorine Channel 7 CLCN7 16p13
- **Malabsorption of glucose / galactose -** cotransporter sodium-glucose SLC5A1 22q13.1
- **Congenital Hypothyroidism -** cotransporter sodium-iodine SLC5A5
- **Cystic Fibrosis -** ABCt, subfamily C, member 7 ABCC7