Chapter 2. PLASMA MEMBRANE

I. DEFINIT1ON

The plasma membrane is a dynamic structure that separates the intracellular medium (hyaloplasm or cytosol) from the extracellular medium. It controls the exchanges between the cell and its environment.

II. STRUCTURE AND ULTRASTRUCTURE

1. Photonic microscopy

The plasma membrane appears as a dense area that separates the intracellular medium from the extracellular medium.

2. Transmission Electron Microscopy (TEM)

The observation of thin sections (see TP), has a high magnification, shows that the membrane formed of three sheets or layers:
- A sheet of 2nm thick, dense with electrons called dense outer sheet.
- A sheet of 2nm thick, dense with electrons called inner dense sheet.
- A sheet of 3.5nm thick, clear located between the two previous sheets said clear sheet.

This so-called trilamellar, tripartite or tristratified structure is common to all biological membranes, hence the notion of "unitary membrane". The outer dense sheet is often thicker than the inner dense sheet, this is due to the presence of glycocalyx (fibrous coating or cell-coat), which is responsible for the asymmetry of the plasma membrane. The thickness of this coating varies according to the cell type.

3. Scanning electron microscope (SEM)

The observation of replicas obtained by the cryo-stripping technique (see TP) shows that the plasma membrane formed by two hemi-membranes (half-membranes), one exoplasmic or external and the other protoplasmic or internal, into which intramembrane globular particles are inserted. These particles have a different distribution and density in the two hemi-membranes, hence the asymmetry of the plasma membrane.

III. CHEMICAL COMPOSITION

1. Isolation

The experiments were done on red blood cell membranes. The red blood cells placed in a hypotonic medium; there is then water entry and hemolysis (rupture and fragmentation of the plasma membrane). By simple centrifugation obtained a pellet, which contains the fragmented plasma membranes or phantoms of red blood cells and a supernagent containing the cytoplasm.

2. Results of chemical analysis

The membrane represented on average by 60% protein, 40% fat and a very low carbohydrate content.

a. Lipids

a_1. Nature

These are essentially phospholipids, cholesterol (in the membrane of the animal cell, it is less important in that of the plant cell where it is replaced by other types of sterols: sitosterol and stigmasterol) and glycolipids (carbohydrate chains bound to phospholipids on their extracellular surface).

a_2. Properties

The study of artificial membranes shows that phospholipids placed in aqueous media are able to:

- **Self-assembly**: phospholipids can be organized or assembled in bilayer thanks to their amphiphilic or bipolar character (hydrophilic head and hydrophobic tail).
- **Fluidity**: the plasma membrane is fluid thanks to the movements of lipids, which can be classified into frequent and rapid movements (lateral diffusion and rotation) and rare and very slow movements (flip-flop). The fluidity of the membrane increases proportionally with the percentage of unsaturated fatty acids and decreases with that of cholesterol.
- **Mechanical stability**: the membrane is even more stable as it is rich in cholesterol.
- **Asymmetry**: the lipid composition varies between the two hemimembranes; Example: glycolipids are located exclusively in the outer hemimembrane, hence the asymmetry of the membrane.

a_3. Functions

Lipids determine the basic structure (bilayer) that is fundamental to the organization of all biological membranes. They constitute an impermeable barrier to water-soluble molecules (see transport across the plasma membrane).

b. Protein

b_1. Nature

Proteins are classified into holoproteins (pure proteins) and heteroproteins (glycoproteins consisting of a protein and a carbohydrate fraction with linear or branched chains).

b_2. Properties

Thanks to experiments on artificial membranes, it has been shown that proteins have two modes of organization (**Figure 1**):

- **Integrated proteins** (intrinsic): When they cross the lipid bilayer they are called transmembrane (Figure 1A), they are hydrophobic proteins; they correspond to the intramembrane globular particles visible in the replicas obtained after cryo-stripping. Other proteins are either integrated into the outer dense sheet and linked by a covalent (stable) bond to a phosphatidyl-inositol group (GPI) or integrated into the inner dense sheet by covalent bonds to one or more fatty acids (**Figure 1B**).
- **Peripheral proteins** (extrinsic): these are hydrophilic proteins either, external (exoplasmic) or internal (protoplasmic), they are often bound to transmembrane proteins by non-covalent (unstable) bonds (**Figure 1C**).
- **Fluidity**: protein movements are less frequent, because of the large size of these molecules, compared to that of lipid molecules. They are slow and represented mainly by the lateral diffusion movement within the lipid bilayer. This movement has been demonstrated by different techniques: see the pH variation experiment.
- **Asymmetry**: the distribution of plasma membrane proteins is different, on both sides, which determine their roles in relation to the extracellular matrix (ECM) on the one hand and with the cytoskeleton on the other hand.

b3. Functions

Proteins have multiple functions:

- **Structural proteins**: have a supporting role, anchor point for the molecules of the extracellular matrix on the one hand and those of the cytoskeleton on the other hand.
- **Enzymatic proteins**: capable of transforming a substrate into a product.
- **Transport proteins**: see next paragraph, physiological roles.
- **Receptor-type proteins**: external information, necessary for intercellular communication (see paragraph physiological roles).

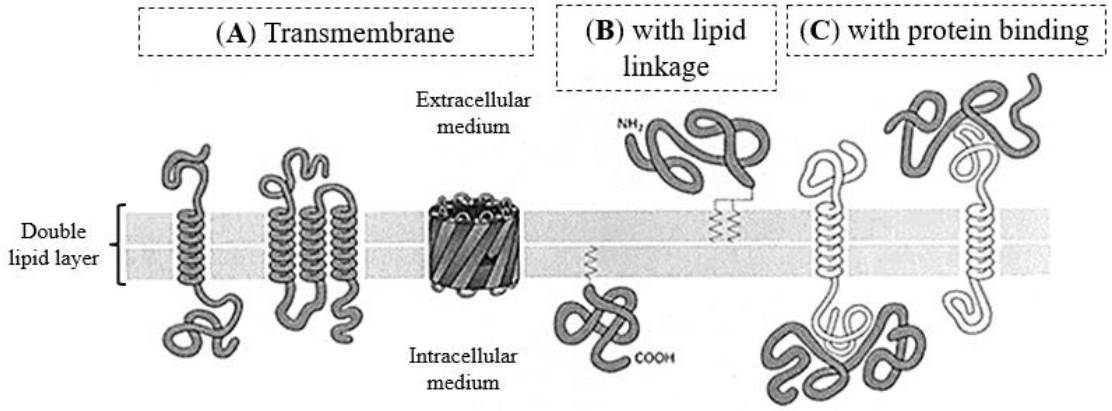

Figure 1: Possible associations of membrane proteins with the lipid bilayer.
(**A**) Transmembrane proteins may extend through the double layer as a single α helix, multiple α helices, or a closed β sheet (a β barrel). (**B**) The other membrane proteins are attached to the double layer only by a covalent bond with a lipid molecule (red zigzag lines). (**C**) Finally, many proteins are attached to the membrane only by relatively simple non-covalent interactions with other membrane proteins.

c. Carbohydrates

c1. Nature

In general, carbohydrates are represented in small quantities in the plasma membrane (5% to 10%) and come in two forms, glycolipids and glycoproteins associated with the dense outer leaflet to form glycocalyx.

c2. Functions of glycocalyx

- **Protection of the cell**,
- **Adhesion** between neighboring cells and / or between cell and extracellular matrix,
- **Cell specificity**: marker of certain cells (blood group antigens),
- **Recognition** between cells for tissue organization
- **Contact inhibition**: controls cell division.

IV. MOLECULAR ARCHITECTURE

The plasma membrane is an asymmetric fluid mosaic (**Figure 2**) according to the model proposed by Singer and Nicholson (1972).

V. PHYSIOLOGICAL ROLES

1. Control of exchanges between the extracellular medium and the intracellular medium

1.1. Exchanges without deformation of the plasma membrane

These are small molecule transports, without the intervention of the cytoskeleton. They are of two types, passive transportation and active transportation.

a. Passive transport

The molecules are transported in the direction of their concentration gradient, without consumption of ATP; they are of two types:

a1. Simple diffusion (without permeases), through the lipid bilayer (hydrophobic and uncharged molecules: H_2O, CO_2, O_2, N_2, benzene, ethanol ...) (**Figure 31**).

a2. Diffusion facilitated via protein channels such as specific ion channels (Na^+, K^+, Cl^-) or water channels (aquaporin's), by either specific carrier proteins or permease for the transport of glucose, amino acids, etc.) (**Figure 32**).

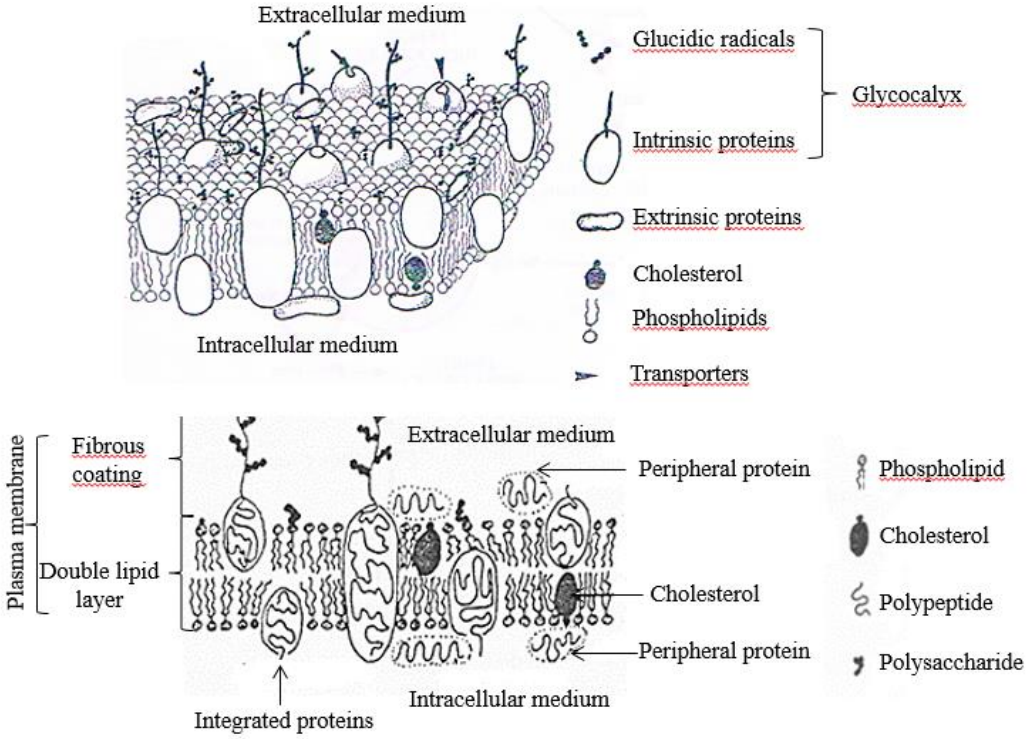

Figure 2: Molecular architecture of the plasma membrane.

b. Active transportation

b.1. Primary: called direct active transport, it consumes energy obtained by the hydrolysis of ATP and is done against the concentration gradient. It involves enzymes called transmembrane ATPase's or pumps (e.g. Na_2^+ / K^+ pump, H^+ pump and Ca_2^+ pump) (**Figure 33**).

b.2. Secondary: unlike direct active transport, it does not use the energy provided by the hydrolysis of ATP, it is the electrochemical potential difference that is used. The two main forms are (**Figure 33**):

- **Symport**: the two substances of different nature are transported in the same direction (Co-transport), one in the direction of its concentration gradient (passive transport) and the other in the opposite direction to its concentration gradient (active transport).
- **Anti-port**: transport of two or more substances of different nature in opposite directions (counter-transport). One is transported in the direction of the concentration gradient and the other counter-concentration gradient.

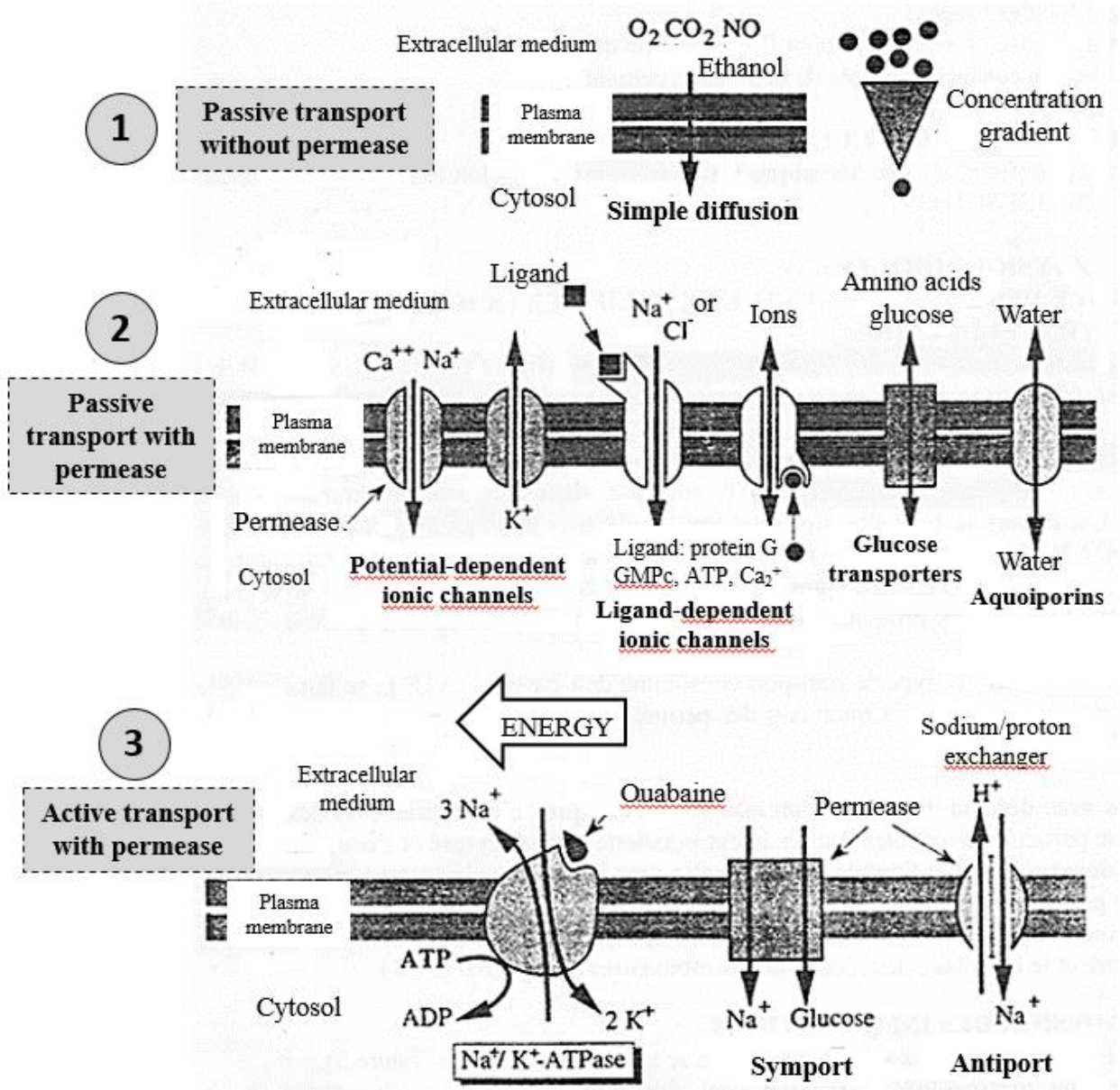

Figure 3: Exchange without deformation of the plasma membrane.

1.2. Exchanges with plasma membrane deformations

It is the transport of large molecules or particles with intervention of the cytoskeleton, case of endocytosis and exocytosis (**Figure 4**).

a. Endocytosis

It allows the entry of molecules to the cell (**Figure 4A**). Three types of endocytosis are known:

- Phagocytosis (**1**),
- Pinocytosis (**2**) and
- Receptor endocytosis (**3**).

b. Exocytosis

On the contrary, exocytosis ensures the exit of secretion molecules to the extracellular medium and allows the recycling of membrane receptors (**Figure 4B**).

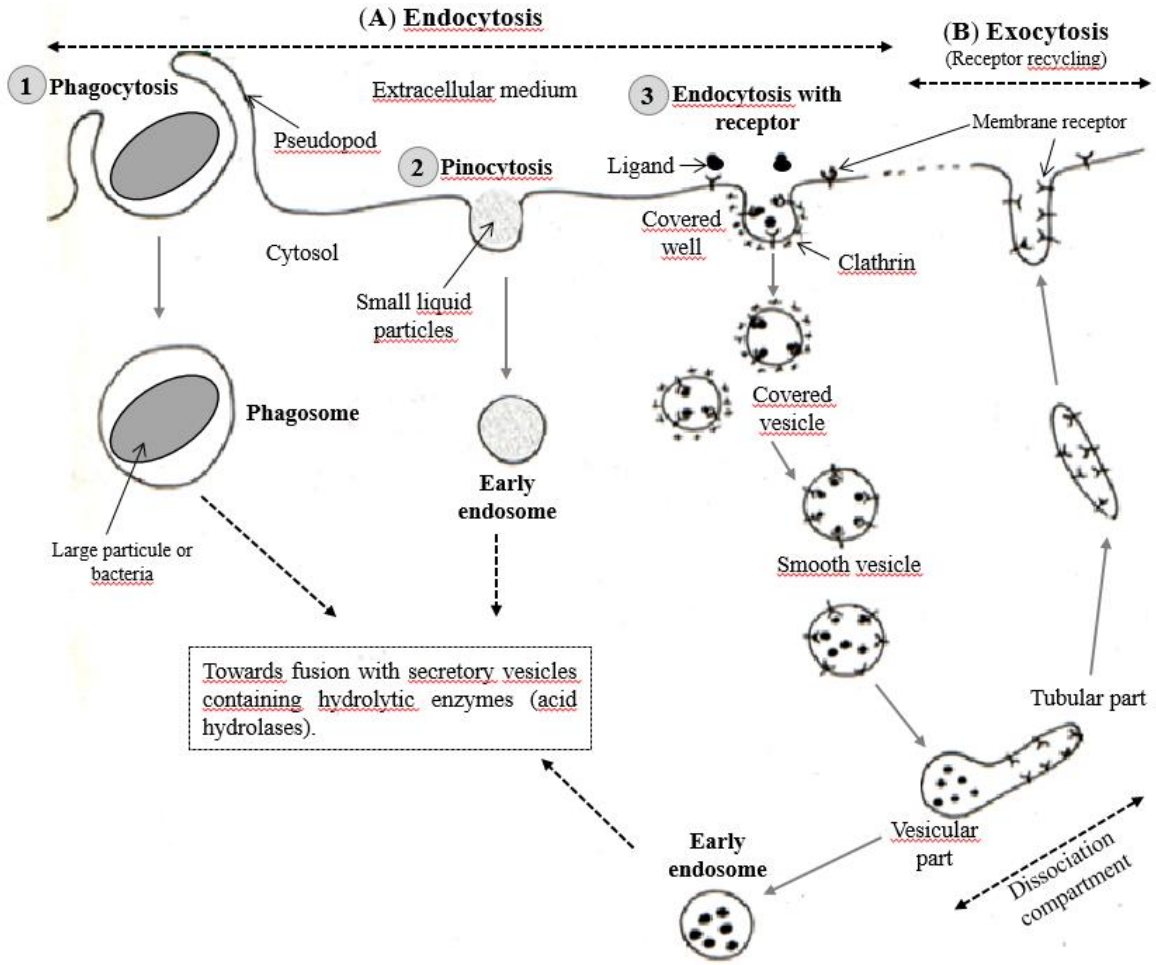

Figure 4: Exchanges with deformation of the plasma membrane.

2. Transmission of information

2.1. Hormonal information

Two types of hormones are involved (**Figure 5**):

a. Water-soluble hormones: a hormone of a protein or glycoprotein nature, it does not cross the plasma membrane and binds to specific receptors in the target cell membrane. This binding induces the intervention of a second messenger (cyclic AMP) in the biological response (**Figure 5$_1$**).

b. Fat-soluble hormones: case of steroid hormones, capable of diffusing across the membrane of the target cell and directly produces a biological response by acting on gene activity (**Figure 5$_2$**).

2.2. Gaseous chemical signal (**Figure 5$_3$**)

2.3. Nerve information (**Figure 6**)

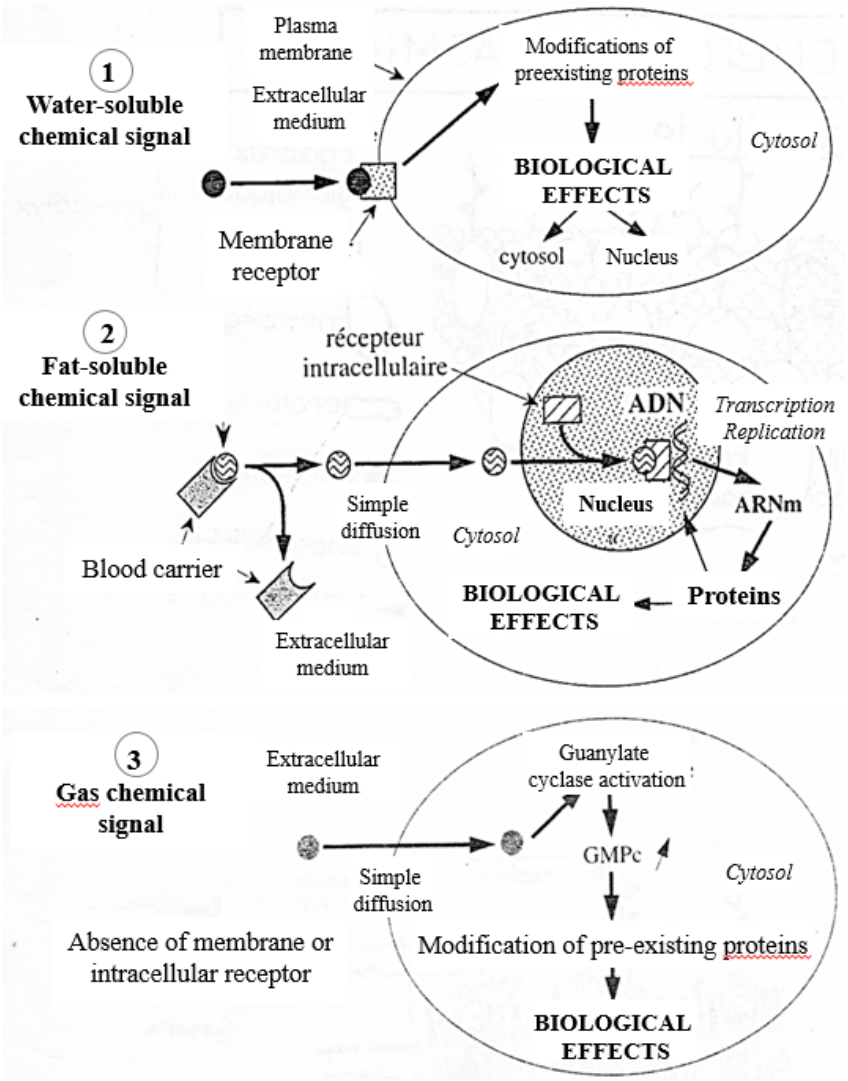

Figure 5: Types of chemical signals: water-soluble (**1**), fat-soluble (**2**) and (**3**) gaseous through the plasma membrane.

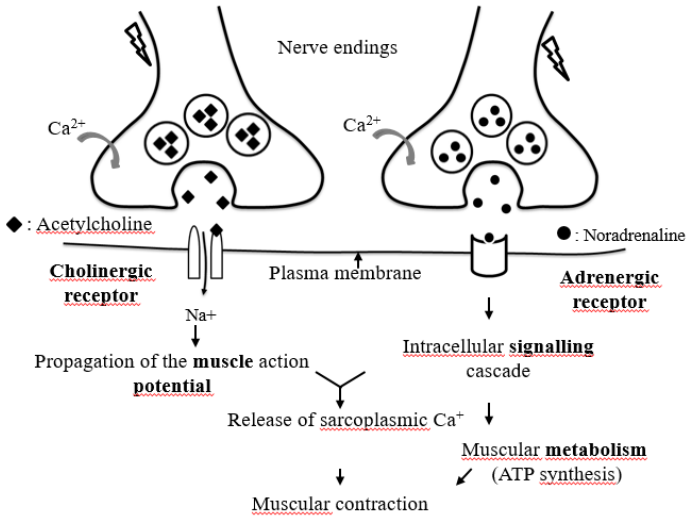

Figure 6: Example of nerve information: neuromuscular junction.

VI. SPECIALIZATIONS OF THE PLASMA MEMBRANE

Specializations of the plasma membrane are differentiations of this membrane and the superficial cytoplasm, which allow the cell to perform one or more specific functions. There are three types of specializations: apical, lateral and basal. They are all located in highly polarized epithelial cells, possessing an apical pole, and a basal pole that rests on an underlying connective tissue through the basal lamina (**Figure 7**).

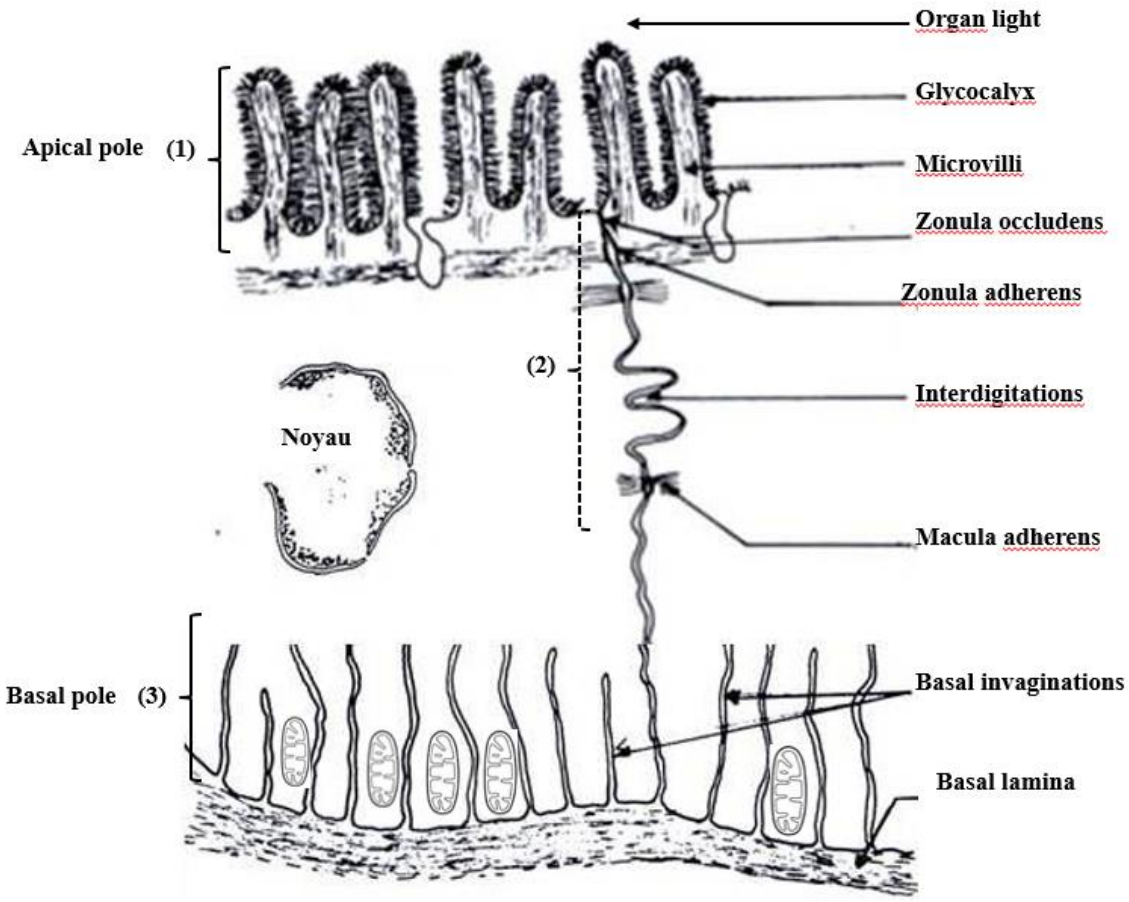

Figure 7: The different specializations of the plasma membrane observed at the transmission electron microscopy (TEM), (**1**) apical, (**2**) lateral and (**3**) basal.

1. Specialization of the apical plasma membrane

1.1. Microvilli

The microvilli are glove finger cytoplasmic expansions, of variable length (0.5 to 1µm) and regular diameter (0.1µm) (**Figure 7₁**). They contain an axis formed by actin microfilaments and many associated proteins (see cytoskeleton course). They occupy the entire free surface of the apical pole of certain epithelial cells specialized in exchanges with the extracellular environment; these microvilli increase the exchange surface and constitute, in particular, the striated plate of enterocytes (microvilli of the same size and regularly spaced) and the brush border of the contoured tubes of the kidney (microvilli of different sizes and irregularly spaced).

1.2. Stereocilia

They correspond to long and flexuous microvilli. The central support of actin microfilaments is less developed than in microvilli. The most typical stereocilia cells are those of the epididymal duct and vas deferens.

1.3. Cilia

They are motile cytoplasmic expansions with a skeleton of microtubules and associated proteins (See cytoskeleton course). They are present on many cells, including the epithelial cells of the trachea and oviduct. They allow the movement of external structures.

2. Specialization of the lateral plasma membrane

2.1. Interdigitations

These are interpenetrations of the lateral plasma membranes of neighboring cells (**Figure 7**$_2$). They increase the contact surface between the two cells as well as their adhesion or adhesion.

2.2. Cell junctions

These junctions can be classified according to two criteria, their shape and the width of the intercellular space. The following junctions are distinguished: *zonula occludens*, *zonula adherens*, *macula adherens* and gap junction.

Form		Intercellularspace	
Zonula	Belt that completely encircles the cell	*Occludens* junction	almost zero
Macula	Circular	*Adherens* junction	wide
Fascia	Beach more or less extensive, with irregular contours	*Gap* junction (communicanting)	reduced

2.2.1. Zonula *occludens* (tight junction)

At high magnification (TEM), it has several points of contact interspersed by intercellular spaces (**Figure 8**$_1$). At these points of contact, the structure appears organized in five sheets (the 2 dense outer sheets of the plasma membranes of neighboring cells are fused).
Role: impermeable barrier, preventing the free passage of molecules from light to the intercellular space.

2.2.2. *Zonula adherens*

It is located below the tight junction; it presents to the MET a structure in six sheets with a wide intercellular space. A dense cytosolic submembrane plate, of protein nature, allows the attachment of cytoskeletal actin microfilaments (**Figure 8**$_2$).
Role: ensures excellent adhesion between cells.

2.2.3. *Macula adherens* or desmosome

Located below the tight junction and the *zonula adherens.* Like the *zonula adherens*, it has a 6-sheet structure with a wide intercellular space. The dense cytosolic plate of rounded shape allows the anchoring of the intermediate filaments (**Figure 8**$_3$).
Roles: it ensures intercellular adhesion, maintains the shape of cells and increases the resistance of tissues subjected to mechanical forces by distributing tensions throughout the cell layer or layers.

Note: The succession of the three junctions of the apical pole to the basal pole de *zonula occludens*, *zonula adherens* and *macula adherens* form what is called a junctional complex.

2.2.4. Gap junction

At the TEM, it presents a 6-sheet structure with a reduced intercellular space. Rounded in shape, it consists of the juxtaposition of many small transmembrane channels (connections) directly communicating the cytoplasm of the two neighboring cells (**Figure 8**[4]).
Role: ensures the transfer of ions and some molecules (water, ATP, cAMP ...).

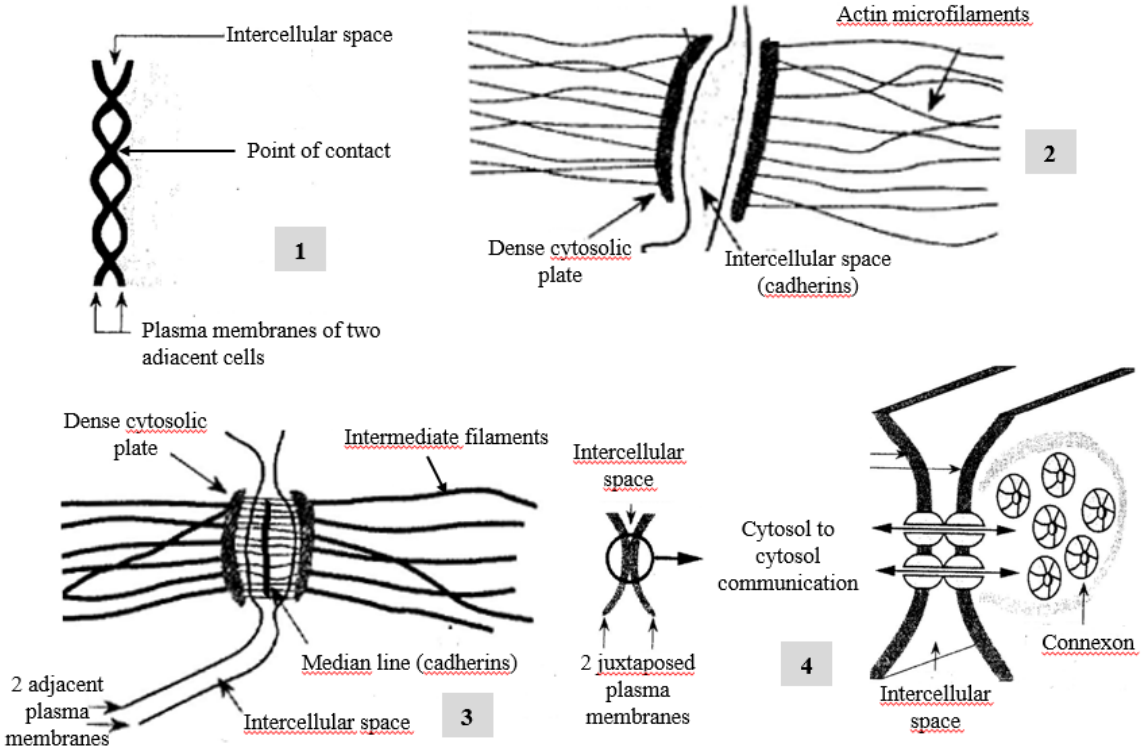

Figure 8: Tight junction or *zonula occludens* (**1**), *Zonula adherens* (**2**), *Macula adherens* or desmosome (**3**), and Gap junction (**4**).

3. Basal plasma membrane specialization

The plasma membrane has two types of differentiation at the basal pole, basal intussusceptions and hemidesmosomes.

3.1. Basal invagination

These are folds of the plasma membrane that divide the cytoplasm into compartments where many elongated mitochondria are housed that provide the energy necessary for active transport. They increase the exchange surface (e.g. renal tubule cell) (**Figure 7**[3]).

3.2. Hemidesmosomes

Present on the plasma membrane of cells in contact with the basal lamina, they are morphologically very close to desmosomes (**Figure 9**). They attach the basal pole of the epithelial cell to the basal lamina through adhesion molecules called integrin's (see animal extracellular matrix course).

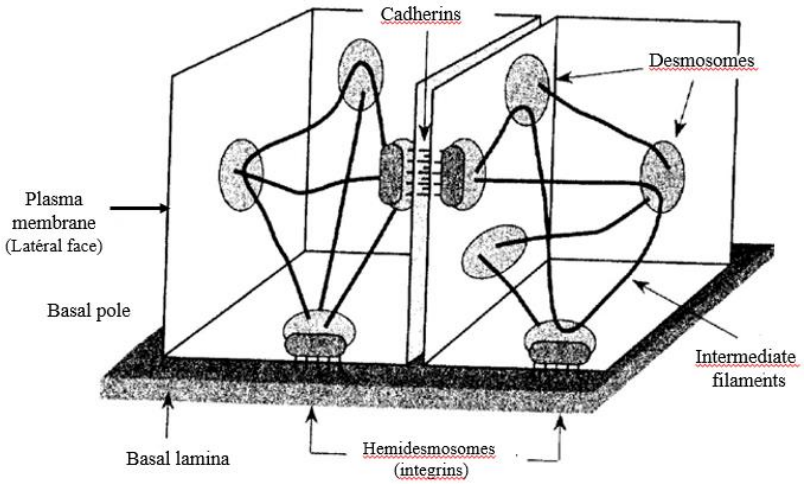

Figure 9: Hemidesmosomes and desmosomes.