physiology

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◉ Sheet ○ Slides

Number

5

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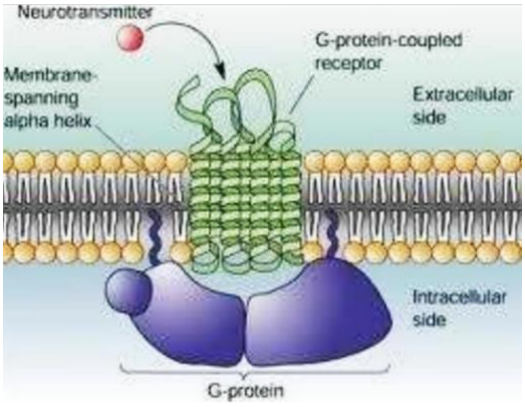
RECALL what we have taken in the past 3 weeks regarding cellular transport:

Table 3.1 Transport of Materials Into and Out of Cells

Transport Process	Description	Substances Transported
Osmosis	Movement of water molecules across a selectively permeable membrane from an area of higher water concentration to an area of lower water concentration.	Solvent: water in living systems.
Diffusion	Random mixing of molecules or ions due to their kinetic energy. A substance diffuses down a concentration gradient until it reaches equilibrium.	
Diffusion through the lipid bilayer	Passive diffusion of a substance through the lipid bilayer of the plasma membrane.	Nonpolar, hydrophobic solutes: oxygen, carbon dioxide, and nitrogen; fatty acids, steroids, and fat-soluble vitamins; glycerol, small alcohols; ammonia. Polar molecules: water and urea.
Diffusion through membrane channels	Passive diffusion of a substance down its electrochemical gradient through channels that span a lipid bilayer; some channels are gated.	Small inorganic solutes, mainly ions: K^+, Cl^-, Na^+, and Ca^{2+}. Water.
Facilitated Diffusion	Passive movement of a substance down its concentration gradient via transmembrane proteins that act as transporters; maximum diffusion rate is limited by number of available transporters.	Polar or charged solutes: glucose, fructose, galactose, and some vitamins.
Active Transport	Transport in which cell expends energy to move a substance across the membrane against its concentration gradient through transmembrane proteins that act as transporters; maximum transport rate is limited by number of available transporters.	Polar or charged solutes.
Primary active transport	Transport of a substance across the membrane against its concentration gradient by pumps; transmembrane proteins that use energy supplied by hydrolysis of ATP.	Na^+, K^+, Ca^{2+}, H^+, I^-, Cl^-, and other ions.
Secondary active transport	Coupled transport of two substances across the membrane using energy supplied by a Na^+ or H^+ concentration gradient maintained by primary active transport pumps. Antiporters move Na^+ (or H^+) and another substance in opposite directions across the membrane; symporters move Na^+ (or H^+) and another substance in the same direction across the membrane.	Antiport: Ca^{2+}, H^+ out of cells. Symport: glucose, amino acids into cells.
Transport In Vesicles	Movement of substances into or out of a cell in vesicles that bud from the plasma membrane; requires energy supplied by ATP.	
Endocytosis	Movement of substances into a cell in vesicles.	
Receptor-mediated endocytosis	Ligand-receptor complexes trigger infolding of a clathrin-coated pit that forms a vesicle containing ligands.	Ligands: transferrin, low-density lipoproteins (LDLs), some vitamins, certain hormones, and antibodies.
Phagocytosis	"Cell eating"; movement of a solid particle into a cell after pseudopods engulf it to form a phagosome.	Bacteria, viruses, and aged or dead cells.
Pinocytosis	"Cell drinking"; movement of extracellular fluid into a cell by infolding of plasma membrane to form a pinocytic vesicle.	Solutes in extracellular fluid.
Exocytosis	Movement of substances out of a cell in secretory vesicles that fuse with the plasma membrane and release their contents into the extracellular fluid.	Neurotransmitters, hormones, and digestive enzymes.

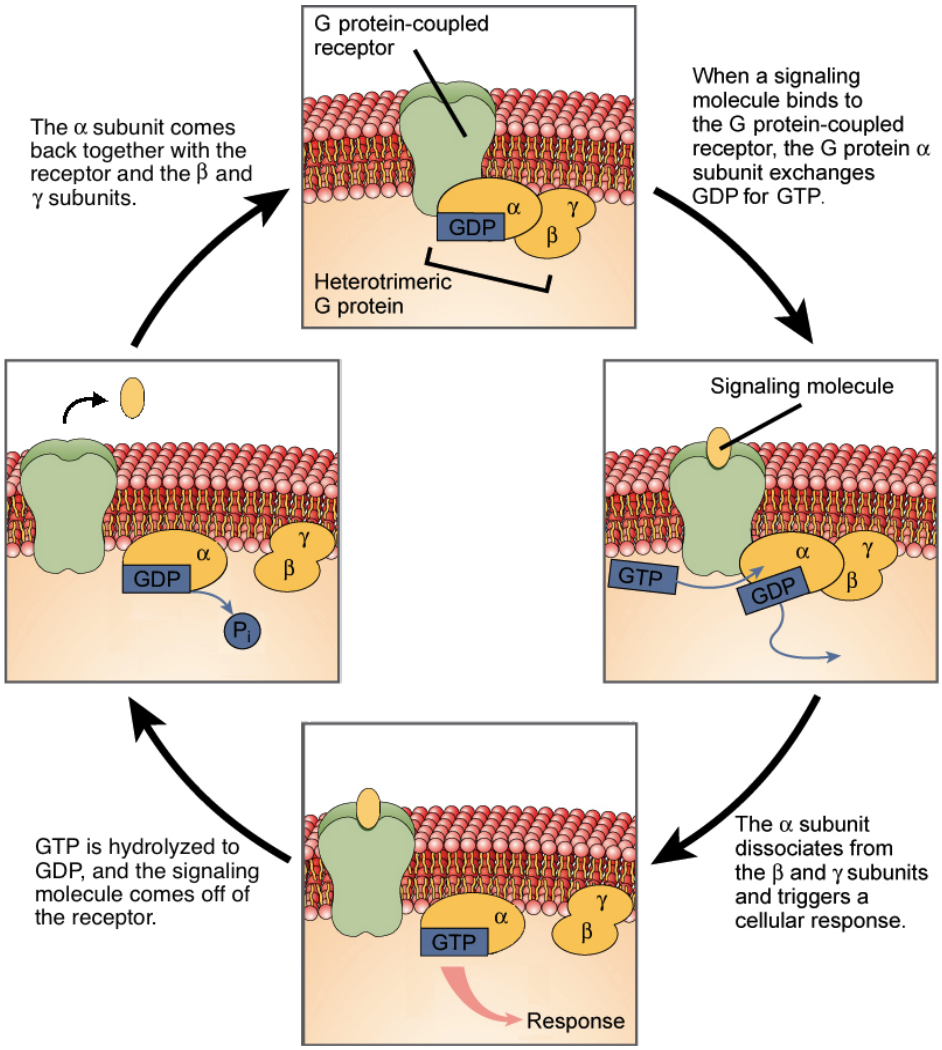
Actually, the process of transport across the plasma membrane is highly controlled, and some aspects of this control will be discussed below.

1. *G-proteins and signal transduction:*
   - G-proteins: guanine nucleotide-binding proteins, each is made up of three subunits (α, β and ϒ). When they are bound to GTP, they are 'on' (activated), and when they are bound to GDP, they are 'off' (inactivated).

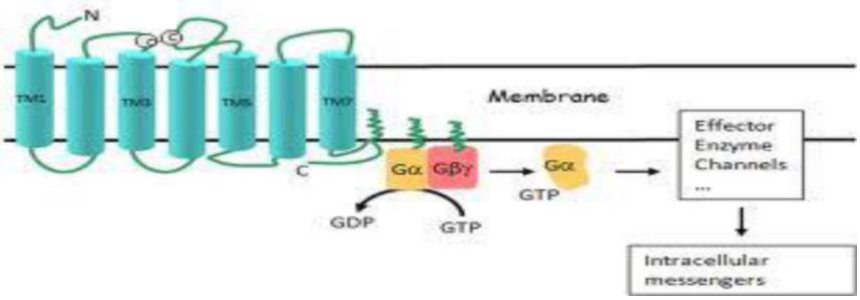


<Figure(1.a)

- The mechanism:
  When a ligand binds to a G-protein coupled receptor (GPCR); the GPCR is activated and causes the G protein to exchange GDP for GTP. Then G-protein separates into two pieces (one is the α subunit, and the other consisting of the β and γ subunits), which are freed from the GPCR. Then the α subunit interacts with other proteins (transporters, enzymes) triggering a signaling pathway that leads to a cellular response. Figures (1.b,1.c,1.d)



< Figure (1.b): Note that this is an additional figure for clarification ONLY.



< Figure (1.c): dr. Khatatbeh's.

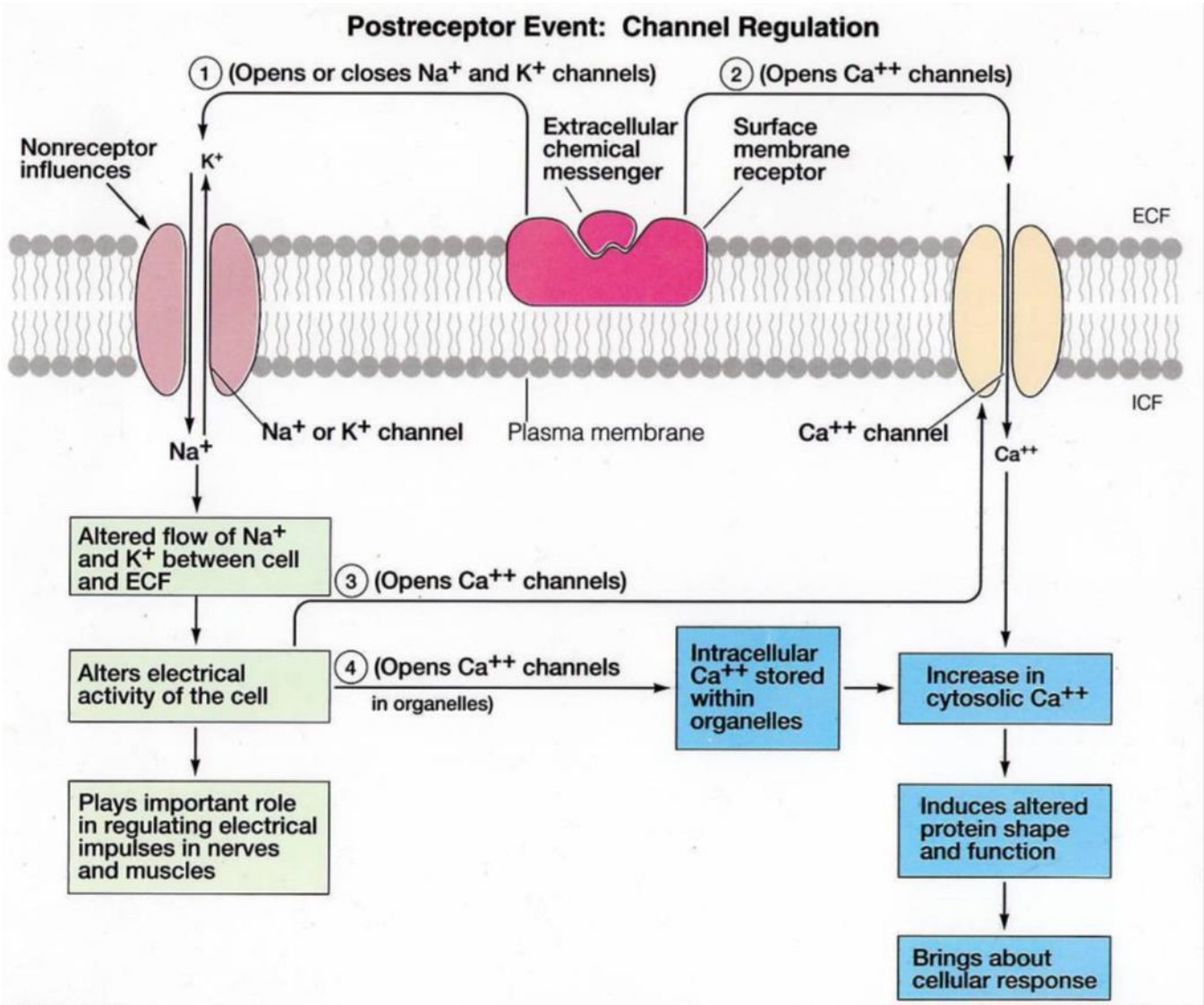


Figure (1.d): triggering or activating a channel means opening it.

Note that there are G-proteins are –surely- present in the example above but they are not shown in the figure. The idea is to understand that G-proteins contribute in controlling transport across the plasma membrane through signal transduction by activating and inactivating channels and enzymes.

2. Enzymes:

) Adenylyl cyclase is an enzyme regulated by G-proteins. Once the α subunit binds to ***adenylyl cyclase*** and causes activation, ***it*** catalyzes the conversion of ATP to cyclic AMP, which leads to an increase in intracellular levels of cyclic AMP.

This increase activates protein kinases in the cytosol that are responsible for phosphorylating certain proteins (e.g: potassium channels). Figure (2.a).

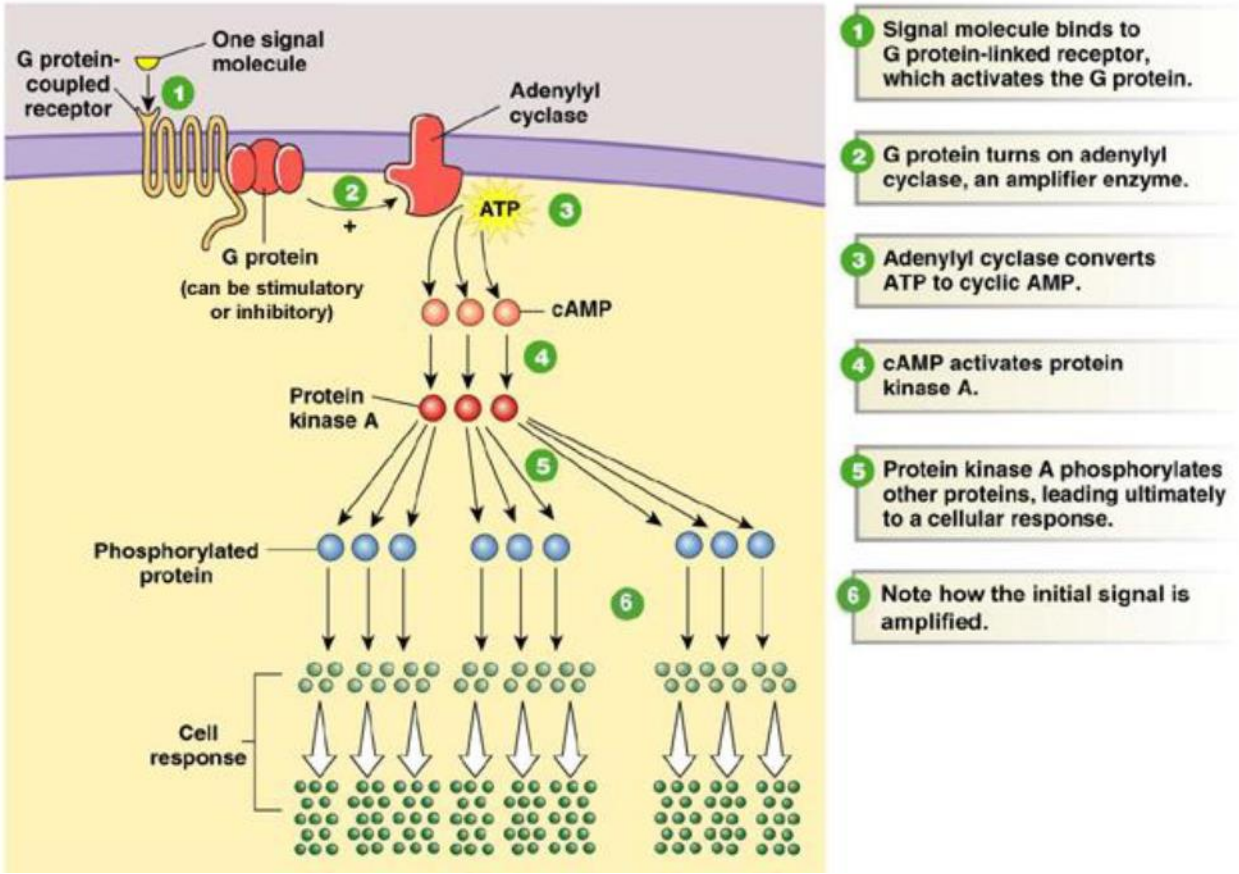


Figure (2.a): Note that the activation of ONE enzyme by binding to ONE ligand increases the activity of many proteins and makes a great change in the cell's activity (amplification).

) PL-C (phospholipase-C): an enzyme that converts phosphatidylinositol 4,5-bisphosphate (a membrane phospholipid) into inositol triphosphate IP3 and diacylglycerol DAG.

On the endoplasmic reticulum of some cells, there are receptors for the IP3.The binding of IP3 can cause activation of Ca+2 channels (chemical gated channels). Calcium ions will diffuse through the open channels down their concentration gradient towards the cytosol. So, we can increase the transport of Ca+2 ions thus changing the activity of the cell by increasing the calcium concentration inside the cytosol. Figure (2.b).

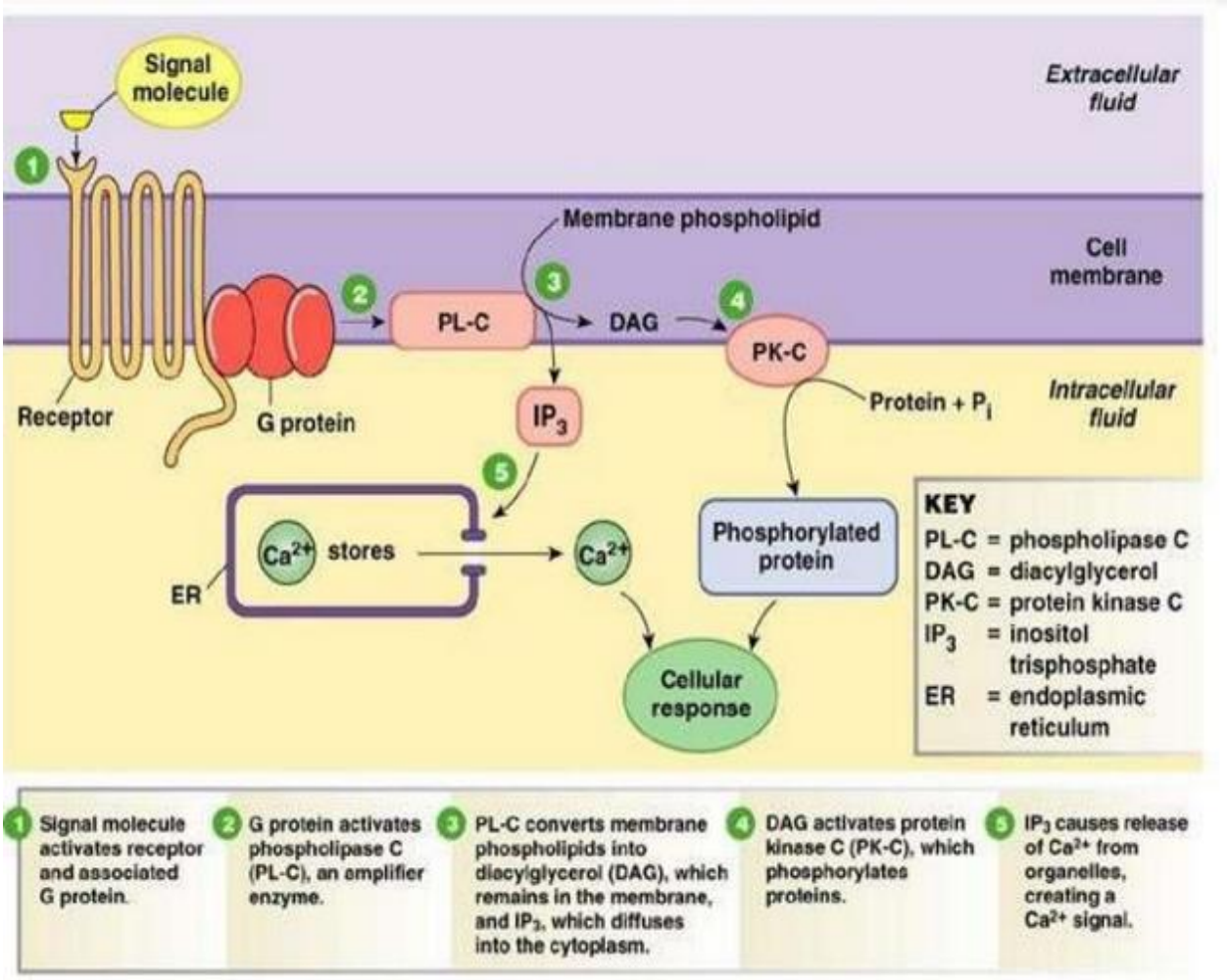


Figure (2.b) shows that we can change the concentration of calcium ions not only by transport calcium ions across plasma membrane, but also between organelles inside the cell.

3- Vesicular transport (specifically exocytosis):

Nerves have terminals at the end of axons which are the storage of neurotransmitters. Once we have a change in the electrical activity, Ca+2 voltage gated channels on the surface of a neuron are activated and calcium ions are transported down their chemical gradient towards the intracellular fluid. Assuming that the vesicles and the axon terminal membrane are both negative; repulsion will occur, but as the Ca+2 concentration increases inside the terminal; the polarity of the vesicles will change allowing them to dock on the membrane and release neurotransmitters. Figure (3.a).

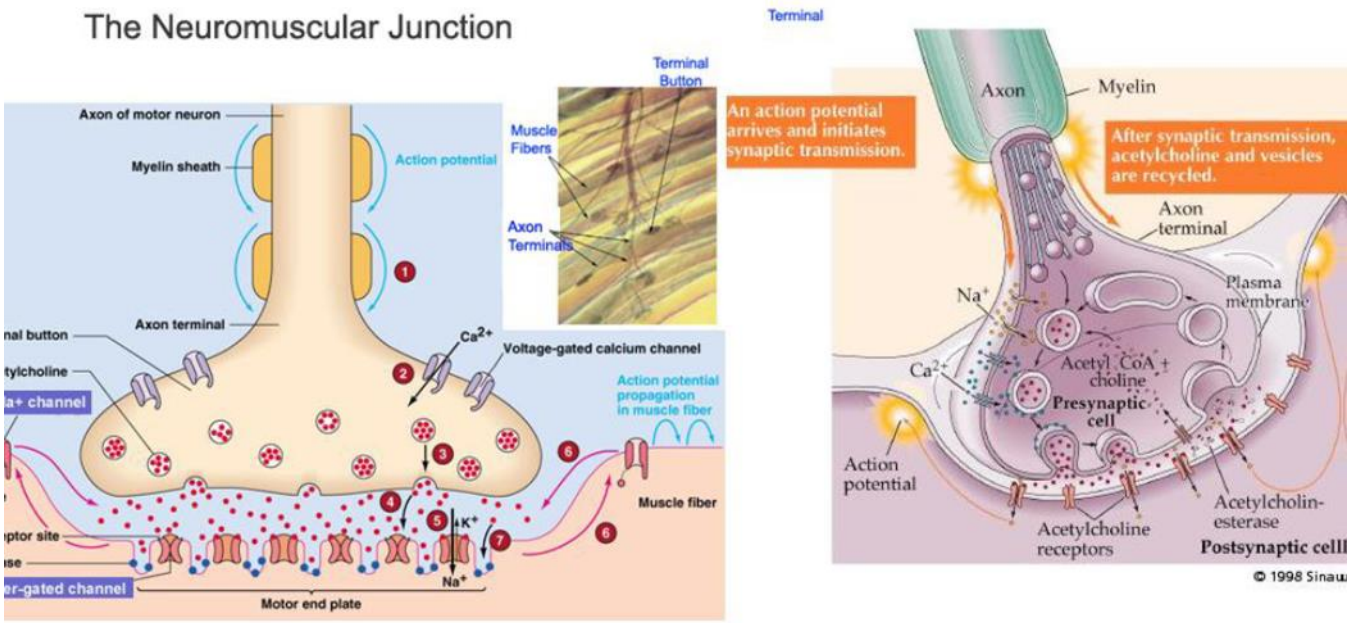


Figure (3.a): vesicular transport (here it is exocytosis) is highly controlled.

Transport of Ions across the Plasma Membrane:

- RECALL the distribution of ions across the plasma membrane:

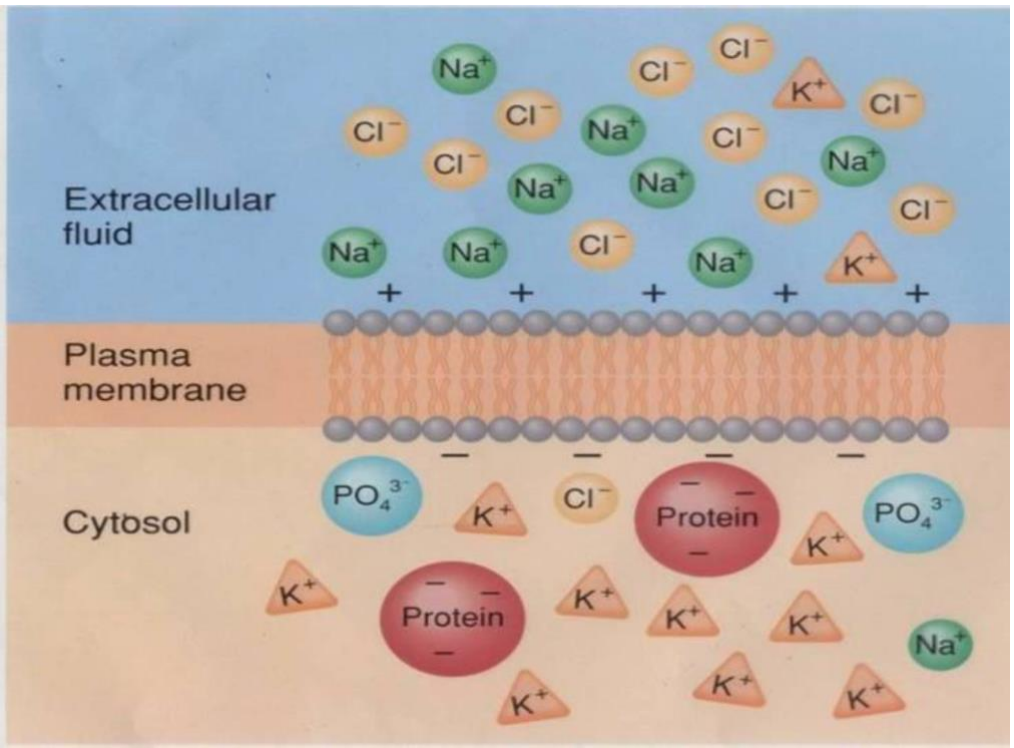


Figure (4.a): The outside of the cell has a high concentration of Na+ and Cl-, whereas the inside of the cell has a high concentration of K+.

- WHAT determines the direction of ion flux across the plasma membrane?
  - ✓ The concentration gradient. (chemical force).
  - ✓ The electrical gradient. (electrical force).

The total forces acting upon ions across a membrane is a combination of both chemical and electrical forces and is referred to as the electrochemical driving force.

- WHAT are excitable cells?
  - ✓ Have the ability to generate membrane potentials (voltages). Examples: neurons, muscle cells (skeletal, cardiac, and smooth).

First, assume that a cellular membrane is permeable only to K+, K+ will diffuse to the extracellular fluid because of the concentration gradient. The diffusion of K+ will result in a movement of positive charges outside the cell and leaving behind negative charges inside the cell. This will create an electrical potential difference across membrane (positive outside and negative outside). Creation of this potential difference will OPPOSE diffusion of K+ to the outside at a certain concentration difference.

When reaching a point at which diffusion of K+ is COMPLETELY OPPOSED by the potential difference and the NET DIFFUSION for K+ is ZERO, even though you still have a concentration gradient, you have reached the "equilibrium potential" for K+ (Ek).

- When saying that the NET DIFFUSION for an ion is zero, it means that ions are moving from inside to outside and from outside to inside at the same rate.

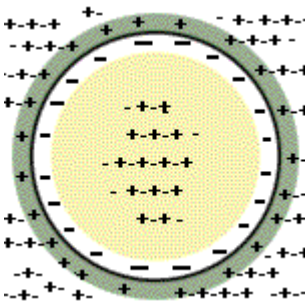
- HOW to calculate the equilibrium potential for an ion?
  - ✓ By Nernst equation

$$E = \frac{RT}{ZF} \ln \frac{[C]out}{[C]in}$$

R (Gas Constant) = 8.314472 (J/K·mol)
T (Absolute Temperature) = t °C + 273.15 (°K)
Z (Valence)
F (Faraday's Constant) = 9.6485309×10^4 (C/mol)
[C]out (Outside Concentration, mM)
[C]in (Inside Concentration, mM)

- FOR a univalent ion (Z= +1) , it could be calculated by:
  - E(mV) = -61.5 * log (Ci/Co)
  - E(mV)= 61.5*log (Co/Ci)

- HOW to measure the membrane potential?
  - ✓ The total number of positive and negative charges that have to be separated across the membrane to account for the potential is an insignificant fraction of the total number of charges actually in the cell, so the two solutions (extracellular and intracellular fluids) are considered to have the same number of positive and negative ions.
  - ✓ Well, the slight excess ions collect along a thin shell on the inner and outer surfaces of the plasma membrane, whereas the bulk of the intracellular and extracellular fluid is electrically neutral.
  - ✓ So, to measure the membrane potential; place two electrodes in the outer and inner surfaces of the plasma membrane. (not too deep in the cytosol). *Note that these are additional information for clarification, till now, we only need to know not to place the electrode too far from the membrane.



*The cell as a RC-circuit:

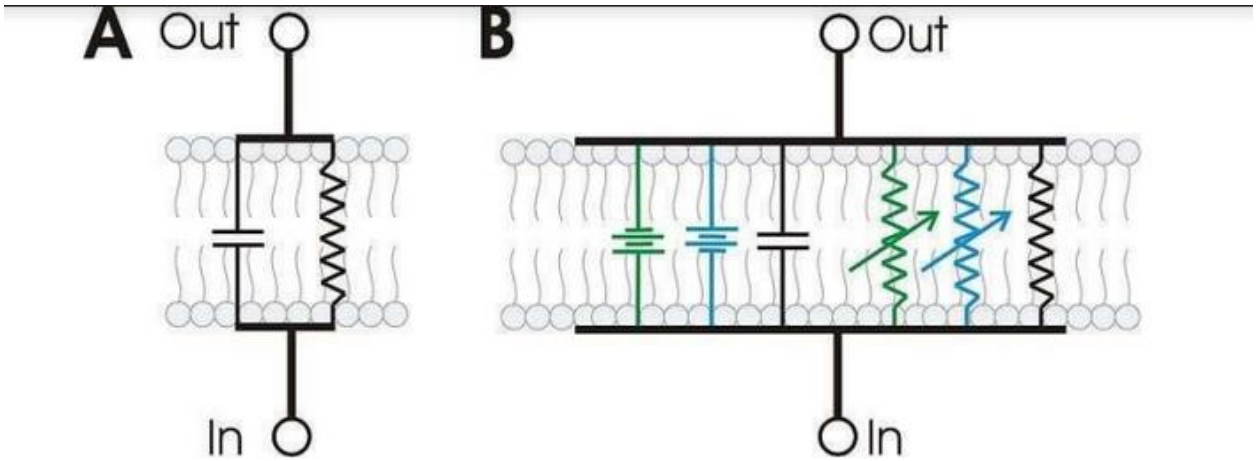
-RC-Circuit: Resistor-Capacitor circuit.

A-Plasma membrane as a capacitor:

Any construct that can separate an electric charge is considered a capacitor, and so does the plasma membrane.

B-Plasma membrane as a resistor:

Any construct that resist the flow of an electrical current is considered a resistor (electrical current: the flow of electric charge (electrons)), and so does the plasma membrane; there are many ion channels embedded in the plasma membrane that allow the flow of ions (charges) across the membrane and thus maintain the flow of ionic currents (ionic current: the flow of ions NOT electrons).



- **Part A:** A basic en:RC circuit, superimposed on an image of a membrane bilayer to show the relationship between the two. **Part B:** A more elaborate en:RC circuit, superimposed on an image of a membrane bilayer. This RC circuit represents the electrical characteristics of a minimal patch of membrane containing at least one Na and two K channels. Elements shown are the transmembrane voltages produced by concentration gradients in potassium (green) and sodium (blue), The voltage-dependent ion channels that cross the membrane (variable resistors;K=green, Na=blue), the non-voltage-dependent K channel (black), and the membrane capacitance.