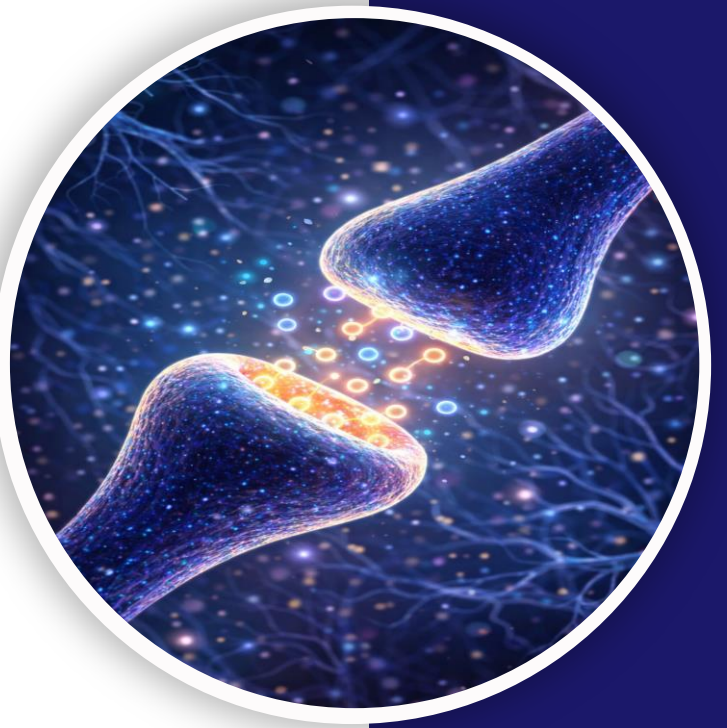
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Physiology | MID 1

Plasma membrane of excitable cells



Written by : Mousa Al-Neimat

Reviewed by : Rawan Okour

مبارك عليكم الشهر

اَللّٰهُمَّ اِنِّیۡ اَسۡـَٔلُكَ
عِلۡمًا نَّافِعًا وَّرِزۡقًا
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Plasma membrane of Excitable Cells

- **Plasma Membrane of Excitable tissues**
- Ref: Guyton, 13th ed: pp: 61-71. 12th ed: pp: 57-69. 11th ed: **p57-71**,

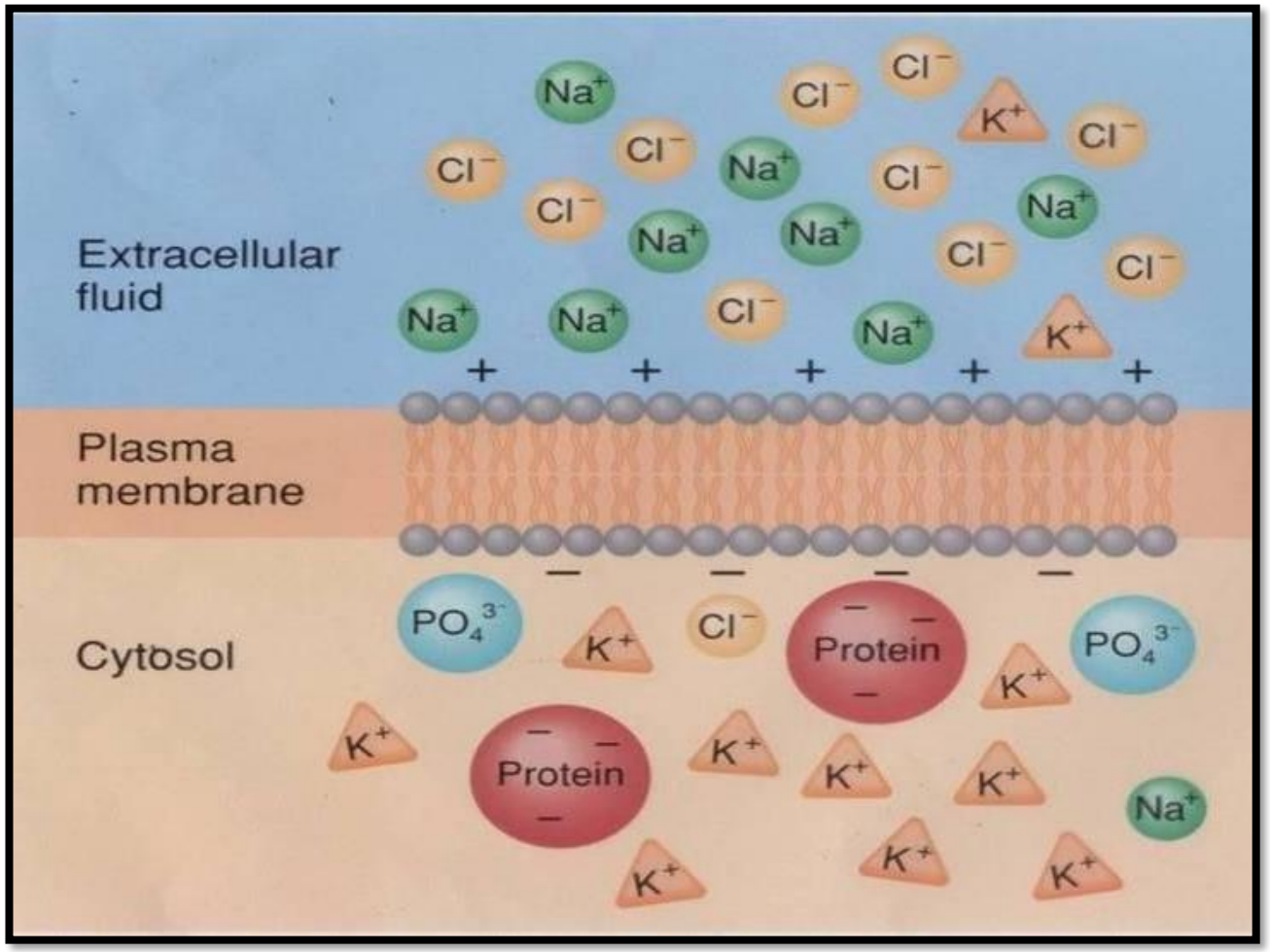
Introduction

Plasma membrane of excitable cell :

The plasma membrane is separating **two** compartments :

1. **intracellular** compartment : we have high concentration of inside.

2. **extracellular** compartment : we have specific ions in high concentration :
   1. **Sodium ions (Na+) .**
   2. **Chloride ions (Cl-).**



- The difference in the concentration, give the ions a potential to move from higher concentration to a lower concentration.

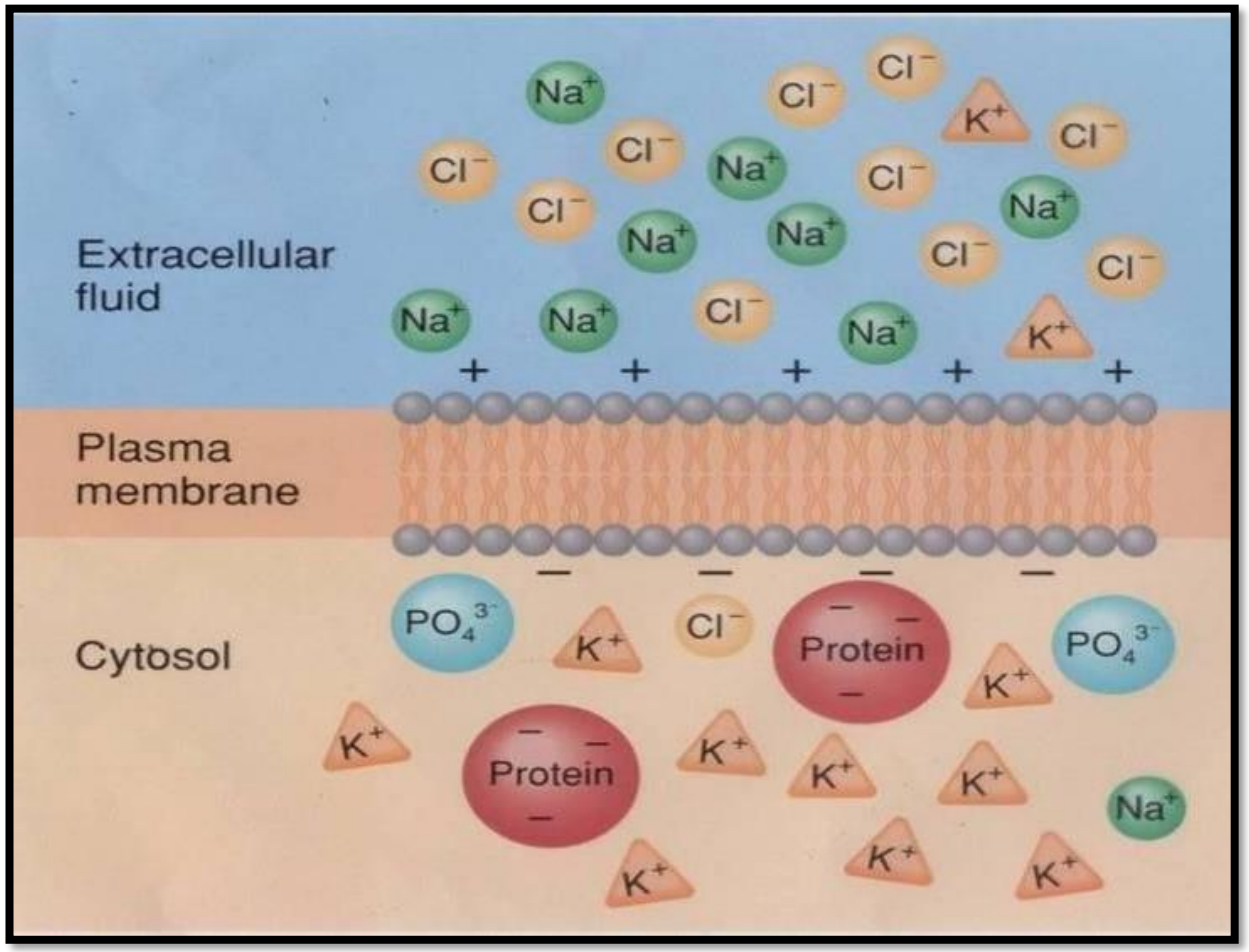
- We have different permeability of the plasma membrane for a ions; **we have higher permeability for Potassium (K+) than Sodium (Na+).**

Introduction

1. We have high potential of potassium ions (K+) to move from inside to outside down their concentration gradient.

2. We have high potential of Sodium ions (Na+) to move from outside to inside down their concentration gradient.

3. We have high potential of chloride ions (Cl-) to move from outside to inside down their concentration gradient.



- The problem is that there is a specific permeability of the membrane for each ions; high for potassium & lower for sodium.

- This make the membrane representing an electrical circuit :
  - The membrane represents the capacitor separating two compartments with opposite charges.
  - The ion channels represent the conductance (1 / Resistance) of ions.

Electrical properties of plasma membranes

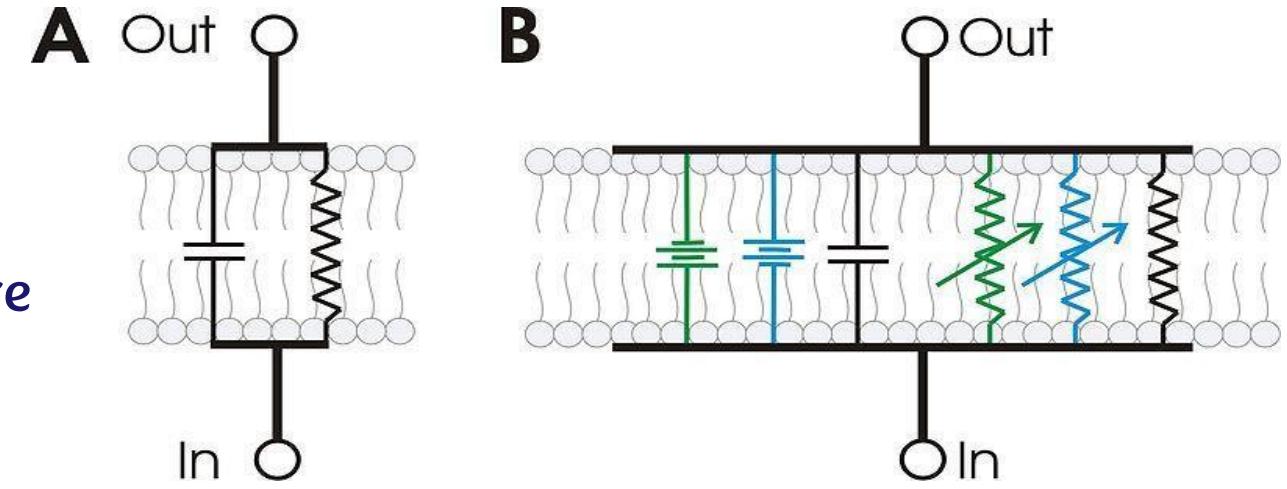
- We can represent the plasma membrane as a **electrical circuit.**

- The concentration gradient which makes ions flow across the membrane from high concentration to low concentration. Also, there is a **specific permeability** for each ion, which can be represented by **resistance**
- **(1 / Conductance)** in electrical circuit for the ions to flow.

- **Conductance :** it is an electrical property. It measures the actual flow of ions (current) across the membrane.

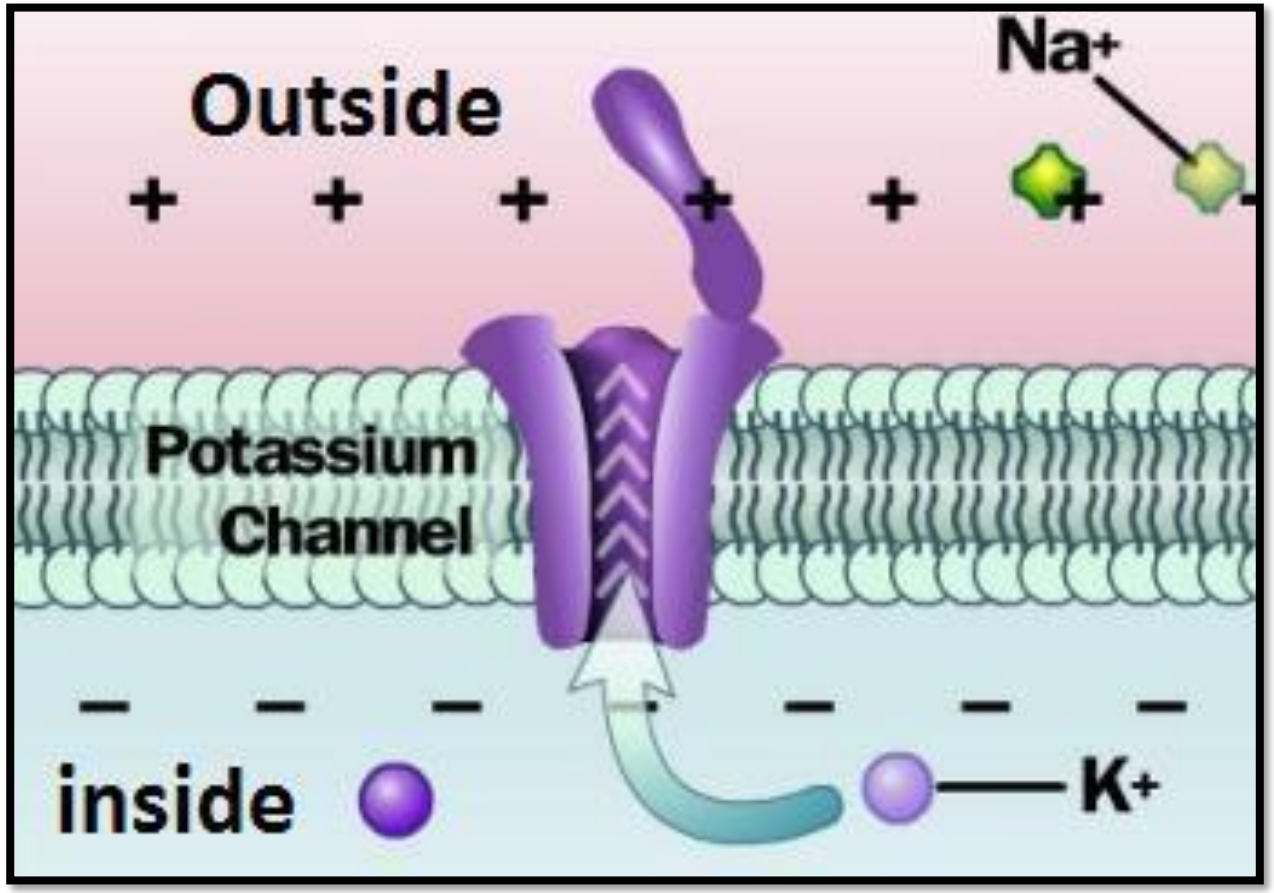
- **Permeability :** it is a structural property of the membrane. it describes the ease with which a specific substance can cross the lipid bilayer or pass through a channel

- **High permeability → High conductance.** (But they are not the same).



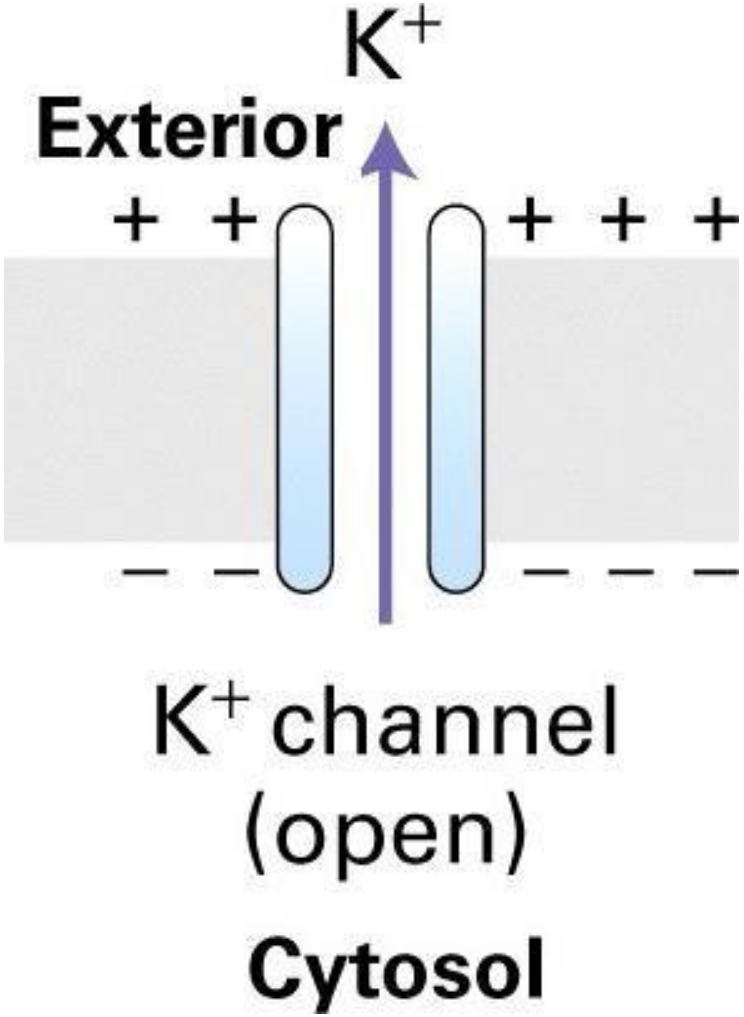
- **Part A:** A basic en:RC circuit, superimposed on an image of a membrane bilayer to show the relationship between the two.
- **Part B:** A more elaborate en:RC circuit, superimposed on an image of a membrane bilayer. This RC circuit represents the electrical characteristics of a minimal patch of membrane 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.

Introduction



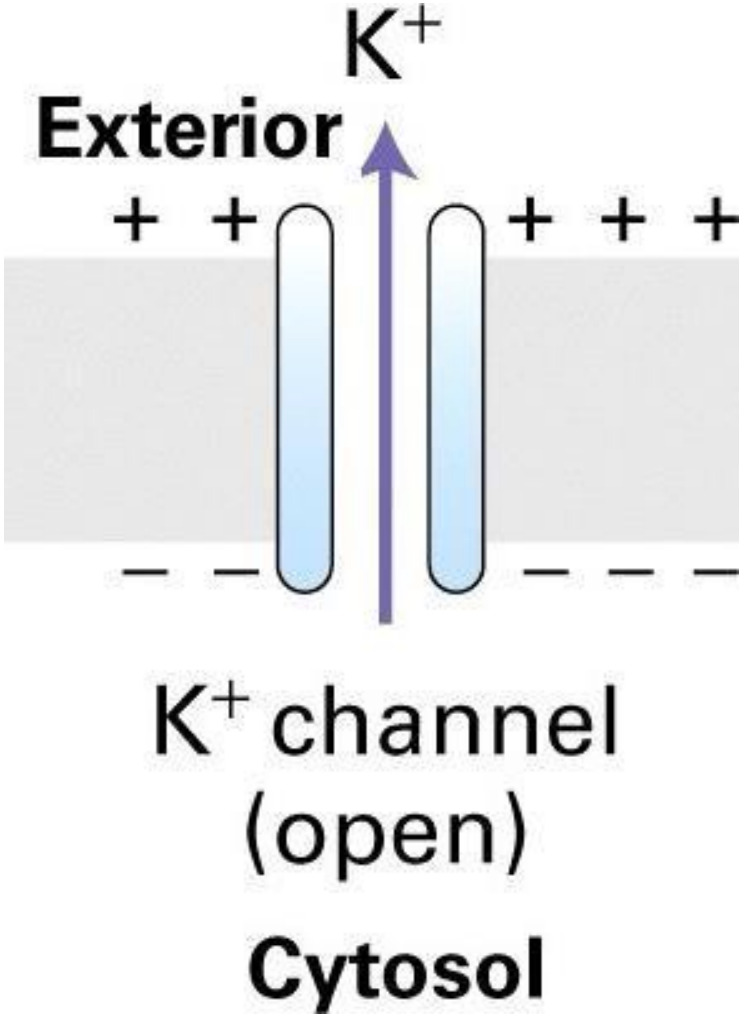
Introduction

- When the channel for a specific ion opens, that ion **moves down its concentration gradient.**
- As these ions **move down their concentration gradient, their electrical charge leads to the development of an electrical potential that opposes further ion movement.** Despite this, a difference in ion concentration between the inside and outside of the cell still exists.
- Therefore, ion movement is ultimately governed by the **electrochemical gradient.**
- To calculate this potential, we will assume that the membrane is **only permeable** for the atom we want to calculate the its potential.
- In the next figure, we are assuming that the membrane is only permeable for potassium (K+), and then we calculate the potential of potassium ions.



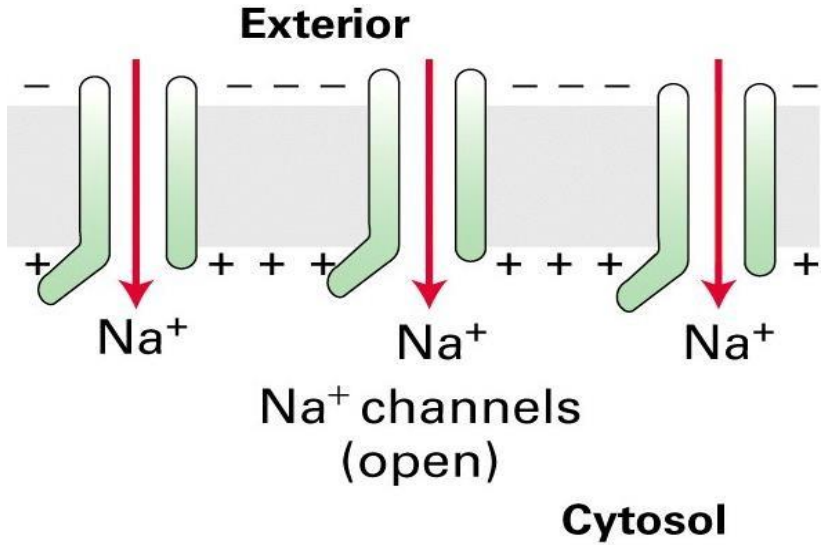
Introduction

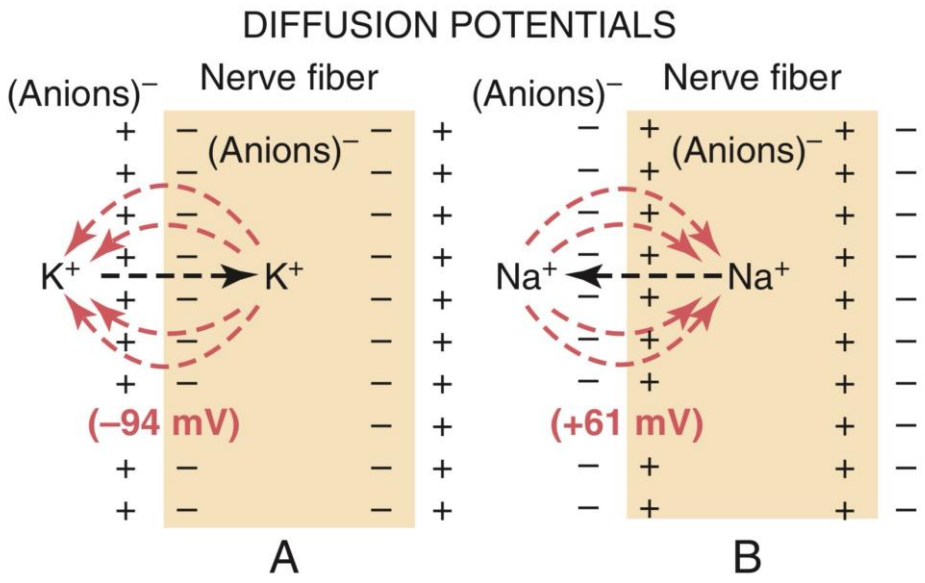
"Let us assume that the membrane in this instance is permeable to the potassium ions but not to any other ions. Because of the large potassium concentration gradient from inside toward outside, there is a strong tendency for extra numbers of potassium ions to diffuse outward through the membrane. As they do so, they carry positive electrical charges to the outside, thus creating electropositivity outside the membrane and electronegativity inside because of negative anions that remain behind and do not diffuse outward with the potassium. Within a millisecond or so, the potential difference between the inside and outside, called the diffusion potential, becomes great enough to block further net potassium diffusion to the exterior, despite the high potassium ion concentration gradient. In the normal mammalian nerve fiber, the potential difference is about 94 millivolts, with negativity inside the fiber membrane".



Introduction

- Here, we are assuming that the membrane is only permeable for sodium (Na+), and then we calculate the potential of sodium ons.
- a high concentration of sodium ions outside the membrane and a low concentration of sodium ions inside. These ions are also positively charged. This time, the membrane is highly permeable to the sodium ions but is impermeable to all other ions.
- Diffusion of the positively charged sodium ions to the inside creates a membrane potential of opposite polarity to that in figure A, with negativity outside and positivity inside. Again, the membrane potential rises high enough within milliseconds to block further net diffusion of sodium ions to the inside; however, this time, in the mammalian nerve fiber, the potential is about 61 milli-volts positive inside the fiber.





Nernest equation

- We can calculate the equilibrium potential of a specific ion (the potential that cause equilibrium of that ion (no net movement of that ion across the membrane).

- We call the energy that forces the ion to flow across the membrane electrochemical gradient; which is composed of two forces :

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

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)

1) Electrical gradient : which is formed by the charged of the ions (towards the compartment that has less similar charge of the ion's charge.

2) Chemical gradient : which is the concentration gradient (from high to low).

➢ These 2 energies are working against each other (if we assume that the membrane is only permeable for a specific ion).

Electro-chemical Equilibrium

- As you see here the two gradient are working against each other, and at equilibrium, these energies are cancelling each other giving no net movement of ions across the membrane.

$$\Delta G_{conc} + \Delta G_{volt} = 0$$

$$zFV - RT \ln \frac{C_o}{C_i} = 0$$

$$V = \frac{RT}{zF} \ln \frac{C_o}{C_i} = 2.3 \frac{RT}{zF} \log_{10} \frac{C_o}{C_i}$$

E_{k+}

- This is the final form of **Nernest equation** after calculating the value of the constants.

$$E_{eq,K+} = 61.54mV \log \frac{[K^+]_o}{[K^+]_i}$$

Here, it's inside/outside, because they change the equation by placing a negative charge before the logarithm and flipping what's inside it.

❖ Note that it is always **(Concentration outside / Concentration inside)** except if we are calculating the equilibrium potential for a negative charge ion, we will flip it to be **(concentration inside / concentration outside).**

E (mV) = - 61.log (Ci/Co)

E = Equilibrium potential for a univalent ion

Ci = conc. inside the cell.

Co = conc. outside the cell.

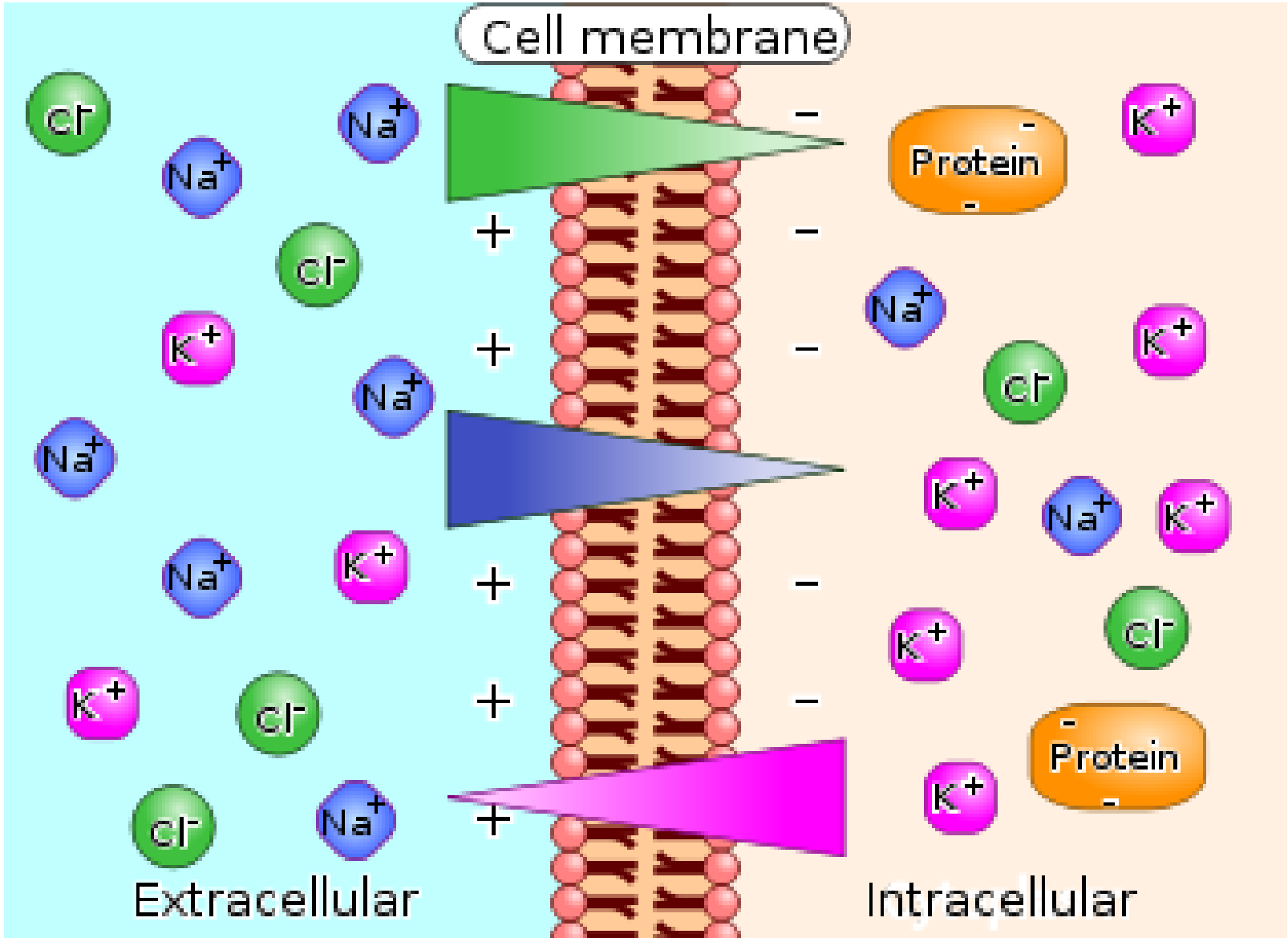
Concentration of Ions

- Here is the intracellular & extracellular concentration & the equilibrium potential of the most important ions contributing to the membrane potential.

Ion	Extracellular (mM)	Intracellular (mM)	Nernst Potential (mV)
Na^+	145	15	60
Cl^-	100	5	−80
K^+	4.5	160	−95
Ca^{2+}	1.8	10^{-4}	130

The membrane has the **highest permeability for potassium**, so the membrane potential **will be closer to the of potassium equilibrium potential than other ions equilibrium potential.**

Membrane permeability



Goldman Hodgkin Katz equation

The membrane potential is determined by ions that are moving across it, and it is affected by **permeability and concentration of that ion at both sides of the membrane.**

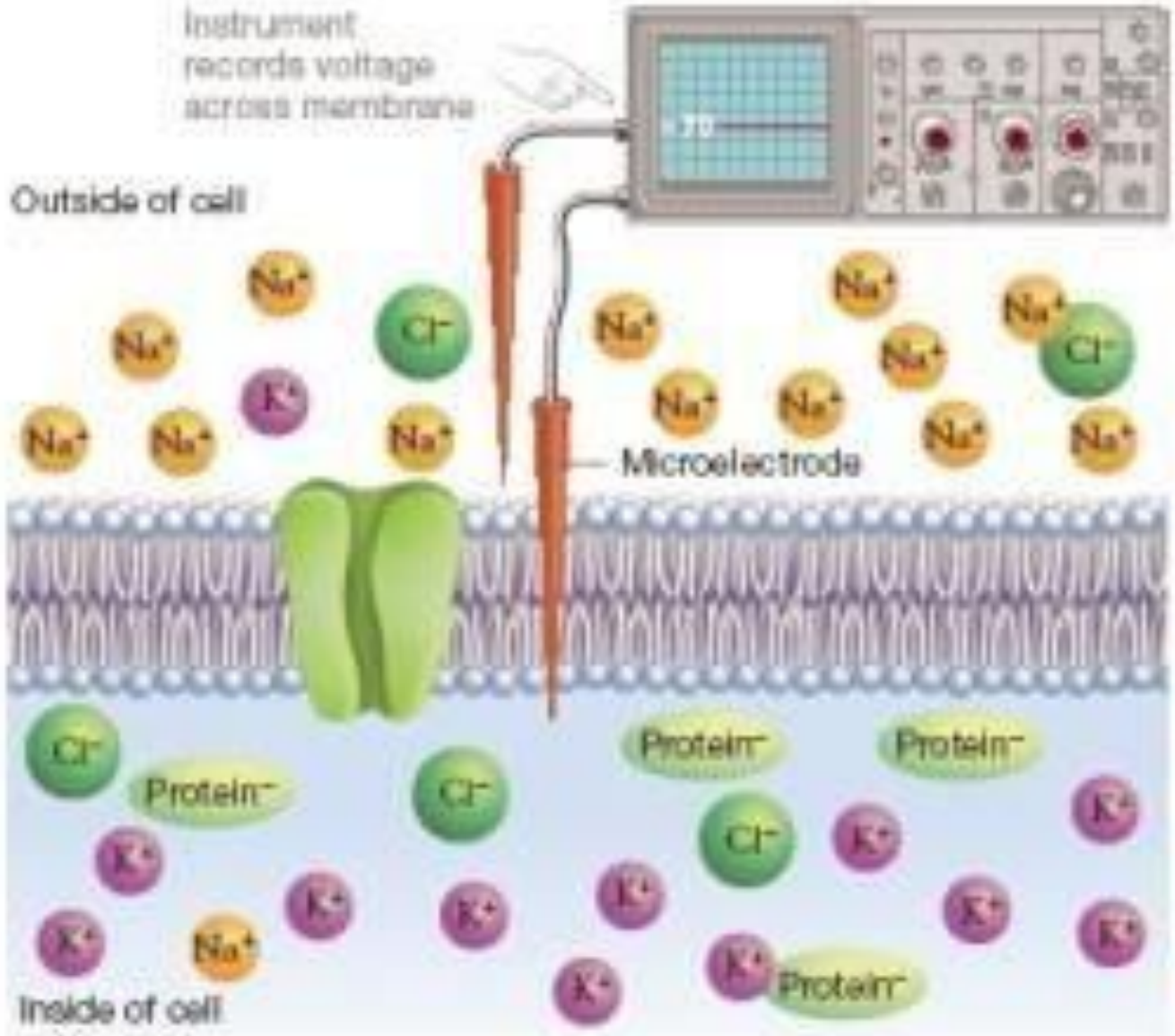
By this equation, we can calculate the equilibrium potential of the membrane.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{Na+}[Na^+]_o + P_{K+}[K^+]_o + P_{Cl-}[Cl^-]_i}{P_{Na+}[Na^+]_i + P_{K+}[K^+]_i + P_{Cl-}[Cl^-]_o} \right)$$

i = Conc. inside

o = Conc. outside

P = permeability of the membrane to that ion.


Instrument
records voltage
across membrane
Outside of cell
Microelectrode
Protein⁻
Protein⁻
Protein⁻
Inside of cell

Resting membrane potential

We now can identify the resting membrane potential which is the **steady negative voltage inside a cell relative to the outside when the cell is at rest (no ions transmitting across the membrane).**

It is close to Equilibrium potential of K+ but not equal to it since we still have sodium that makes the membrane potential less negative.

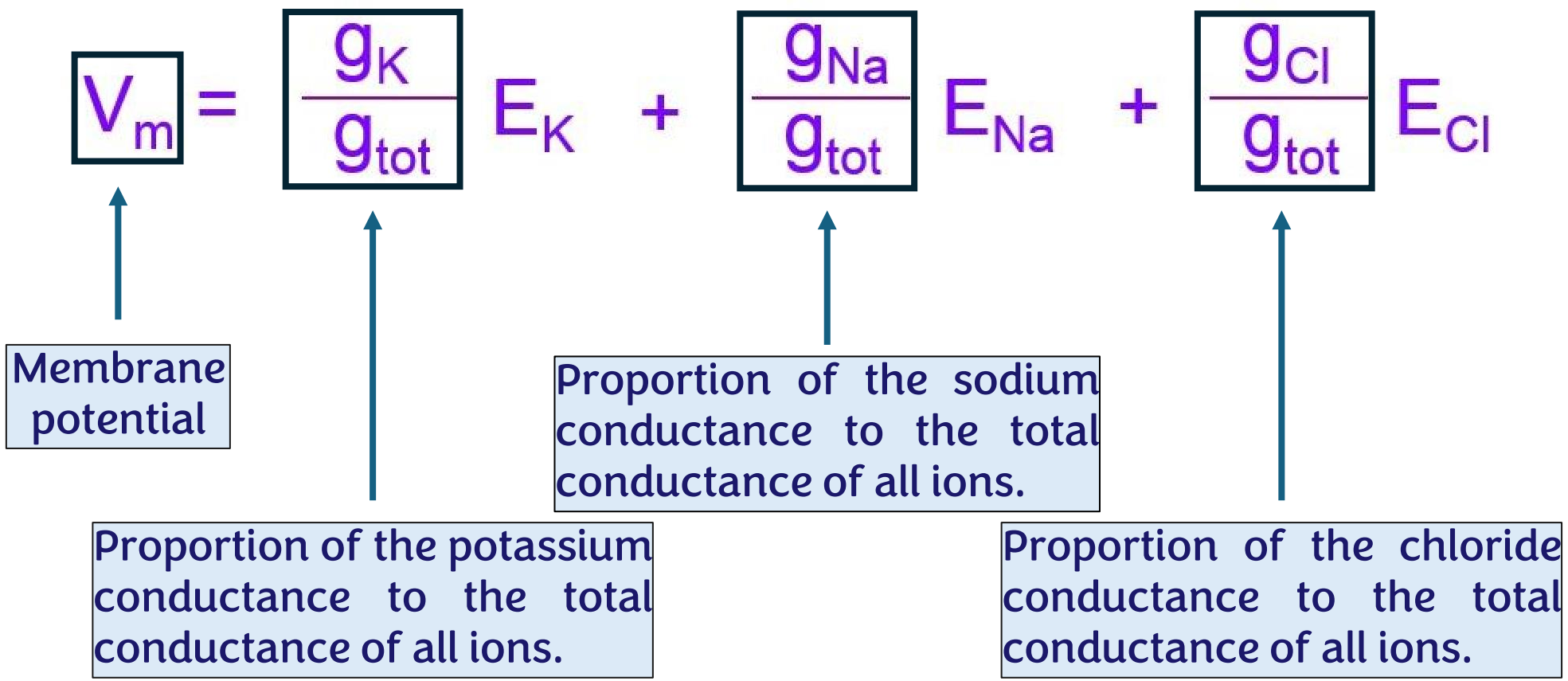
- Activity K+ channels
- Activity of Na+ channels
- Na+/K+ pumps

Conductance of plasma membrane (Ohm's Law)

- $I = \Delta V/R$
- G (conductance)= 1/R
- $I = G.\ \Delta V$

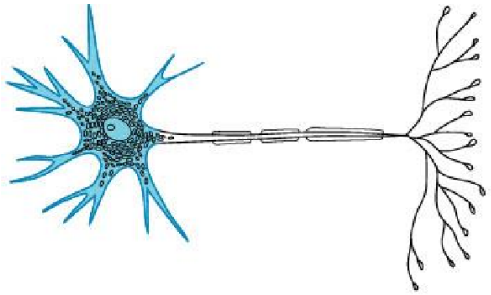
The resistance is negatively proportional with the conductance of ions across the membrane.

The Cord Conductance equation describes the contributions of permeant ions to the resting membrane potential



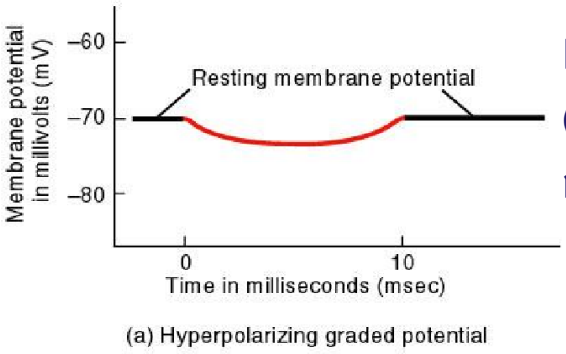
• Changes in Resting membrane potential

Which generate an **action potential** (2nd property of plasma membrane of excitable cells).



➢ **What happens to the membrane potential if we increase the Sodium concentration in the extracellular compartment ?**

- **Depolarization;** if we increase the sodium in the extracellular compartment, their will be increased movement of sodium from outside towards inside, which will cause it to be more positive inside, decreasing the negativity of the membrane potential.

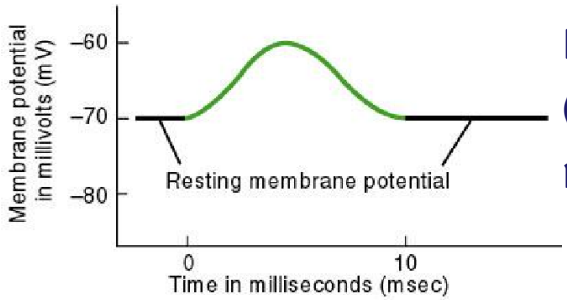


(a) Hyperpolarizing graded potential

Hyperpolarization (increase in the negativity).

➢ **What happens to the membrane potential if we increase the potassium concentration in the extracellular compartment ?**

- **Depolarization,** if we increase the potassium concentration in the extracellular compartment, their will be resistance to the movement of potassium from inside to outside, which will cause it to be more positive inside, decreasing the negativity of the membrane potential.



(b) Depolarizing graded potential

Depolarization (decrease in the negativity).

12.10

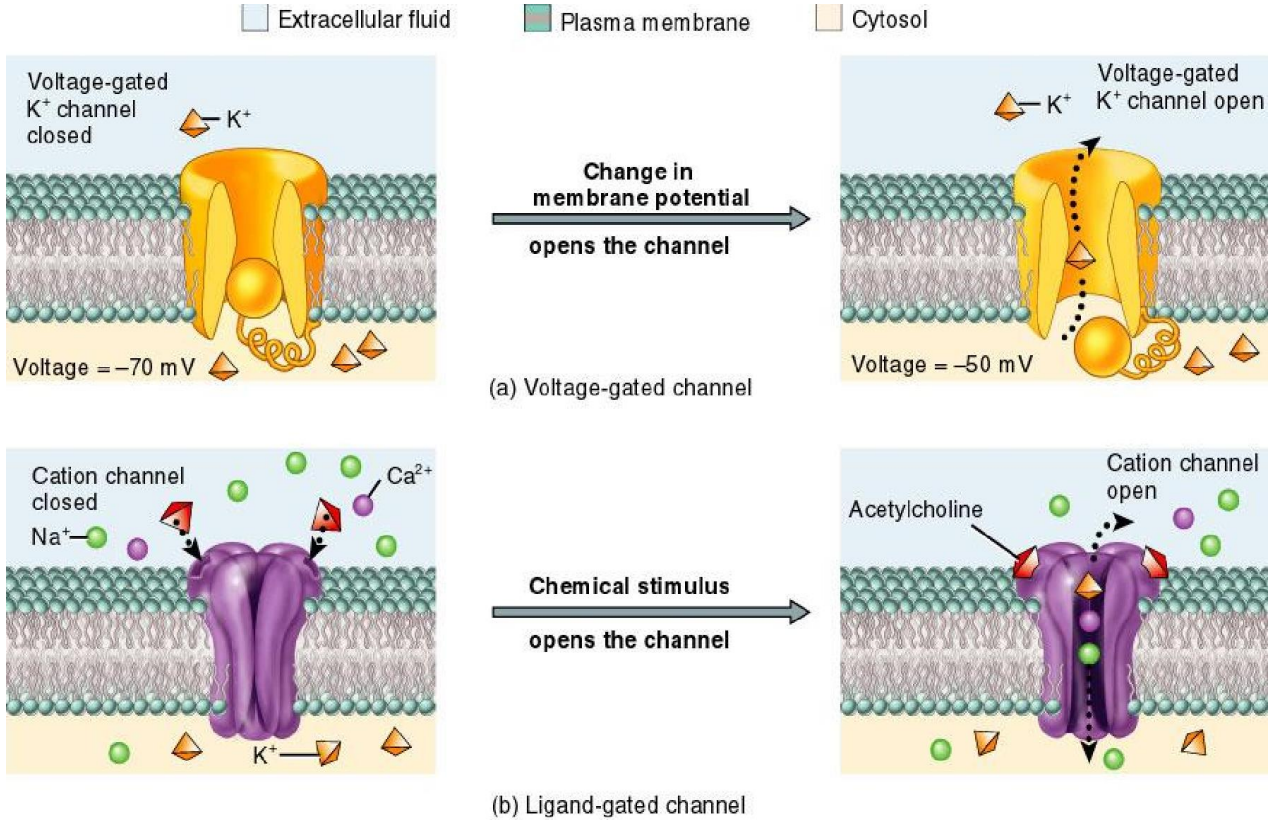
❖ Note : Don't mix between <u>hyperpolarization and repolarization</u>
Hyperpolarization : increase the negativity.
Repolarization : Baking to the resting potential after depolarization.

Action potential

- Nerve signals are transmitted by **action potentials,** which are **rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane.** Each action potential begins with a **sudden change from the normal resting negative membrane potential to a positive potential and ends with an almost equally rapid change back to the negative potential.** To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end.
- We can generate action potential by **changing the activity (activation or inactivation) of ion channels**, we can do that in two ways :

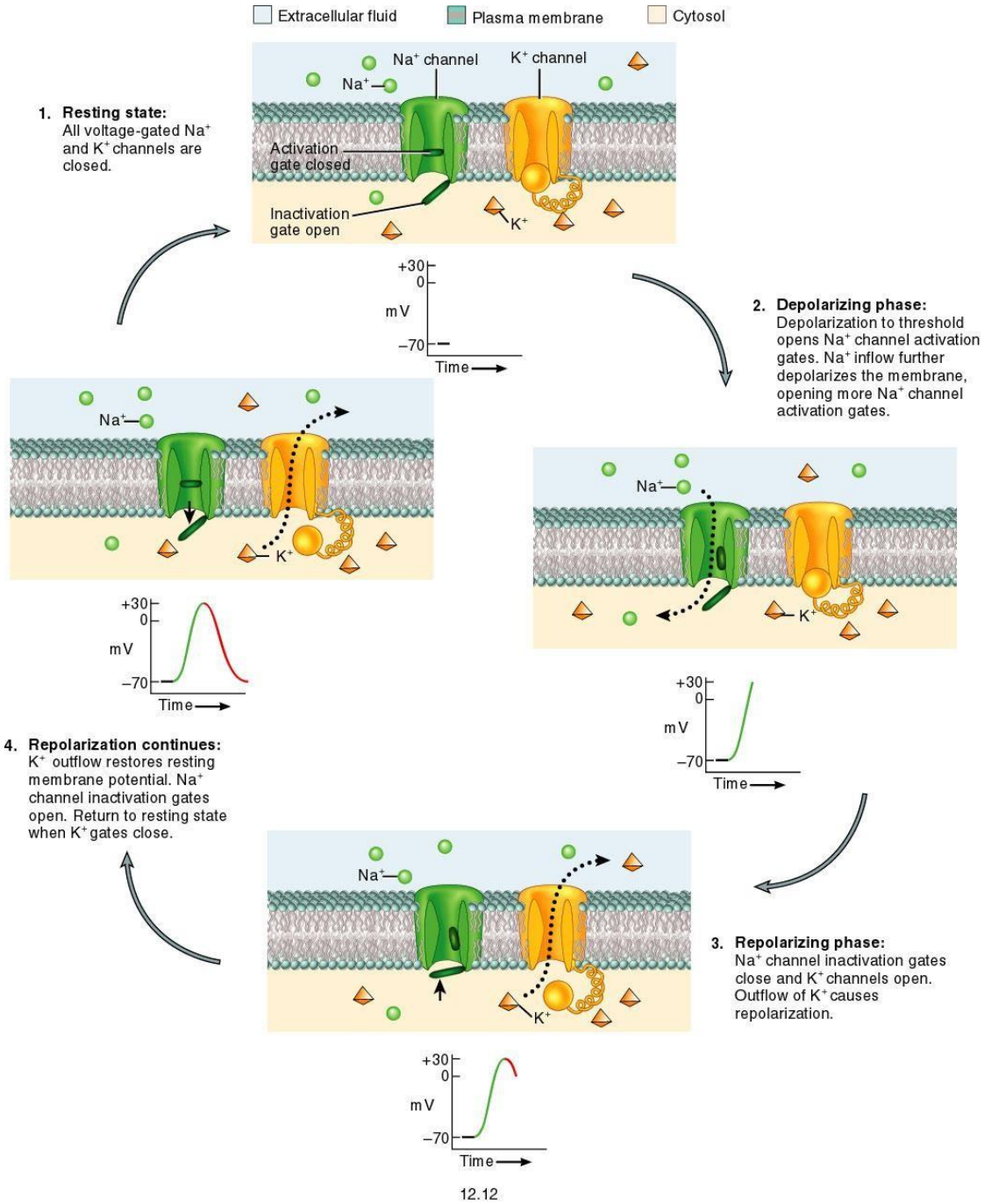
1) <u>Chemical gated ion channels:</u> opens upon the binding of a ligand to the channel binding domain.

2) <u>Voltage gated ion channels:</u> opens upon the membrane potential reaching a specific valid.

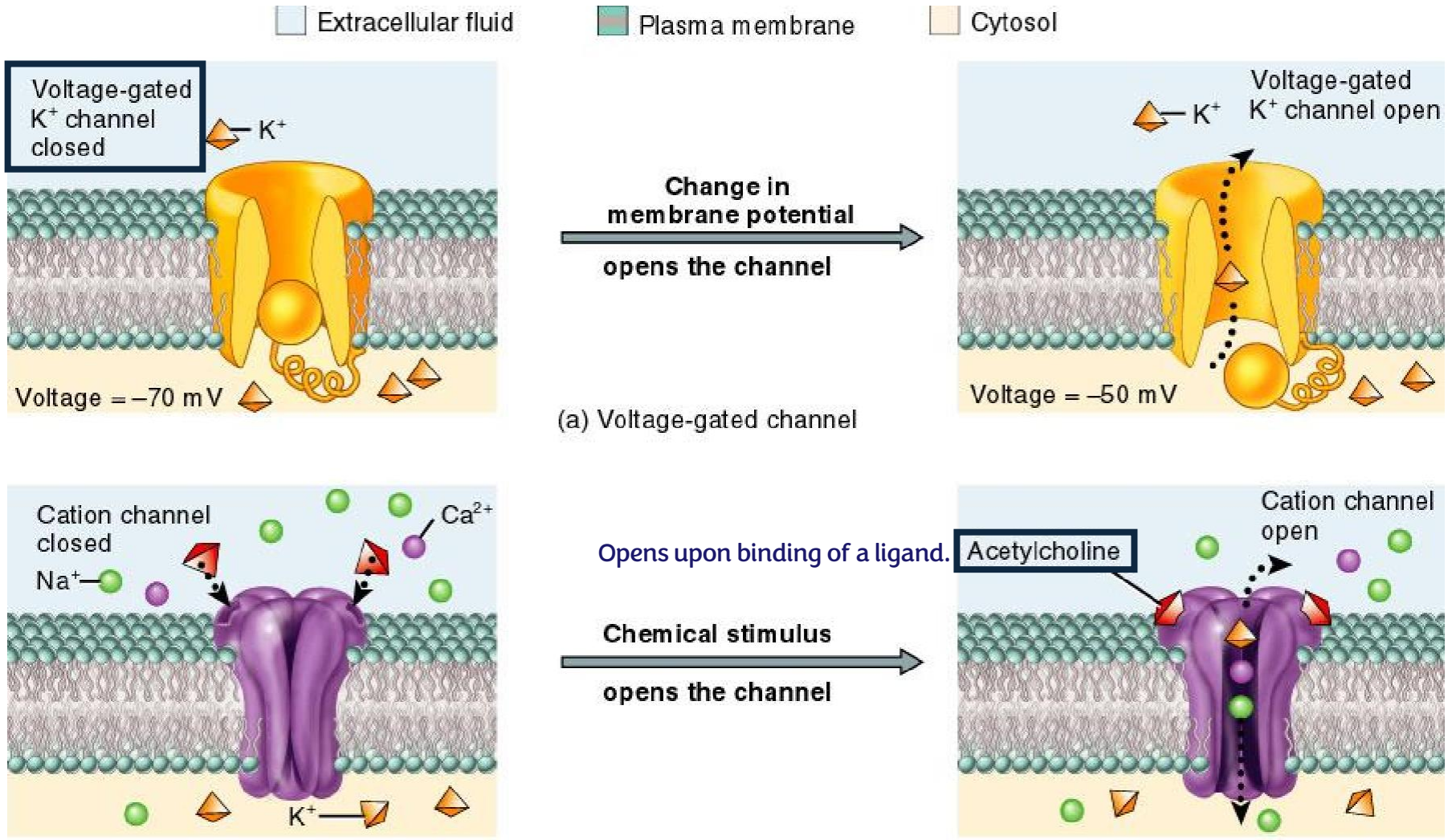


Make sure to read what is written in each stage of Action potential.

- Changes in Channels activity results in action potential



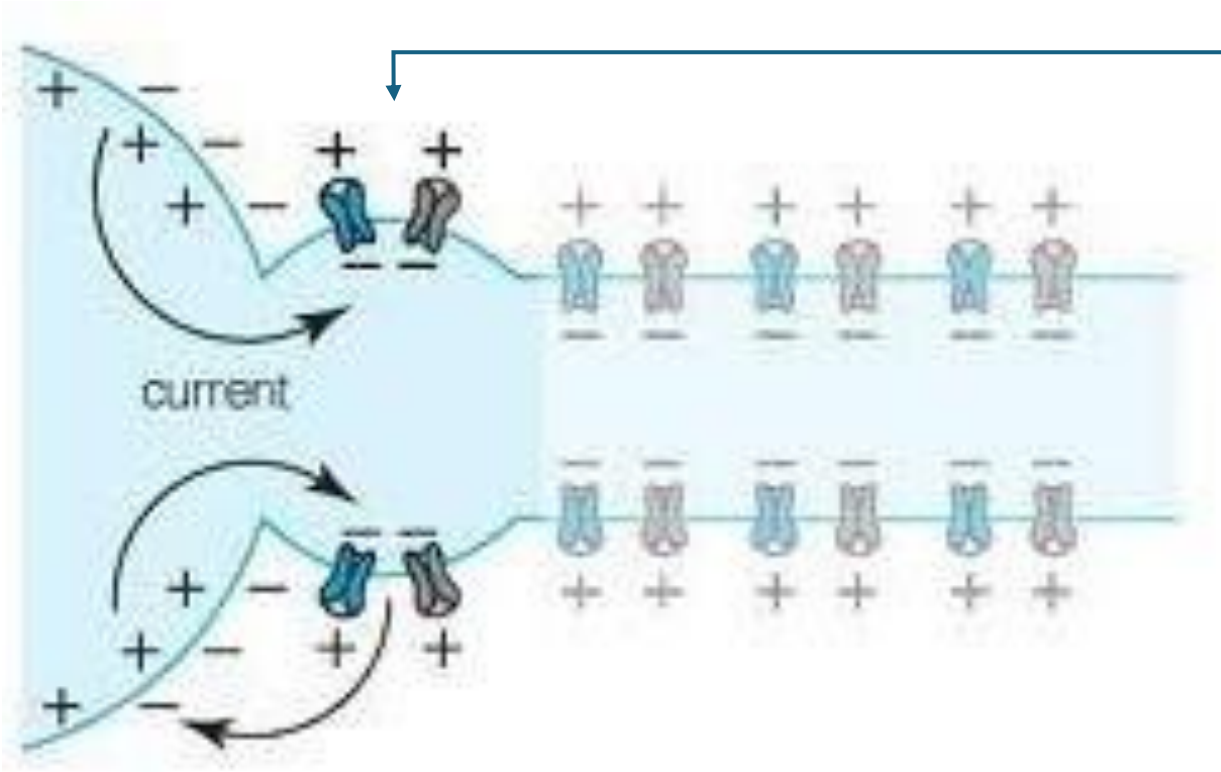
12.12


Extracellular fluid
Plasma membrane
Cytosol
Voltage-gated K+ channel closed
K+
Voltage = –70 mV
Change in membrane potential
opens the channel
Voltage-gated K+ channel open
K+
Voltage = –50 mV
(a) Voltage-gated channel
Cation channel closed
Ca2+
Na+
K+
Opens upon binding of a ligand.
Acetylcholine
Chemical stimulus
opens the channel
Cation channel open
(b) Ligand-gated channel

12.08

Ionic currents cause depolarization

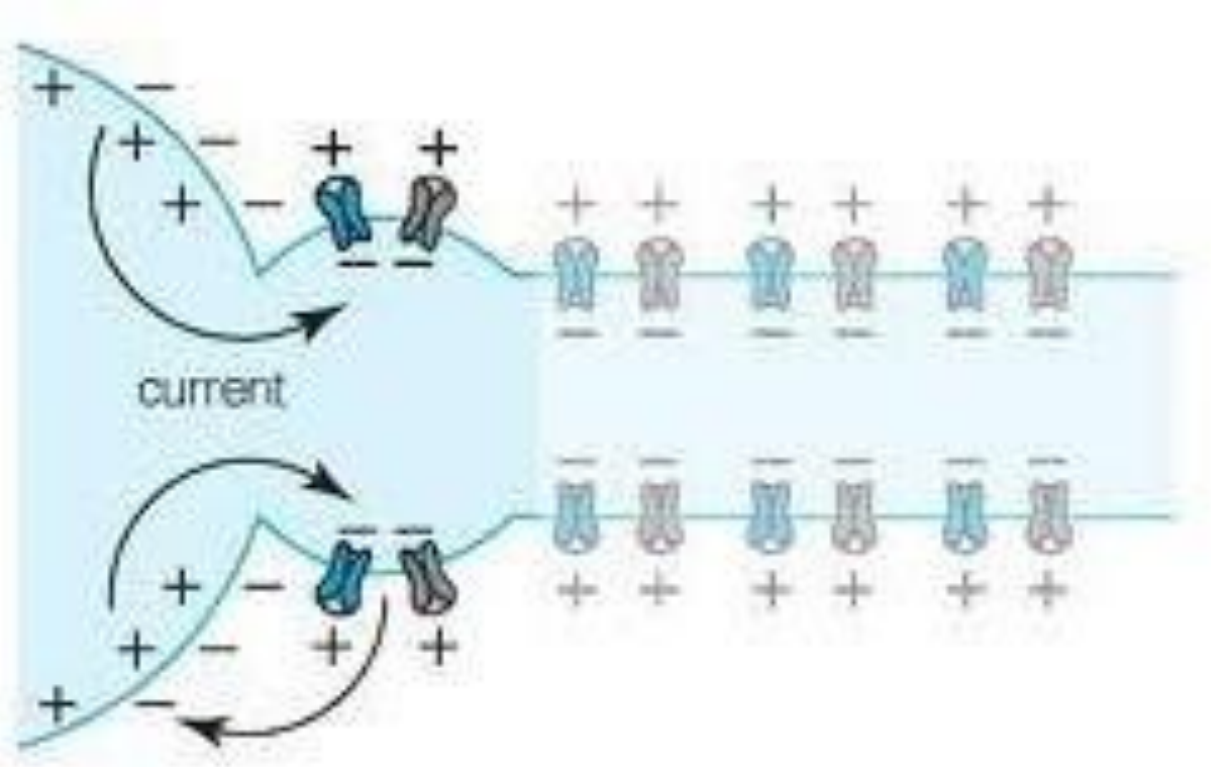
We can also generate an action potential by current.



Voltage gated channels that open upon the current changing the membrane potential.

Resistance to Ionic currents and activation of channels

Action potentials

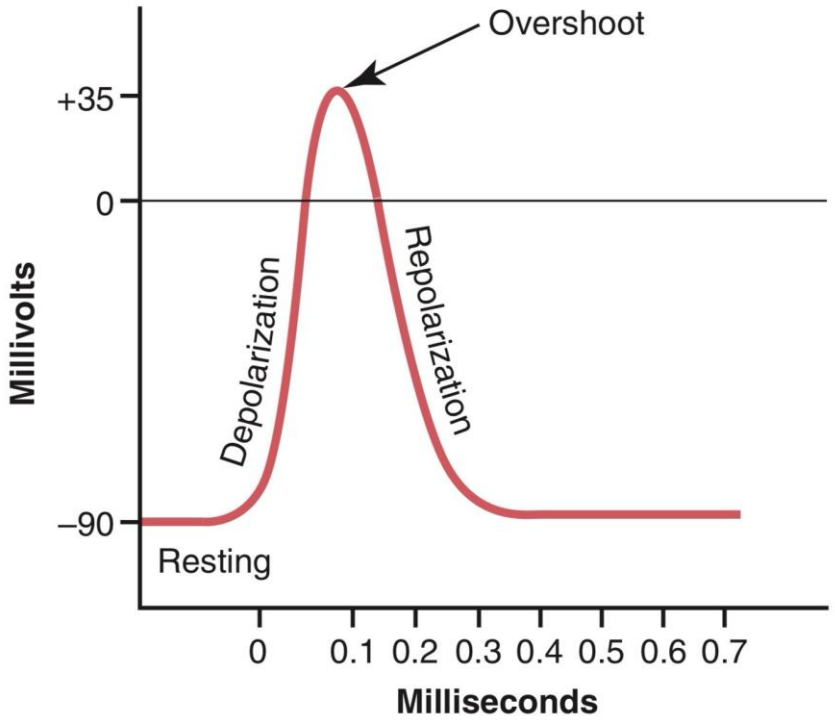


اللهم صل وسلم وبارك على سيدنا
محمد وعلى آله وصحبه أجمعين

Action potential

The successive stages of the action potential are as Follows :

Resting Stage :
The resting stage is the resting membrane potential before the action potential begins. The membrane is said to be “polarized” during this stage because of the -90 millivolts negative membrane potential that is present.



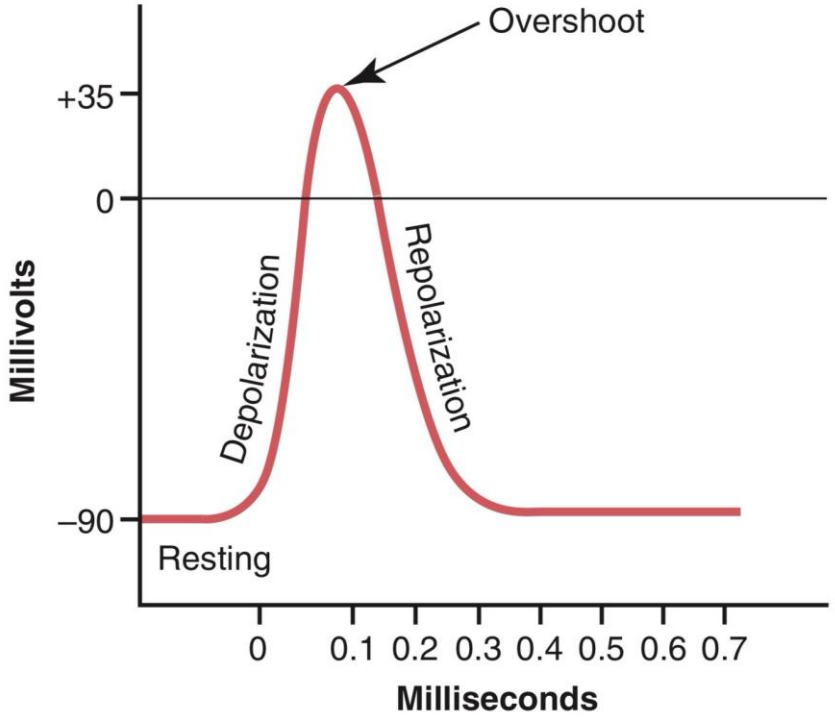
Depolarization Stage :
At this time, the membrane suddenly becomes permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to diffuse to the interior of the axon.

The normal “polarized” state of -90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction—a process called depolarization. In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually “overshoot” beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.

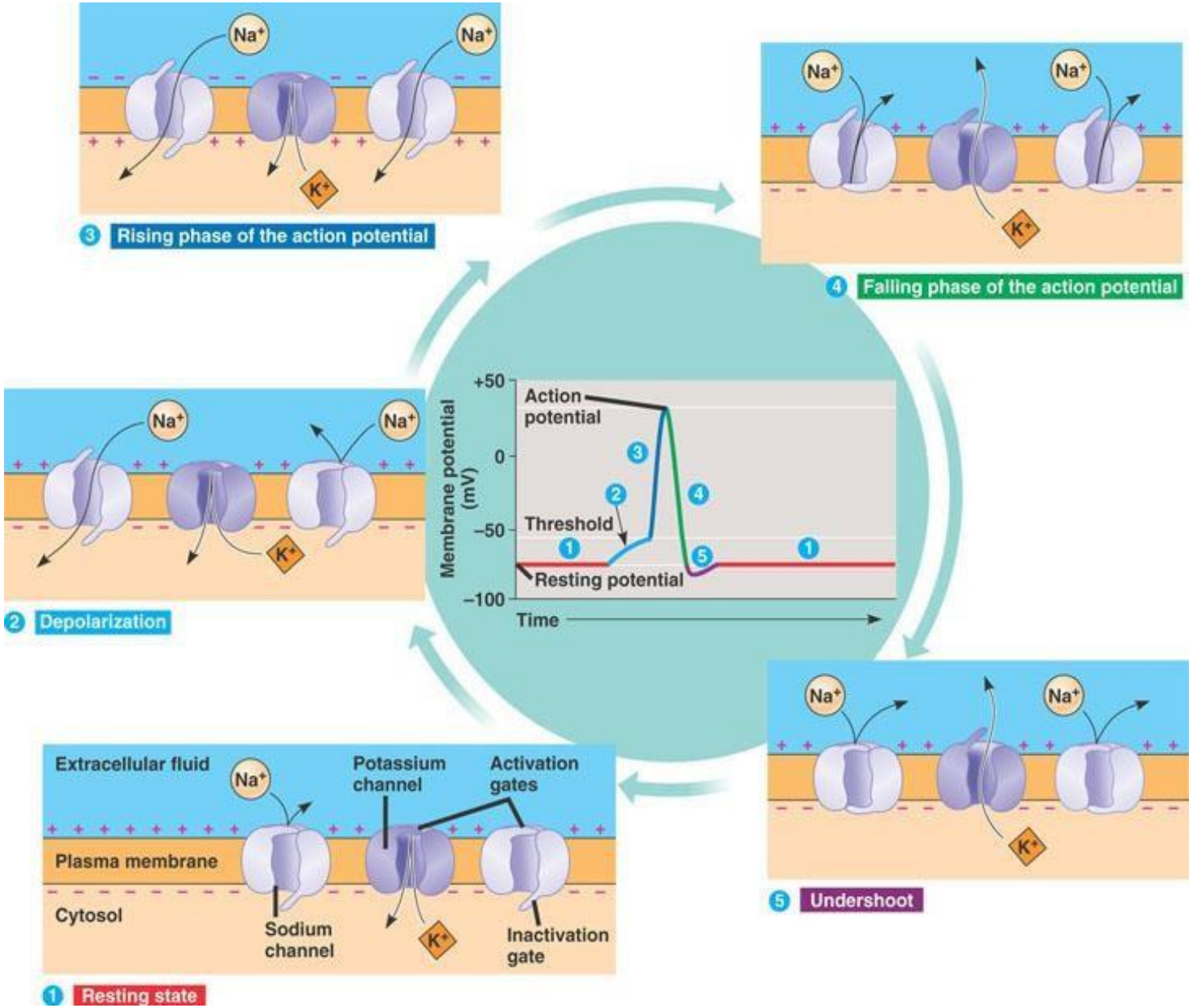
Action potential

Repolarization Stage :

Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open to a greater degree than normal.
Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential, which is called repolarization of the membrane.



Action potential

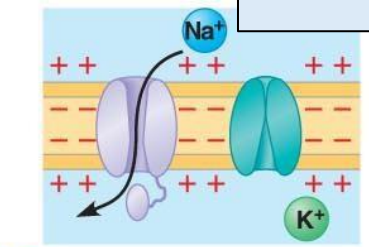


Generation of action potentials

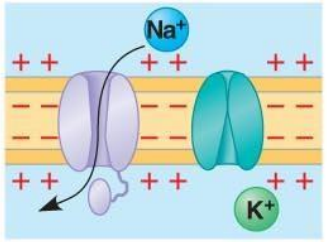
Make sure to read what is written in each stage on this slide.

At the **threshold** (a specific membrane potential), most voltage gated sodium channels are open which cause the rapid flow of sodium from outside to inside, which causes the firing of the action potential.

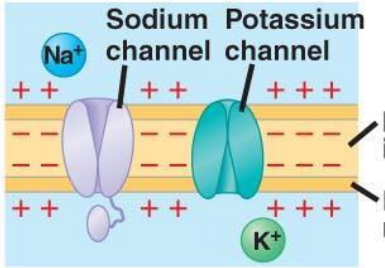
Also, at the threshold we are having faster activation of sodium channels than potassium channels (slower),



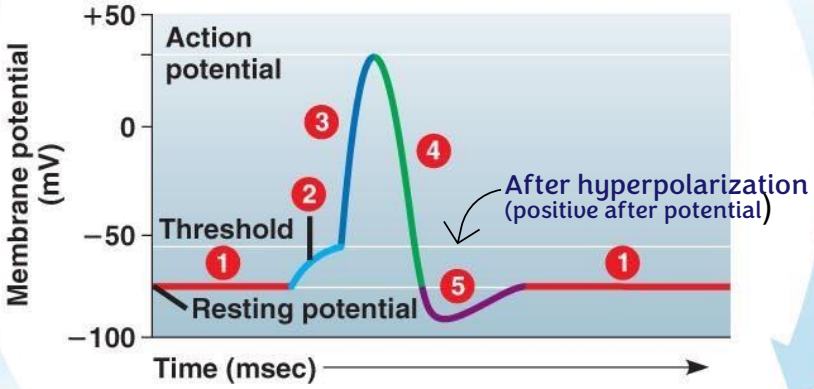
3 Additional Na^+ channels open, K^+ channels are closed; interior of cell becomes more positive.

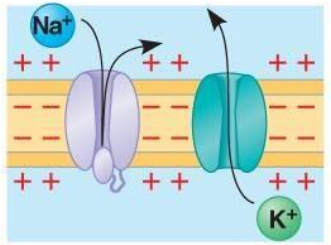


2 A stimulus opens some Na^+ channels; if threshold is reached, action potential is triggered.



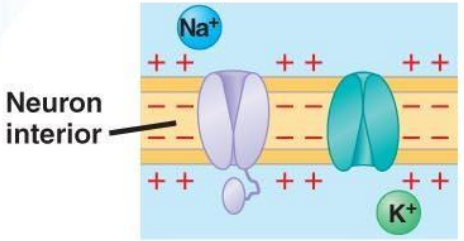
1 Resting state: voltage-gated Na^+ and K^+ channels closed; resting potential is maintained.



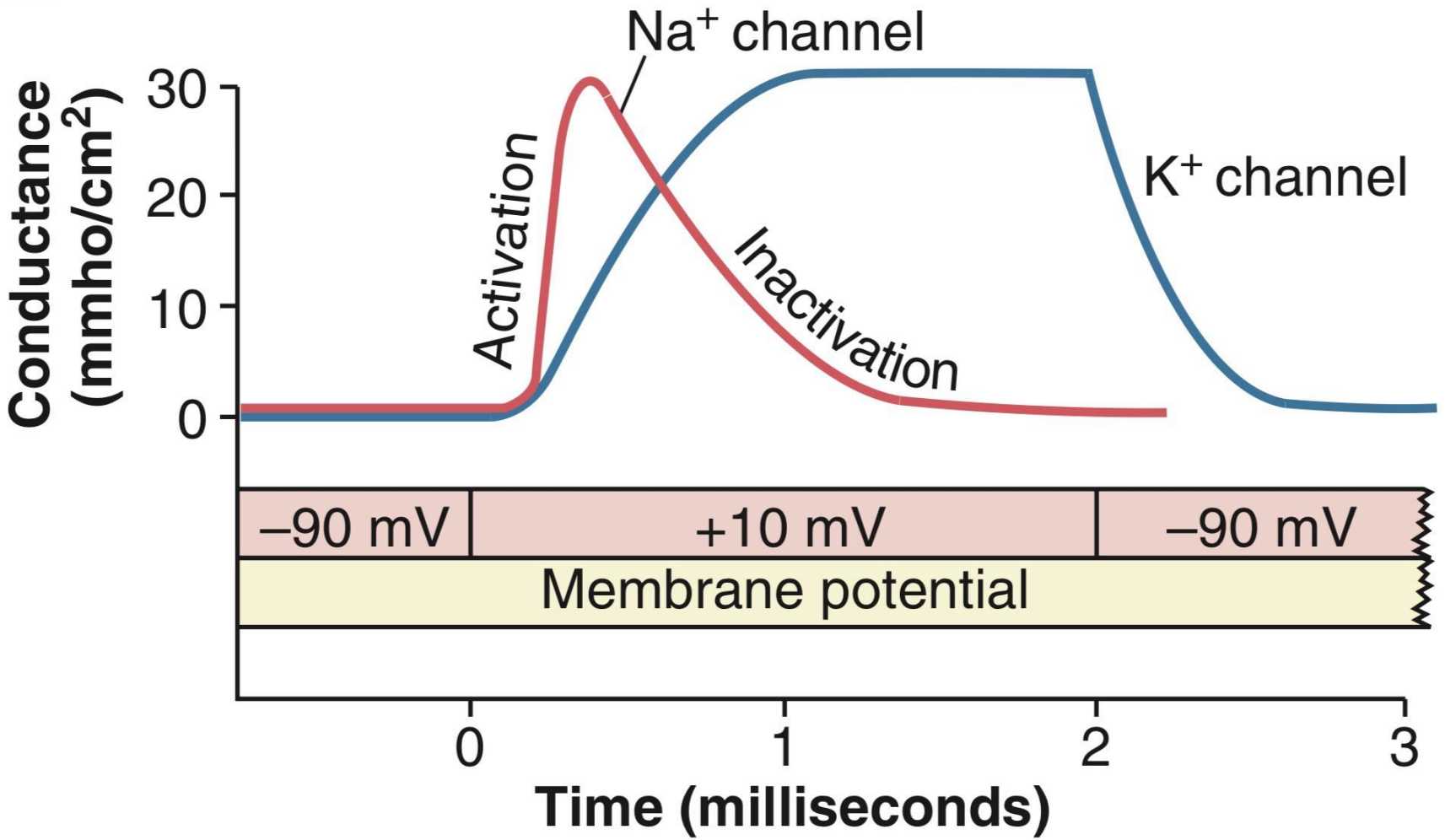


4 Na^+ channels close and inactivate. K^+ channels open, and K^+ rushes out; interior of cell more negative than outside.

5 The K^+ channels close relatively slowly, causing a brief undershoot.



1 Return to resting state.

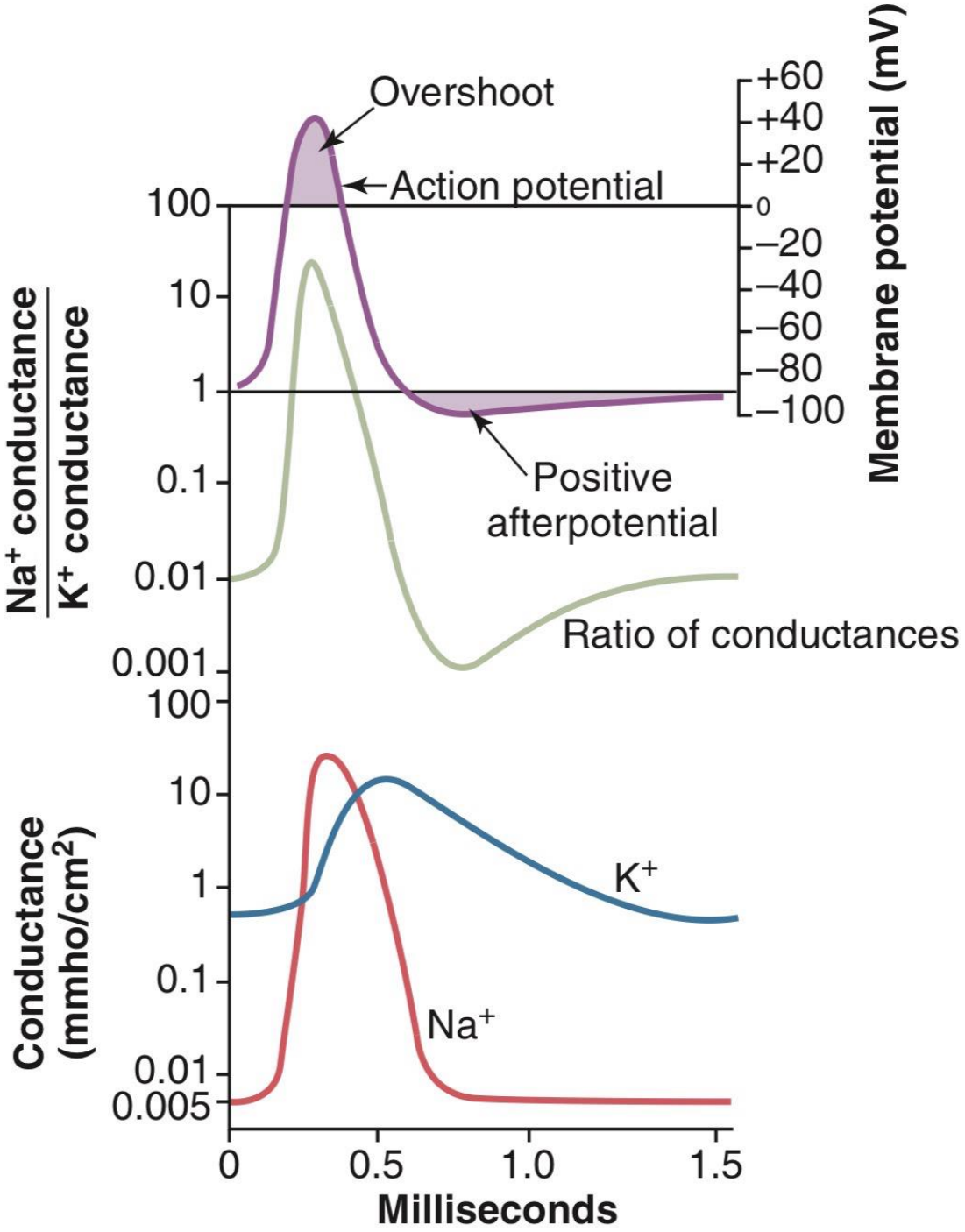


Typical changes in conductance of sodium and potassium ion channels when the membrane potential is suddenly increased from the normal resting value of −90 millivolts to a positive value of +10 millivolts for 2 milliseconds. This figure shows that the sodium channels open (activate) and then close (inactivate) before the end of the 2 milliseconds, whereas the potassium channels only open (activate), and the rate of opening is much slower than that of the sodium channels.

- Na+ and K+ conductance at resting potentials

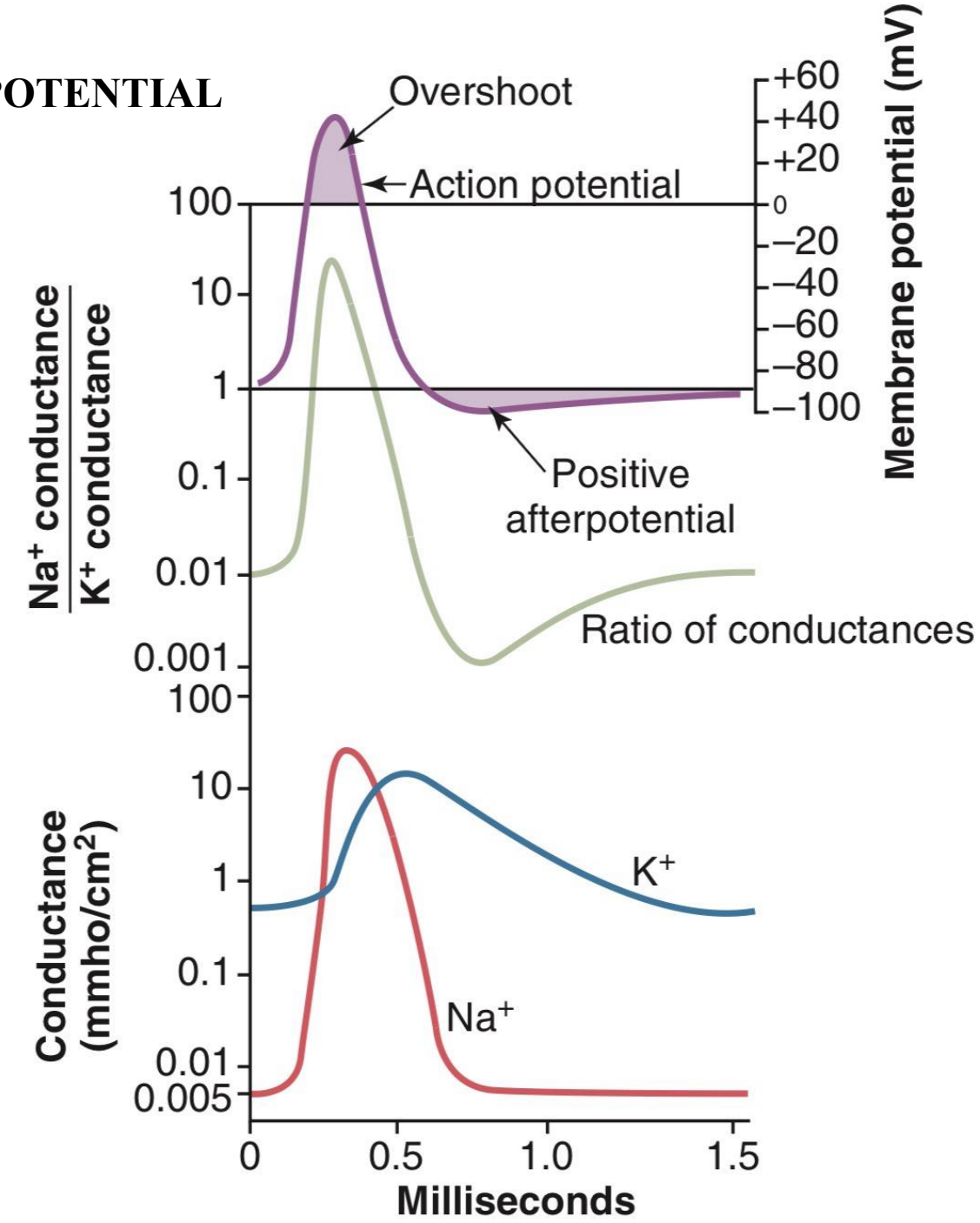
- We have the highest tendency of sodium to move from outside to inside at the resting stage.
  - The reason is that you have the highest concentration gradient (high outside, low inside) and the inside is negative.

- We have the highest tendency for potassium to move from inside to outside at the overshoot.
  - The reason is the very high concentration gradient, and the inside is positive and outside is negative.



SUMMARY OF THE EVENTS THAT CAUSE THE ACTION POTENTIAL

Figure 5-10 summarizes the sequential events that occur during and shortly after the action potential. The bottom of the figure shows the changes in membrane conductance for sodium and potassium ions. During the resting state, before the action potential begins, the conductance for potassium ions is 50 to 100 times as great as the conductance for sodium ions. This disparity is caused by much greater leakage of potassium ions than sodium ions through the leak channels. However, at the onset of the action potential, the sodium channels instantaneously become activated and allow up to a 5000-fold increase in sodium conductance. The inactivation process then closes the sodium channels within another fraction of a milli-second. The onset of the action potential also causes voltage gating of the potassium channels, causing them to begin opening more slowly a fraction of a millisecond.



Refractory periods

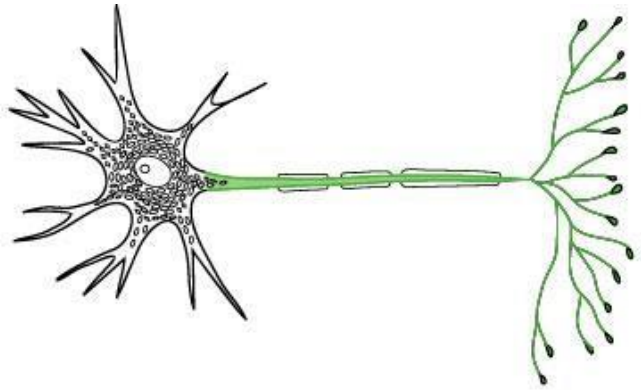
DURING THE ABSOLUTE REFRACTORY PERIOD AFTER AN ACTION POTENTIAL A NEW ACTION POTENTIAL CANNOT BE ELICITED

A new action potential **cannot** occur in an excitable fiber as long as the membrane is **still depolarized from the preceding action potential.** The reason for this restriction is that shortly after the action potential is initiated, the sodium channels (or calcium channels, or both) become **inactivated**, and **no amount of excitatory signal applied to these channels at this point will open the inactivation gates. The only condition that will allow them to reopen is for the membrane potential to return to or near the original resting membrane potential level.** Then, within another small fraction of a second, the inactivation gates of the channels open, and a new action potential can be initiated.

The period during which a second action potential cannot be elicited, even with a strong stimulus, is called the absolute refractory period. This period for large myelinated nerve fibers is about 1 millisecond. Therefore, one can readily calculate that such a fiber can transmit a maximum of about 1000 impulses per second.

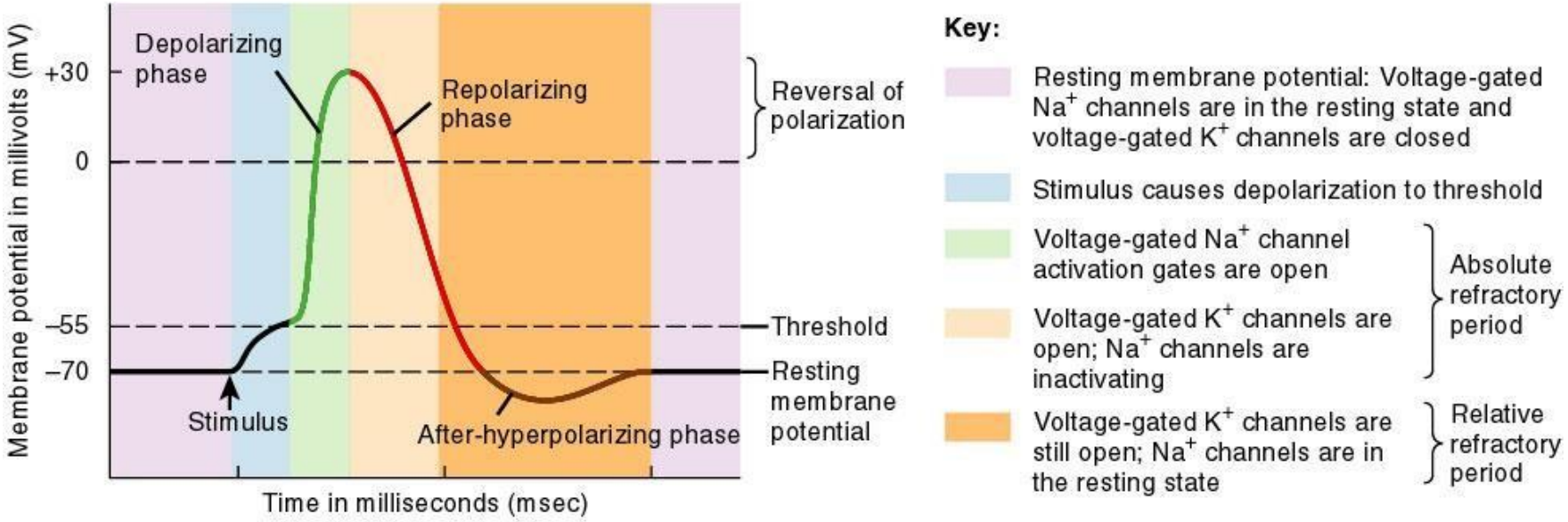
During the relative refractory period, which occurs for 2 to 4 milliseconds during the hyperpolarization phase, the neuron can develop another action potential, but a greater stimulus is required compared to the stimulus needed to elicit an action potential in a resting neuron.

Refractory periods



- **Absolute Refractory Period :** The period of the action potential in which, **whatever was the strength of the new stimulus, it can't generate an new action potential.**

- **Relative Refractory Period :** The period in which the weak stimulus can't generate new action potential. However, **a strong stimulus may be able to initiate an action potential.**

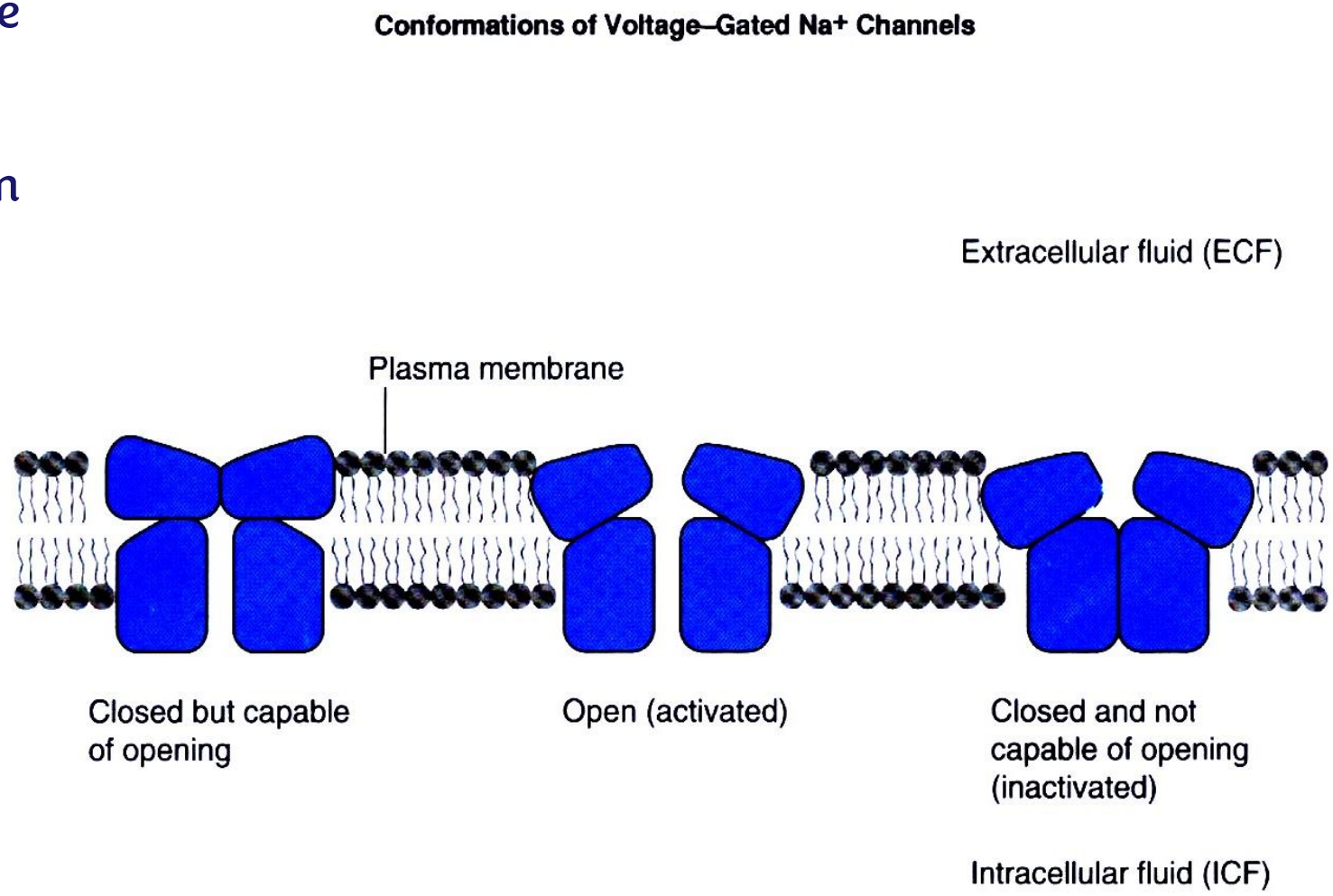


12.11

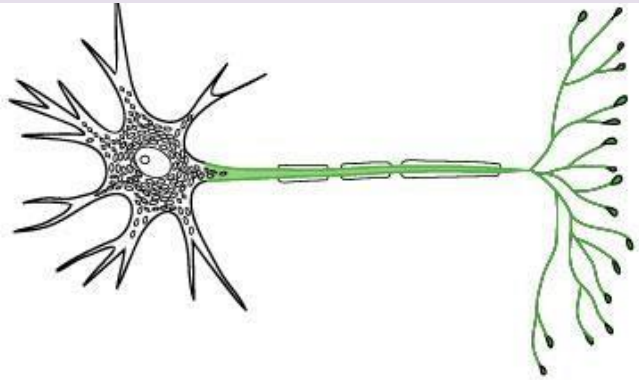
Refractory periods and Na+ Channels

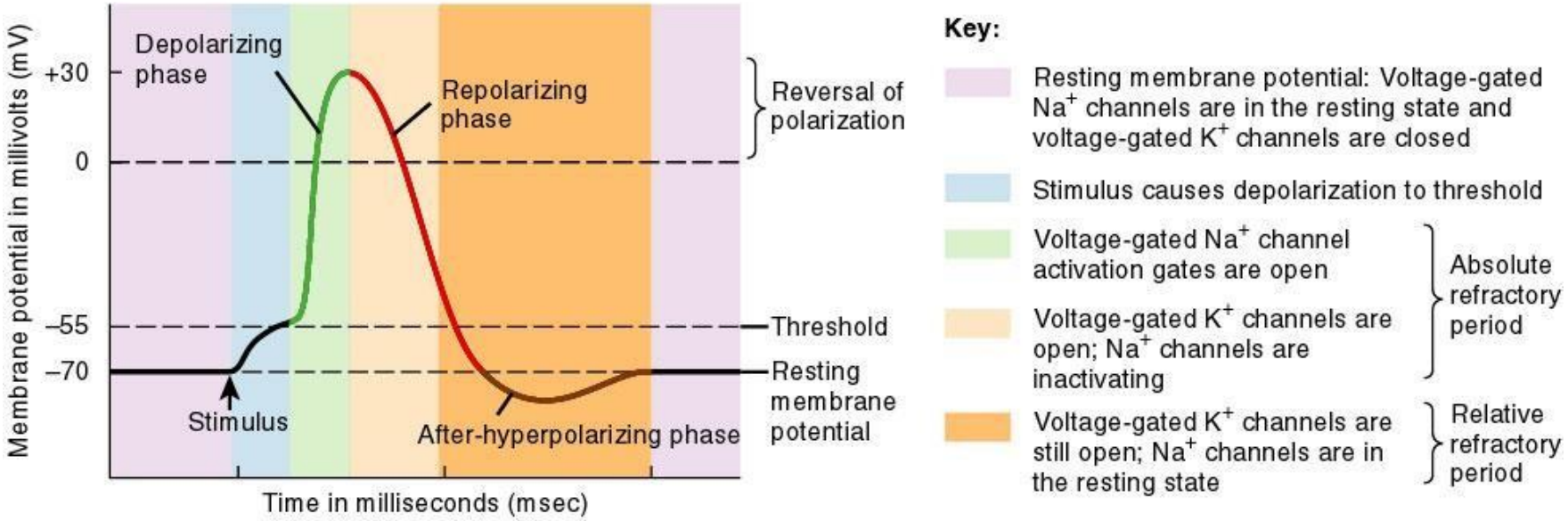
- The refractory period depends on the state of the sodium channels.
- There are three states of the sodium channels, which are :

1. **Open (activated) →Absolute Refractory Period.**
2. **Closed but capable of opening → Relative Refractory Period.**
3. **Closed and not capable of opening → Replarization → Absolute Refractory Period.**



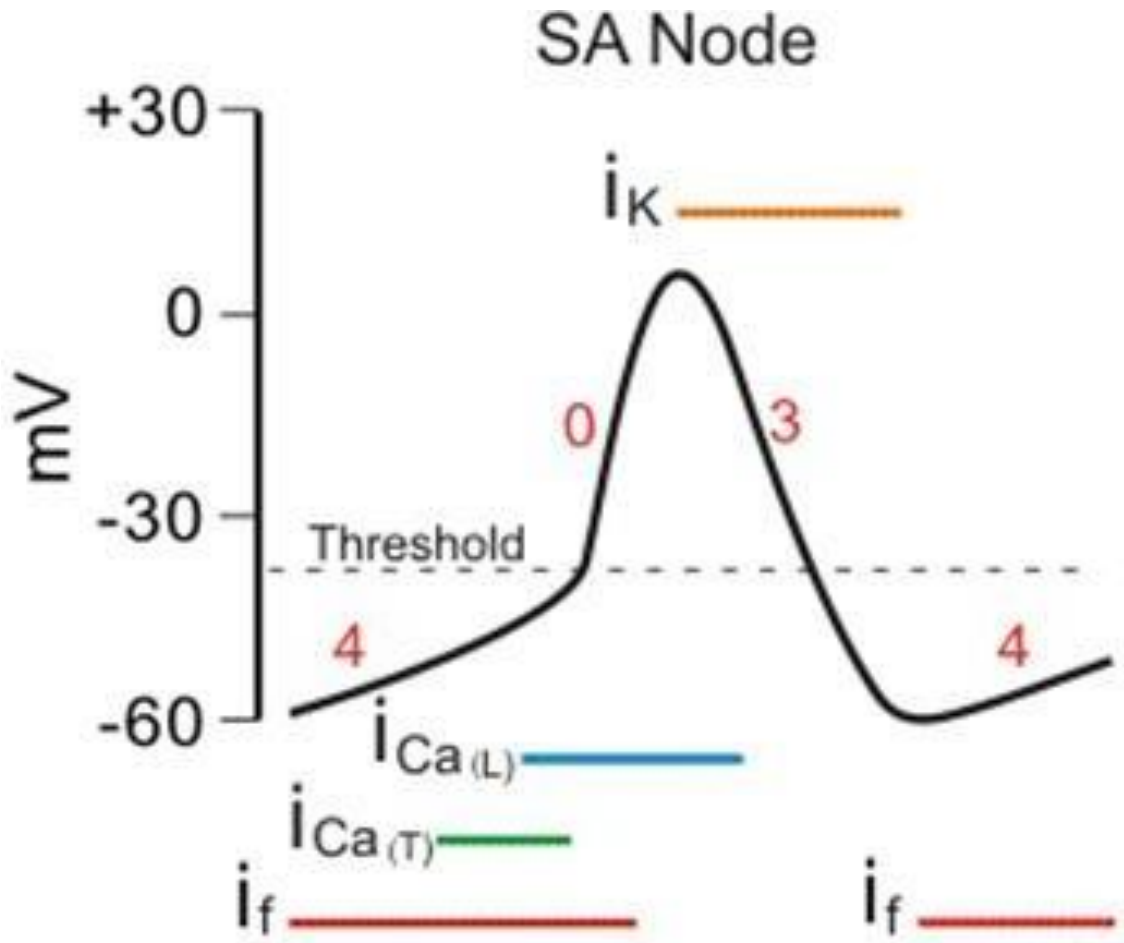
Refractory periods





12.11

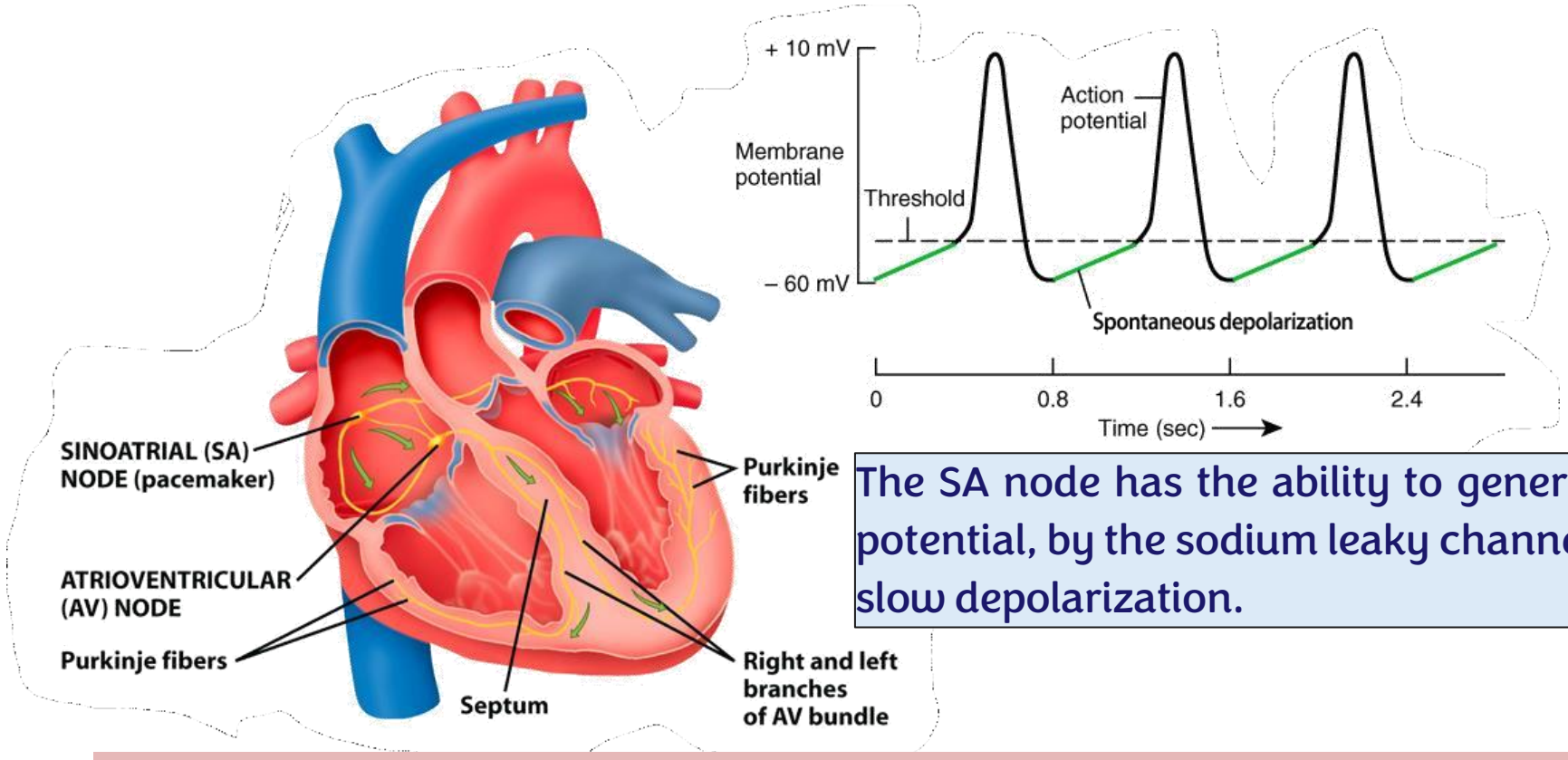
Involvement of other Ions in Action potential



i_f = Funny current (leaky channels)
i_k = current of the potassium channels
i Ca (T) = current of the Transient Calcium channels
i Ca (L) = current of the Long Lasting Calcium channels

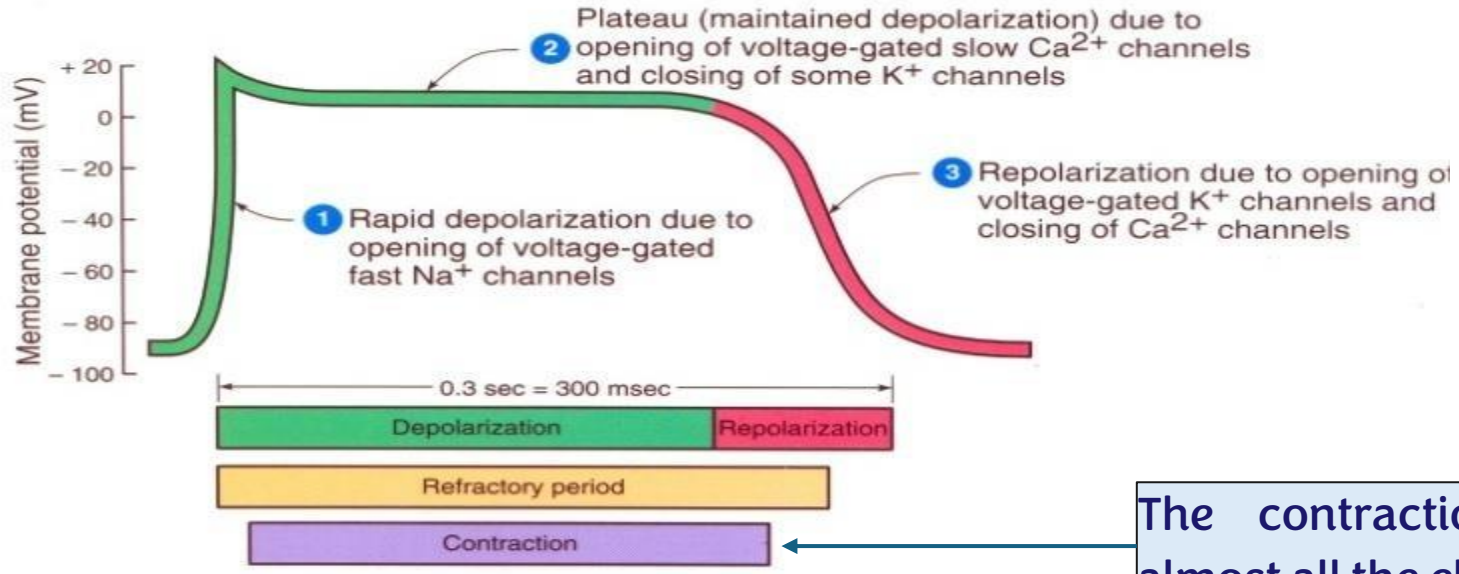
The Funny channels (leaky channels) causes slow depolarization which causes the membrane potential to reach the threshold in an automated way and initiate an action potential.

Cardiac Conduction



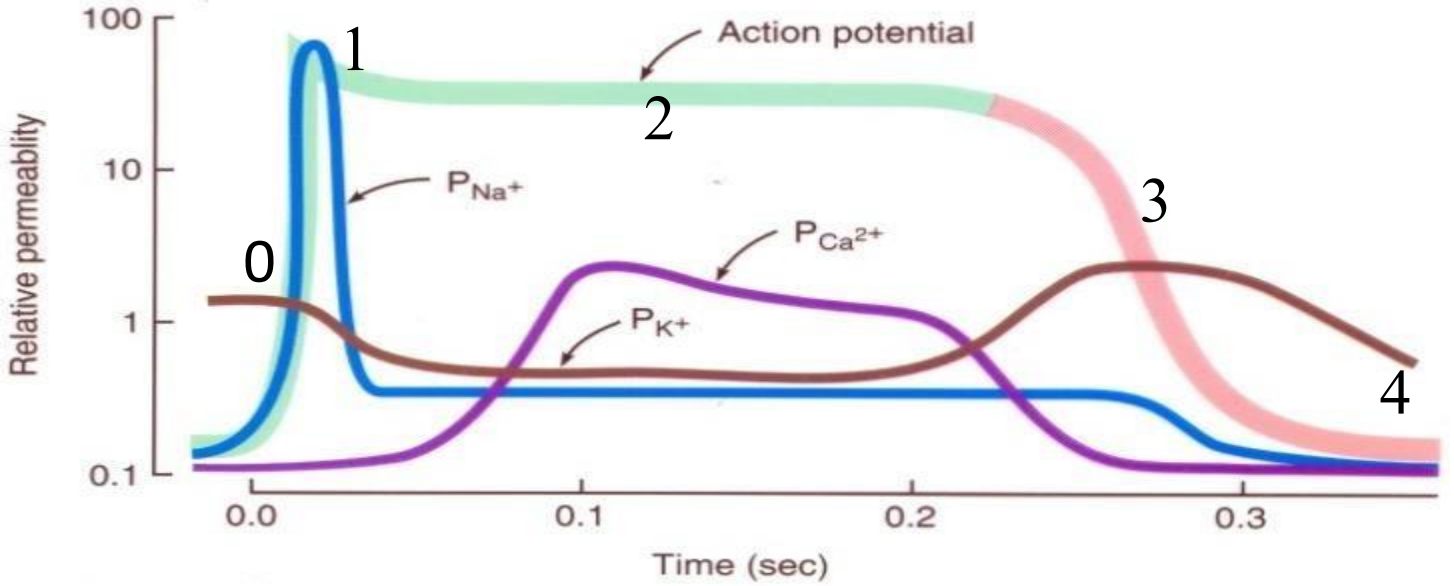
The SA node has the ability to generate its action potential, by the sodium leaky channels that cause slow depolarization.

Generation of Action potential every 0.8 seconds, or 75 action potentials per minute at the SA node (Pacemaker of the heart)



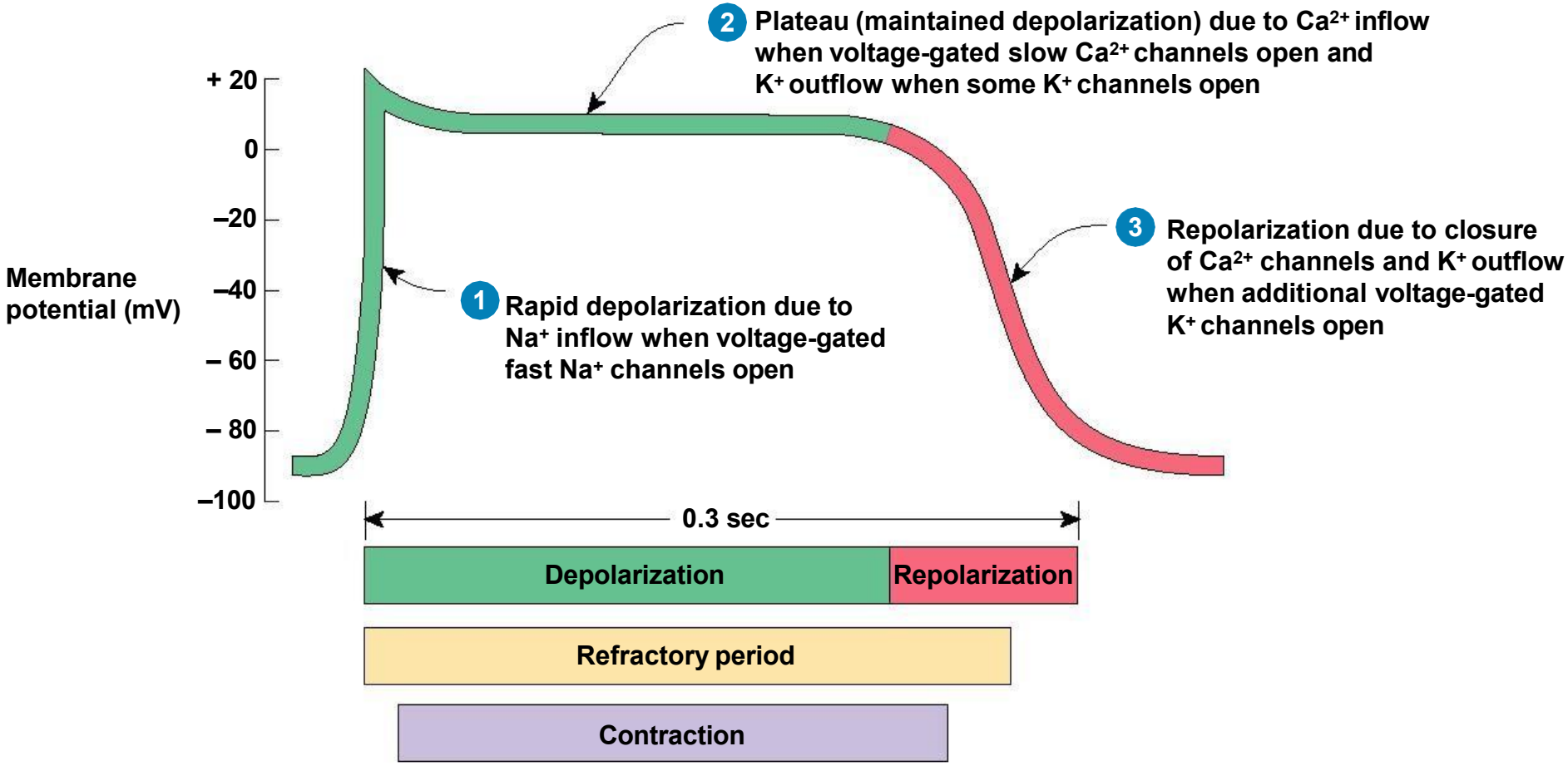
(a) Action potential, refractory period, and contraction

The contraction is covering almost all the electrical activity.

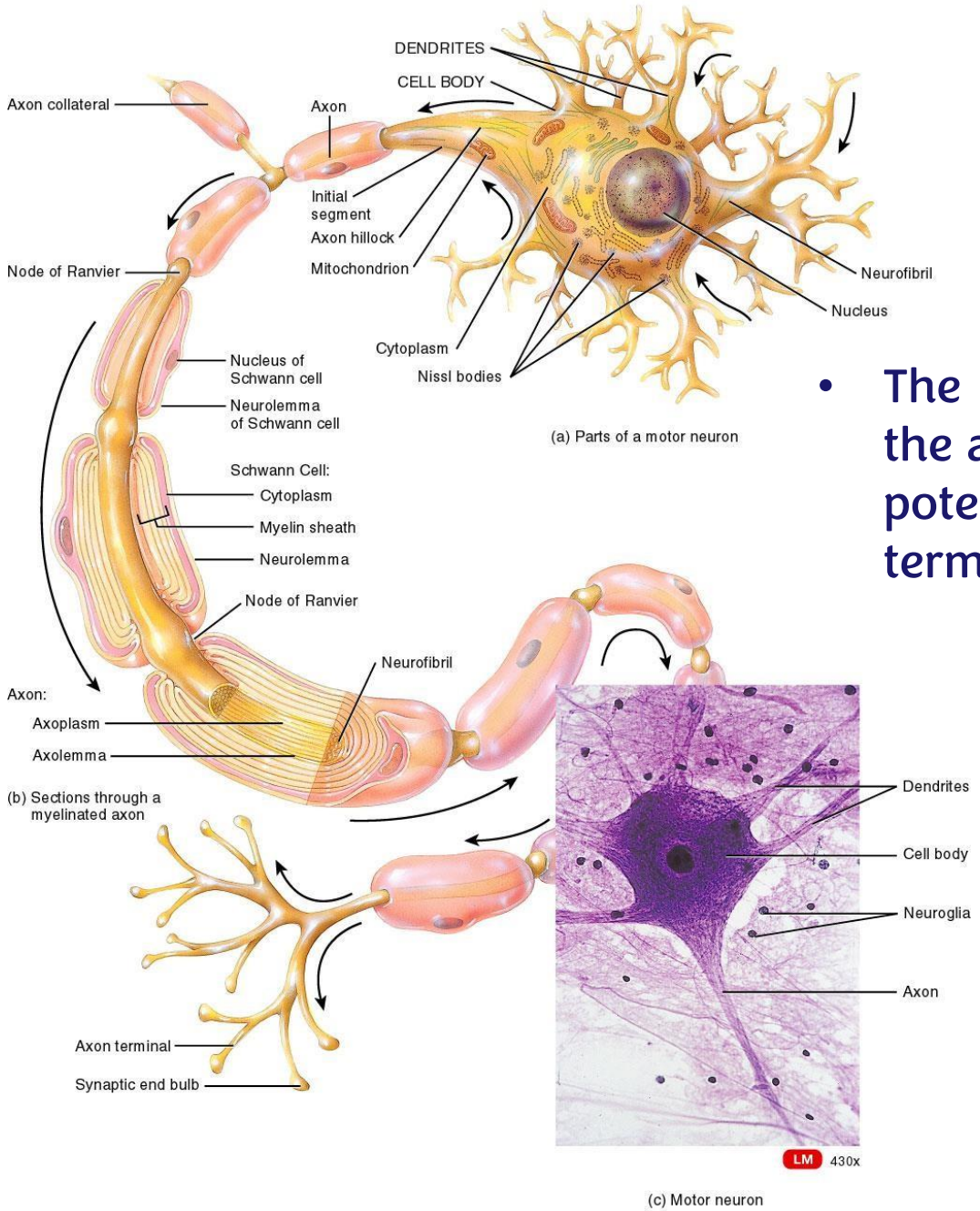


(b) Membrane permeability (P) changes

Cardiac Muscle Action Potential

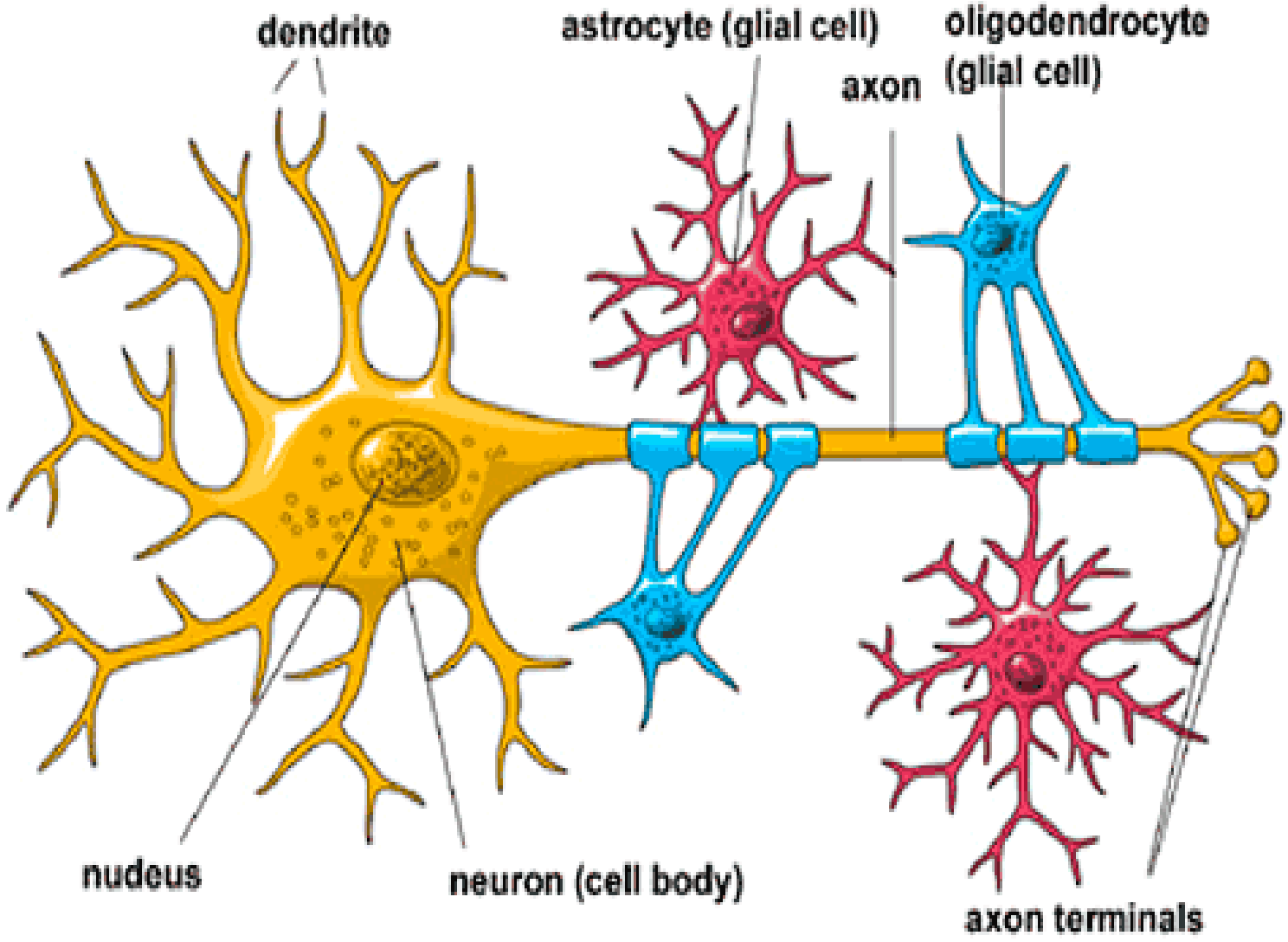


Generation of action potential at Neural cells



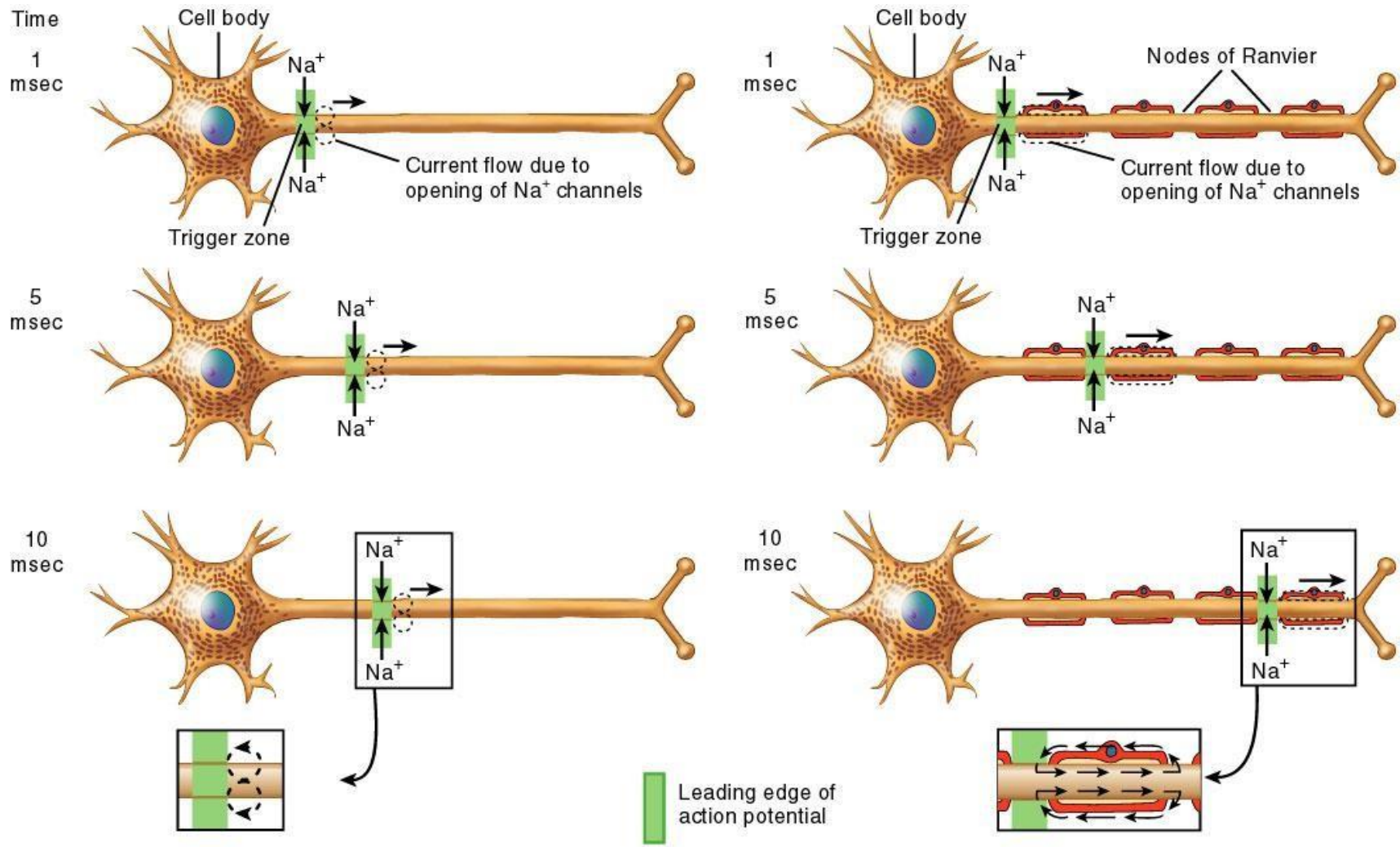
- The action potential is generated at the axon hillock and then the action potential is transmitting towards the terminals through the axon.

Supportive cells



Conduction of impulse

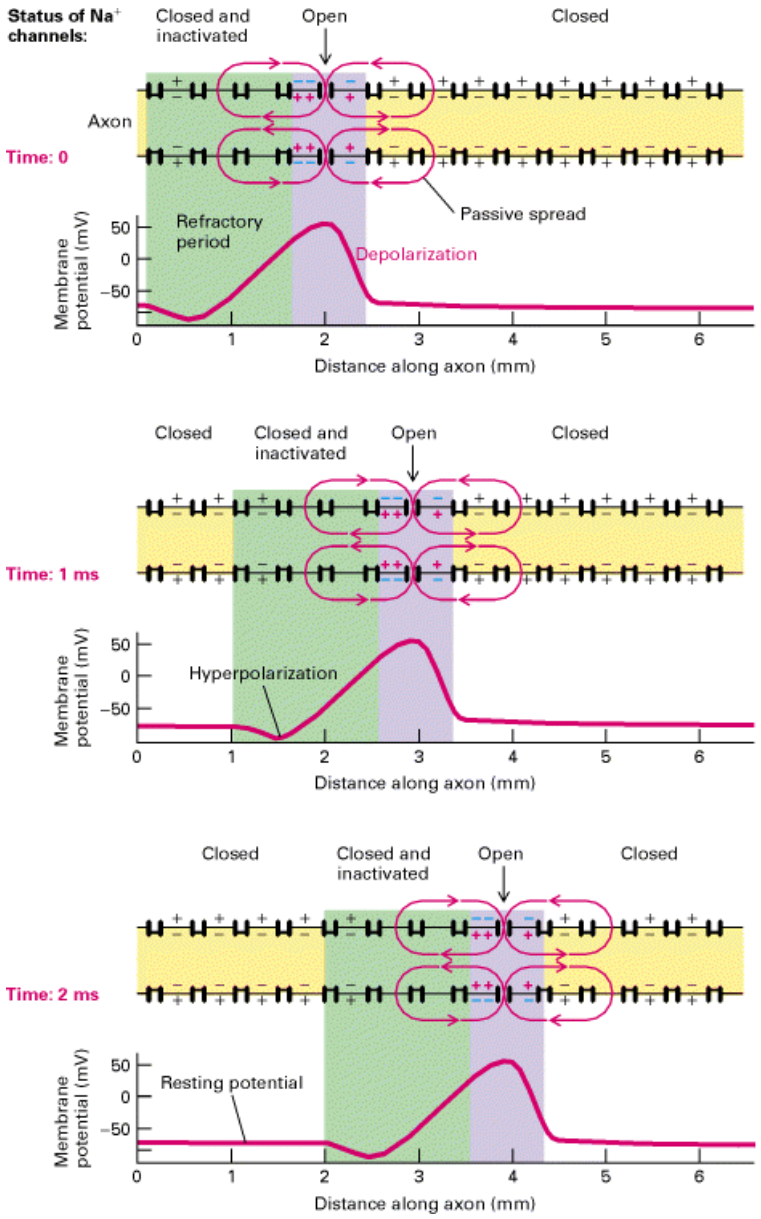
- **Continuous conduction:** it is the propagation of the action potential along every part of the axon membrane step by step.
  - It happens in unmylinated axons
- **Saltatory conduction:** Saltatory conduction is when the action potential jumps from one Node of Ranvier to the next.
  - It happens in myelinated axons.


Time
1 msec
Cell body
Na+
Na+
Current flow due to opening of Na+ channels
Trigger zone
5 msec
Na+
Na+
10 msec
Na+
Na+
Leading edge of action potential
(a) Continuous conduction
1 msec
Cell body
Na+
Nodes of Ranvier
Na+
Current flow due to opening of Na+ channels
Trigger zone
5 msec
Na+
Na+
10 msec
Na+
Na+
(b) Saltatory conduction

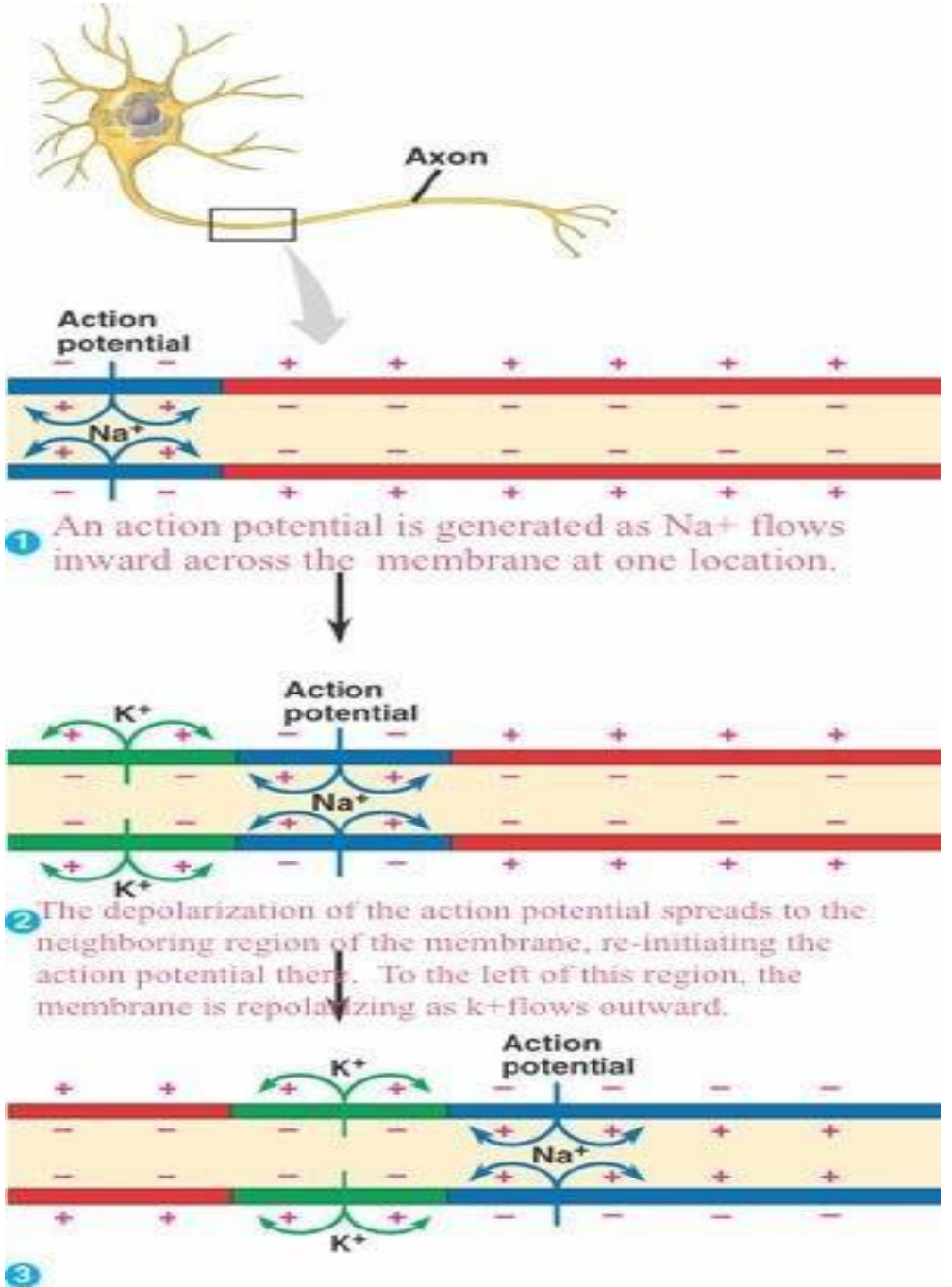
- Continuous Conduction in Unmyelinated axons

The action potential is transmitted in one way, and not bidirectional.

The reason for that is when the action potential is transmitted it can't be transmitted back to because the previous sodium channels are in closed and not capable of opening state, while the next ones are in closed and capable of opening state.

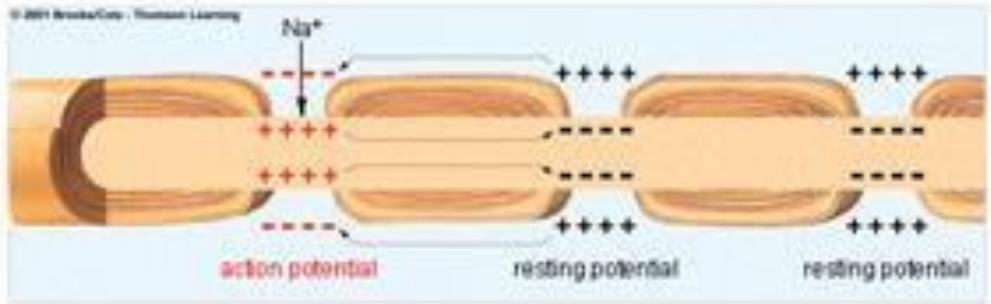


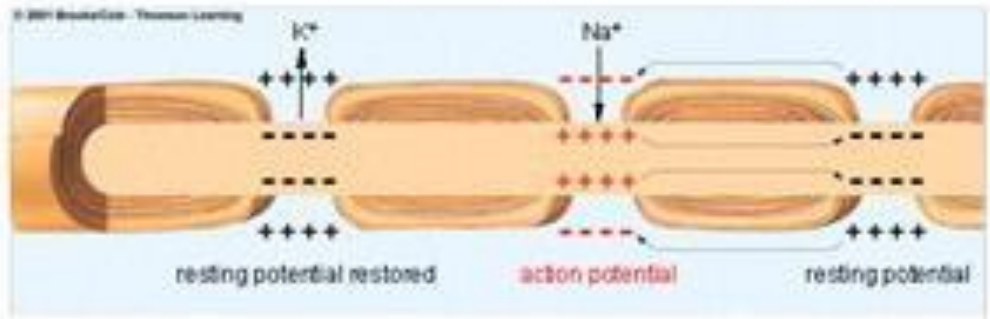
- Continuous Conduction in Unmyelinated axons



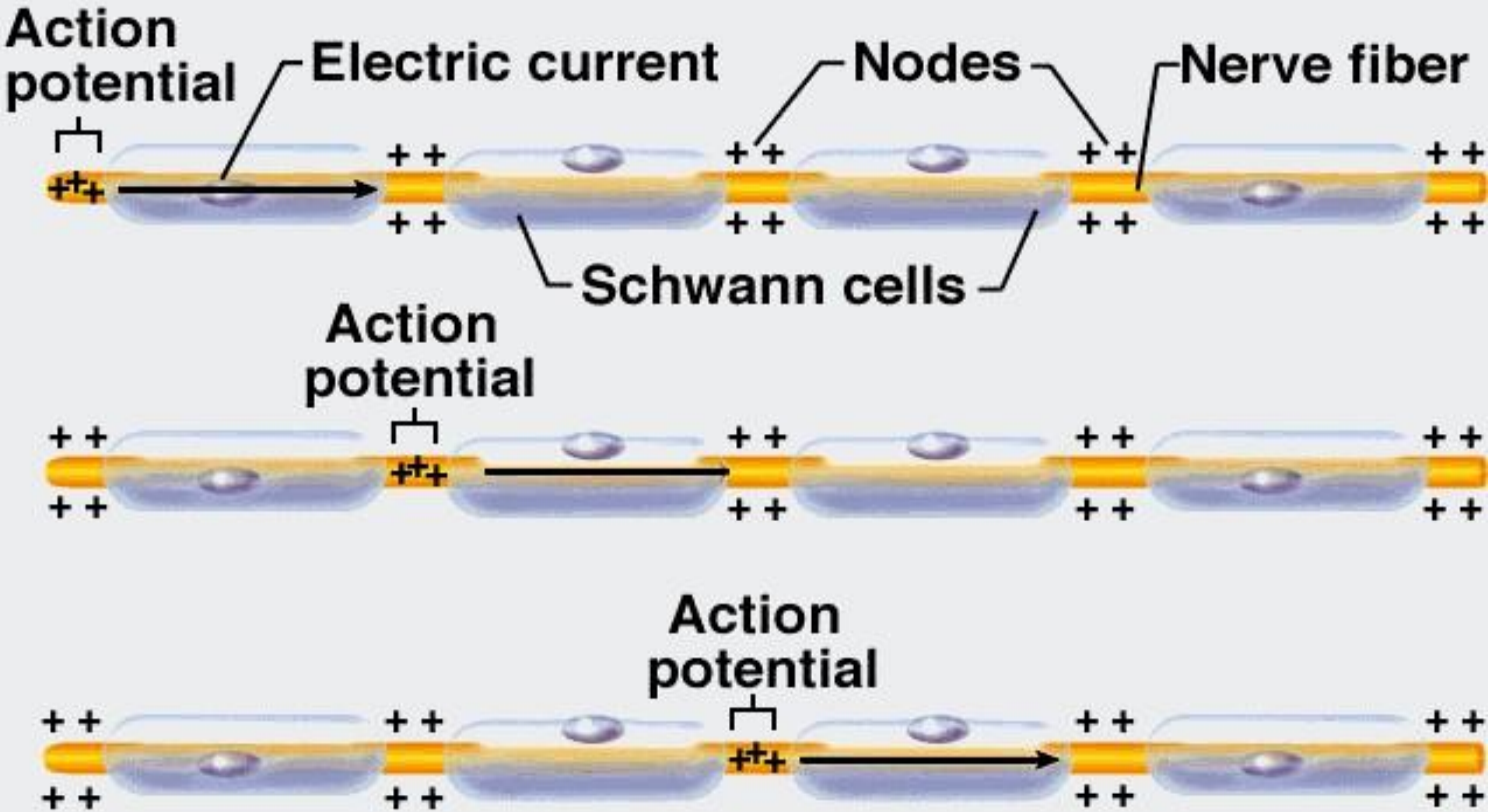
Myelin Sheath

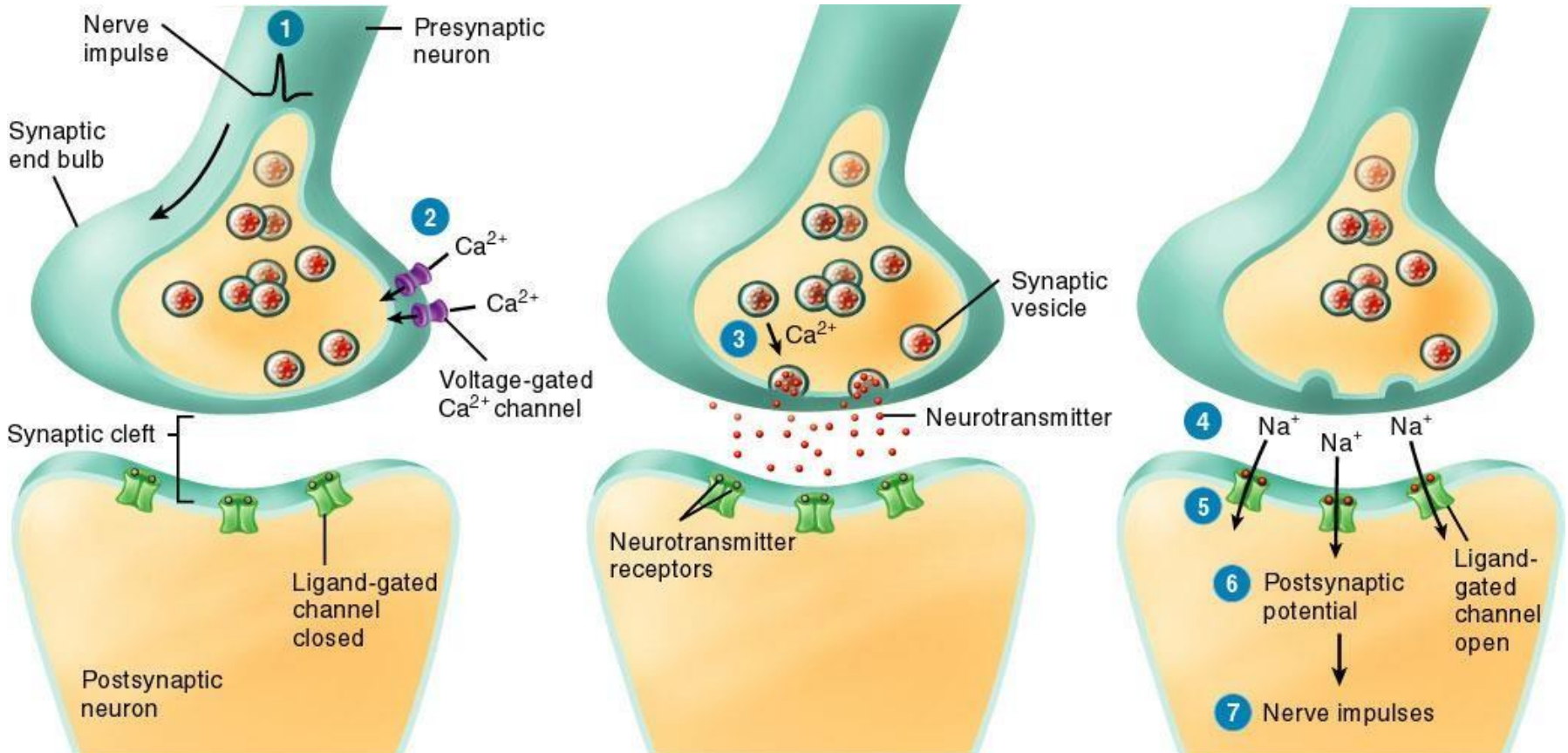
Saltatory Conduction in Myelinated axons



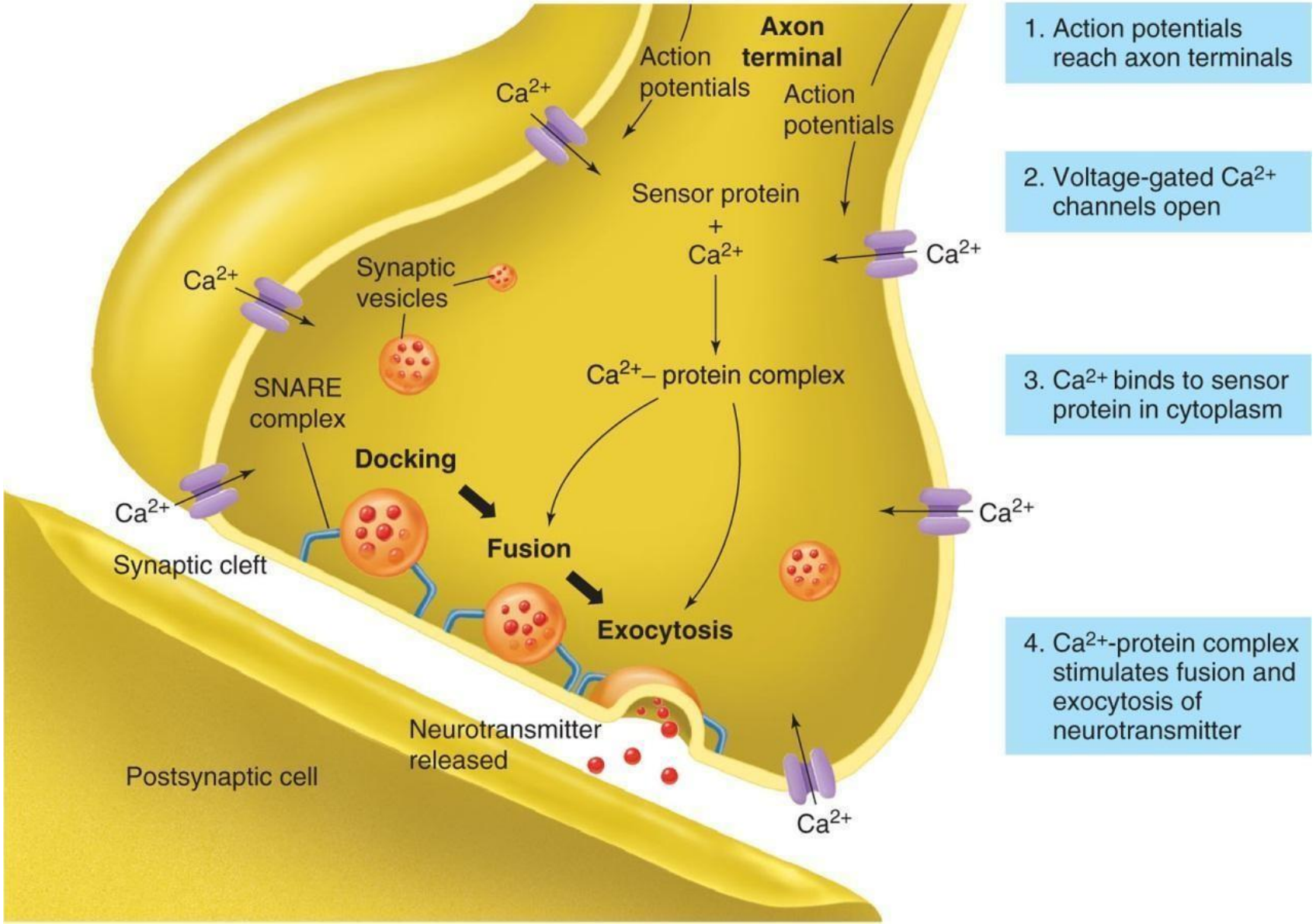


Nerve Impulse on Myelinated Fiber

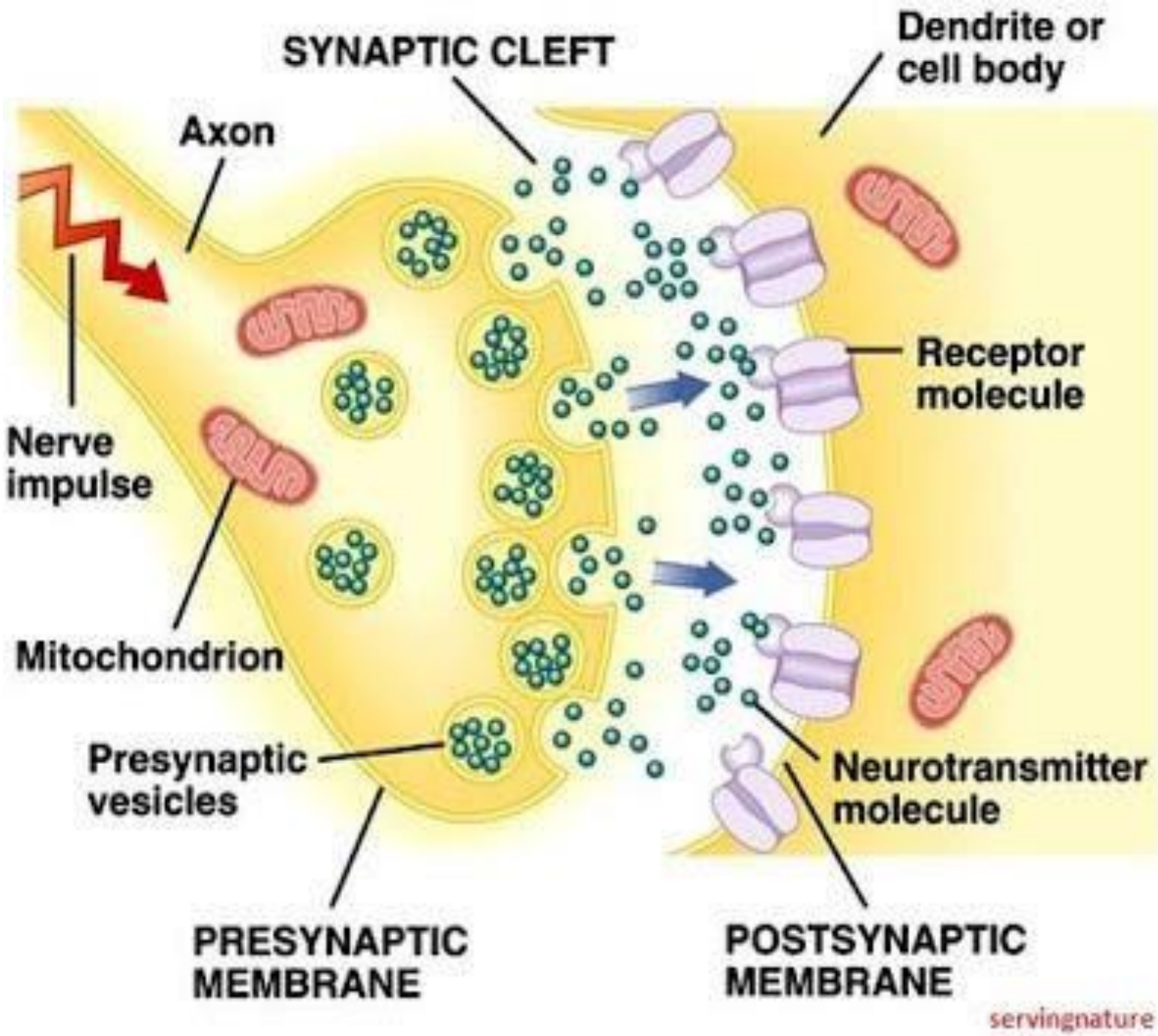



Nerve impulse
1
Presynaptic neuron
Synaptic end bulb
2
Ca^{2+}
Ca^{2+}
Voltage-gated Ca^{2+} channel
Synaptic cleft
Ligand-gated channel closed
Postsynaptic neuron
3
Ca^{2+}
Synaptic vesicle
Neurotransmitter
Neurotransmitter receptors
4
Na^+
Na^+
Na^+
5
6
Postsynaptic potential
Ligand-gated channel open
7
Nerve impulses

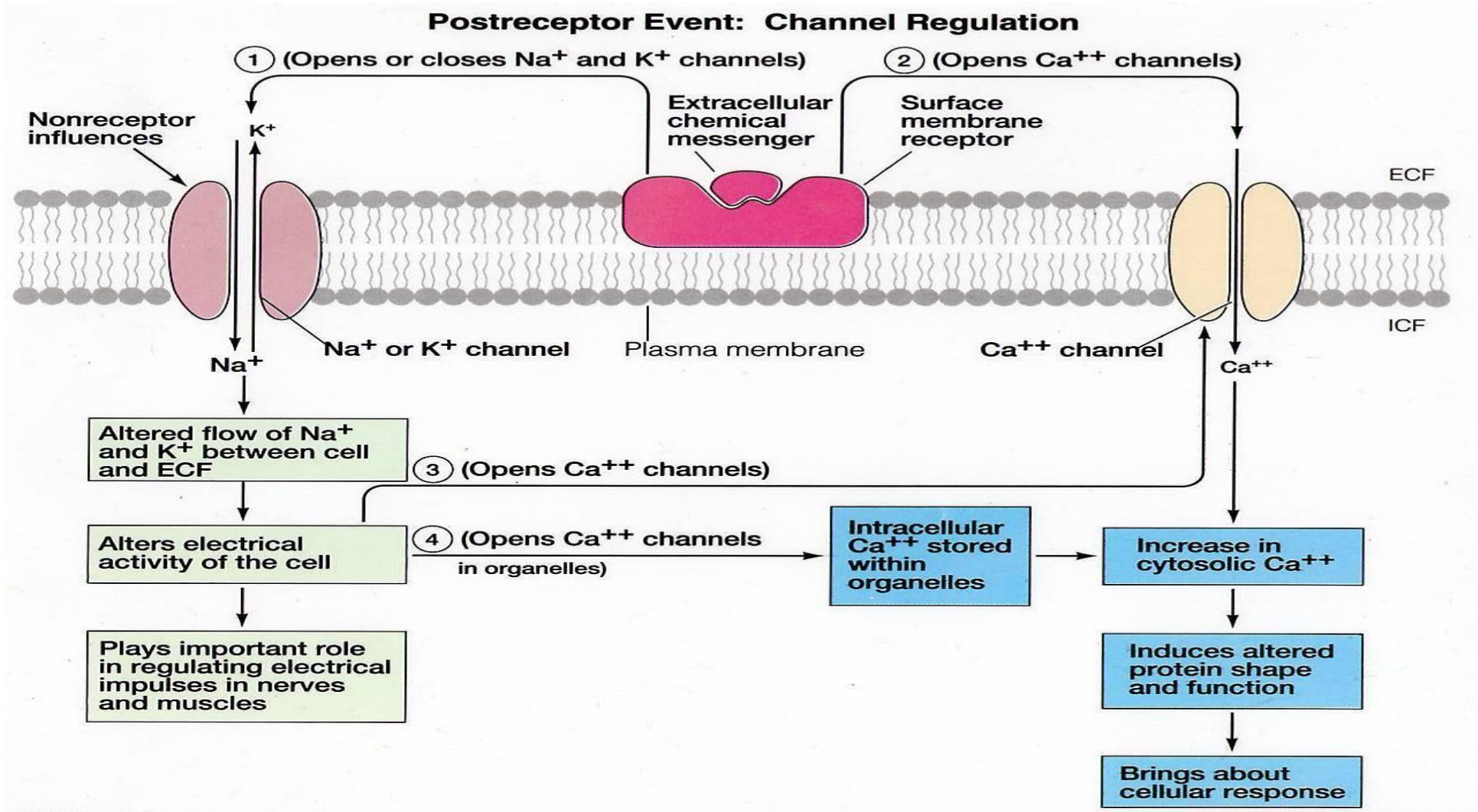
12.14

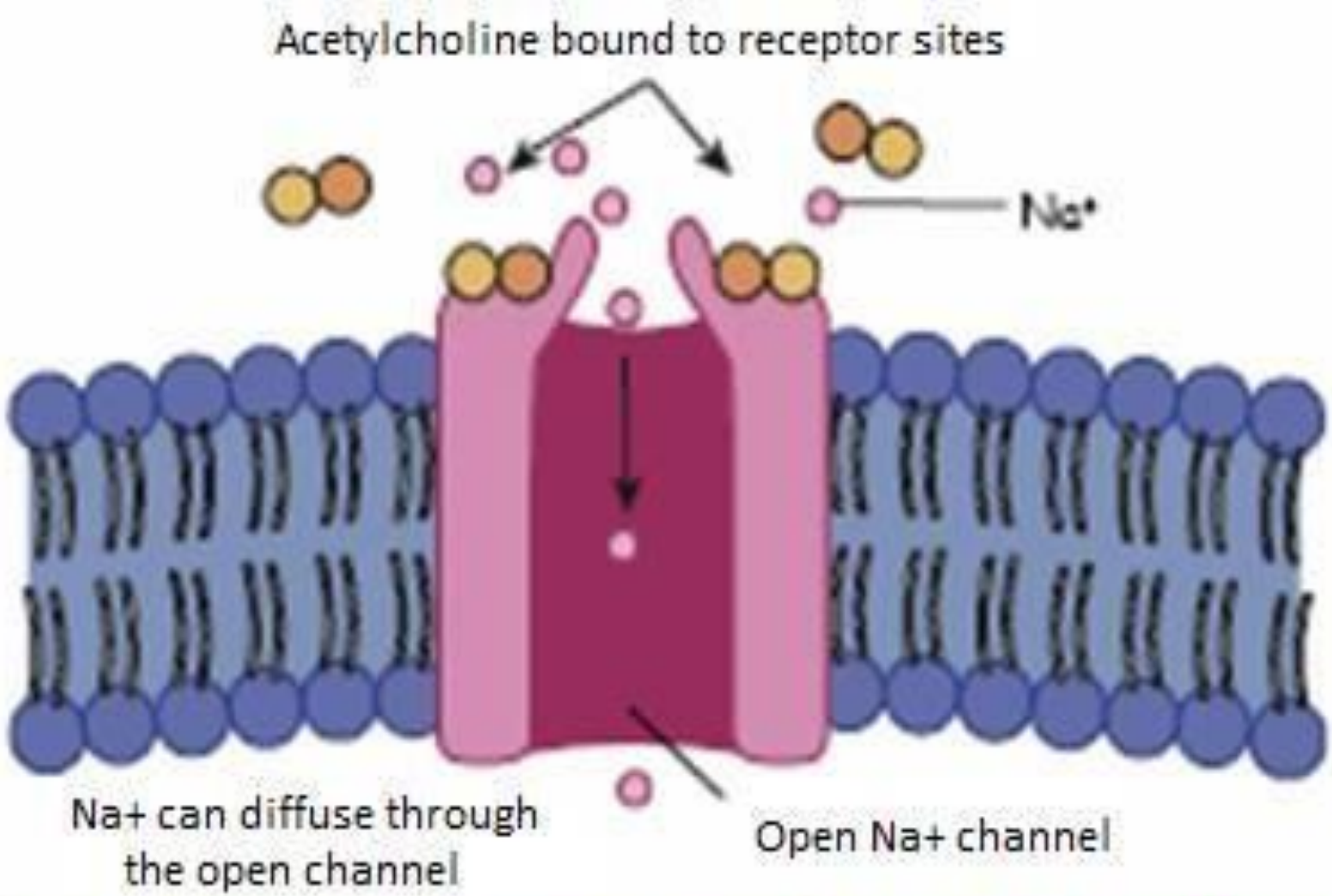


1. Action potentials reach axon terminals
2. Voltage-gated Ca^{2+} channels open
3. Ca^{2+} binds to sensor protein in cytoplasm
4. Ca^{2+}-protein complex stimulates fusion and exocytosis of neurotransmitter


SYNAPTIC CLEFT
Dendrite or cell body
Axon
Receptor molecule
Nerve impulse
Mitochondrion
Presynaptic vesicles
Neurotransmitter molecule
PRESYNAPTIC MEMBRANE
POSTSYNAPTIC MEMBRANE
servingnature

Chemical gated Channels

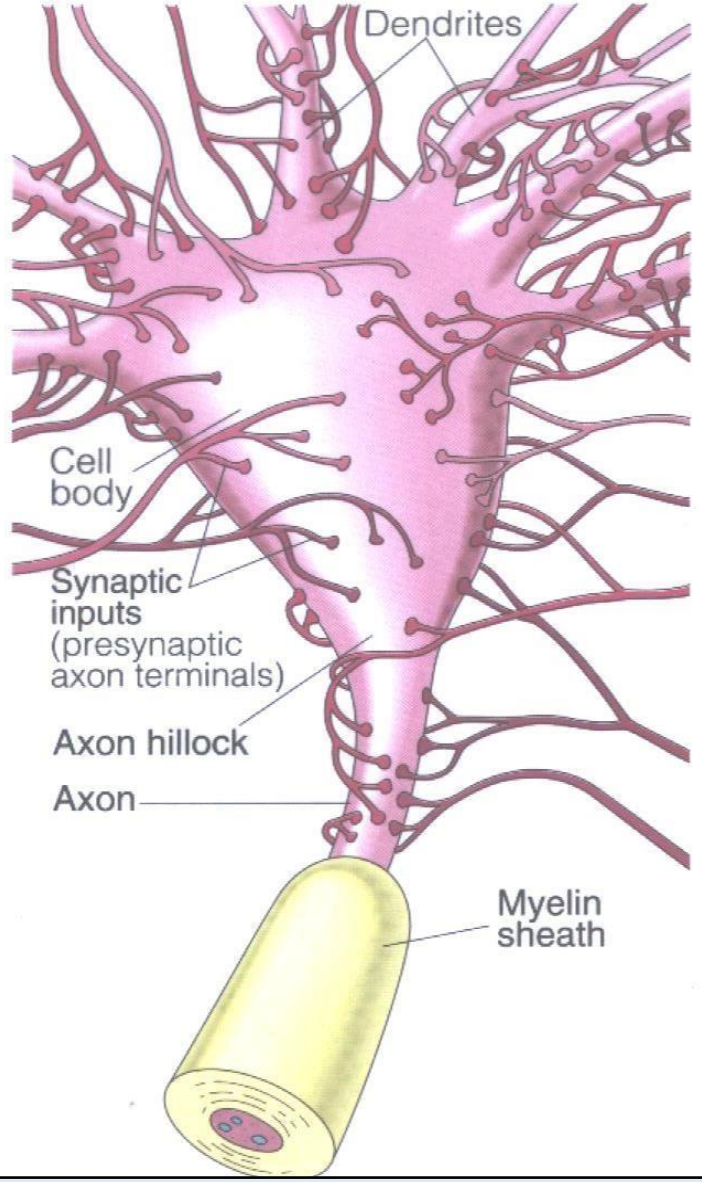


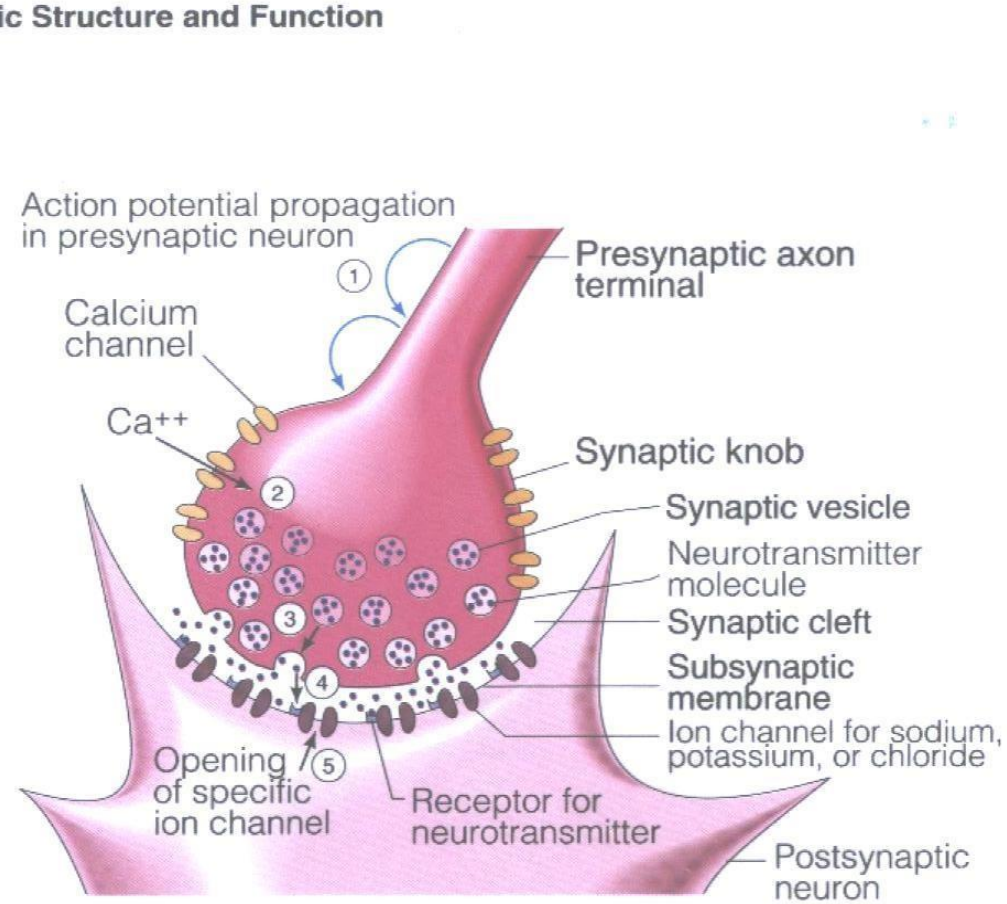


When 2 acetylcholine molecules bind to their receptor sites on the Na+ channel, the channel opens to allow Na+ to diffuse through the channel into the cell

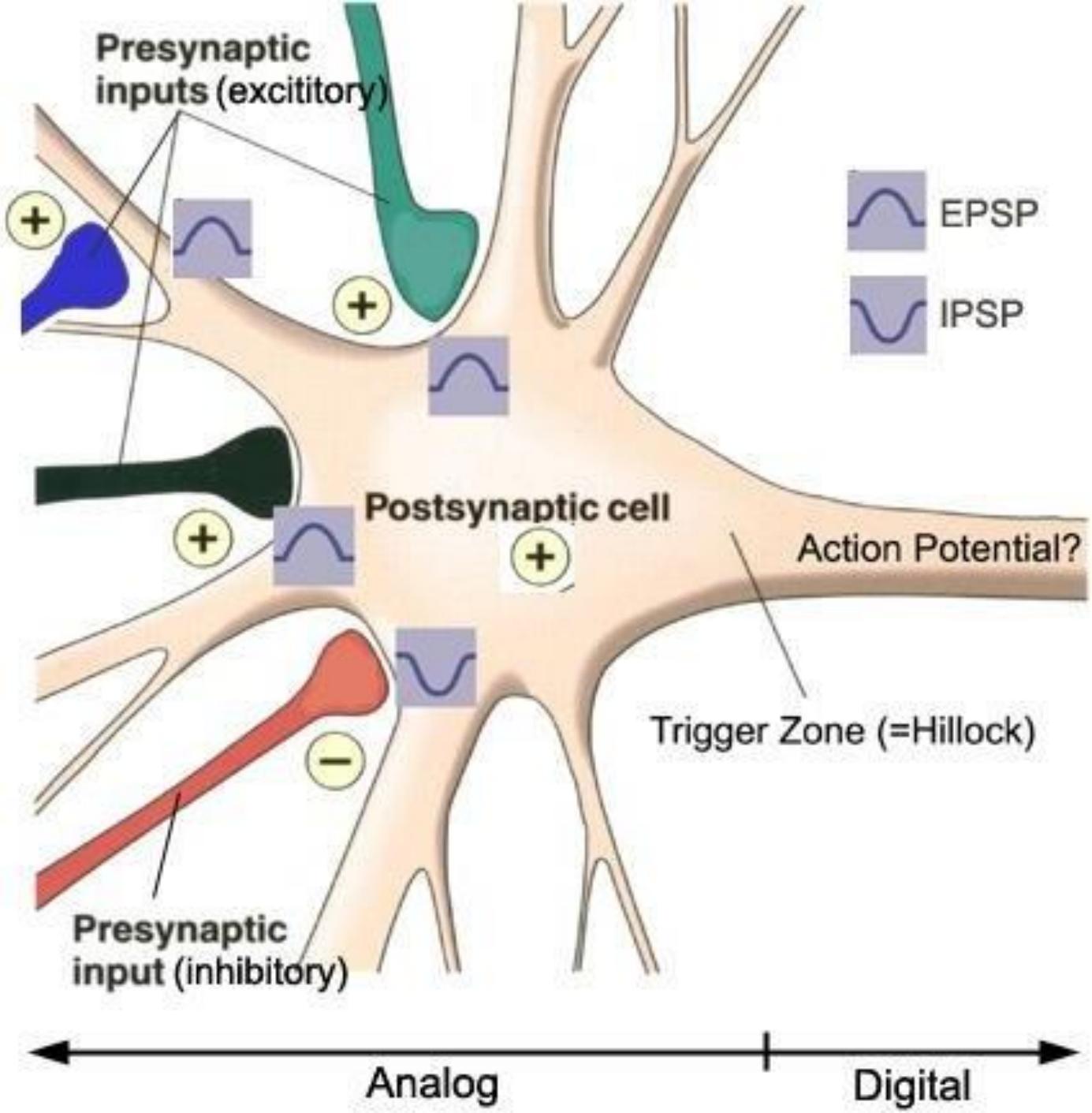
Each one of these terminals may generate excitatory post synaptic potential or inhibitory post synaptic potential, and the total post synaptic potential is the summation of all of them.

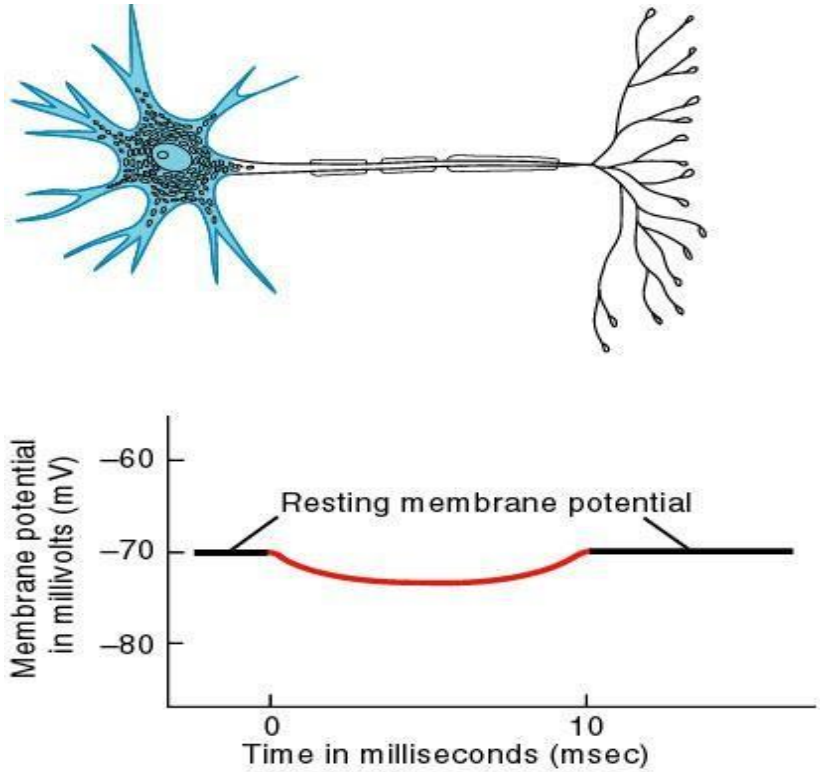
Then if the summation of all these excitatory and inhibitory post synaptic potentials are reaching the threshold, we will have the generation of action potential.



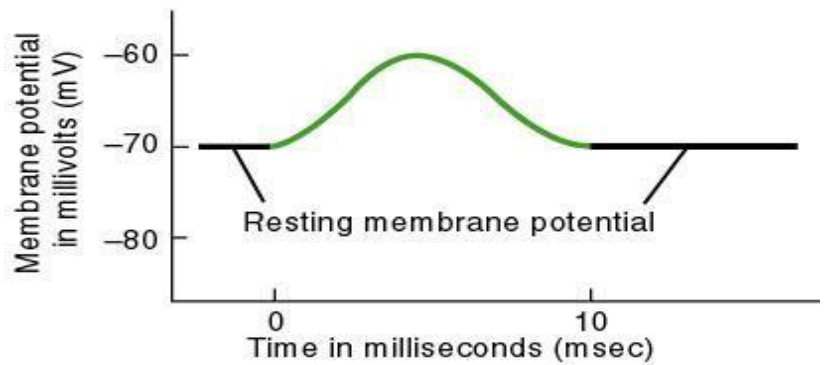


Neuron terminal → opening sodium channels→ Excitatory post synaptic potential.
Neuron terminal → opening of potassium channels → inhibitory post synaptic potential.


Presynaptic
inputs (excititory)
EPSP
IPSP
Postsynaptic cell
Action Potential?
Trigger Zone (=Hillock)
Presynaptic
input (inhibitory)
Analog
Digital

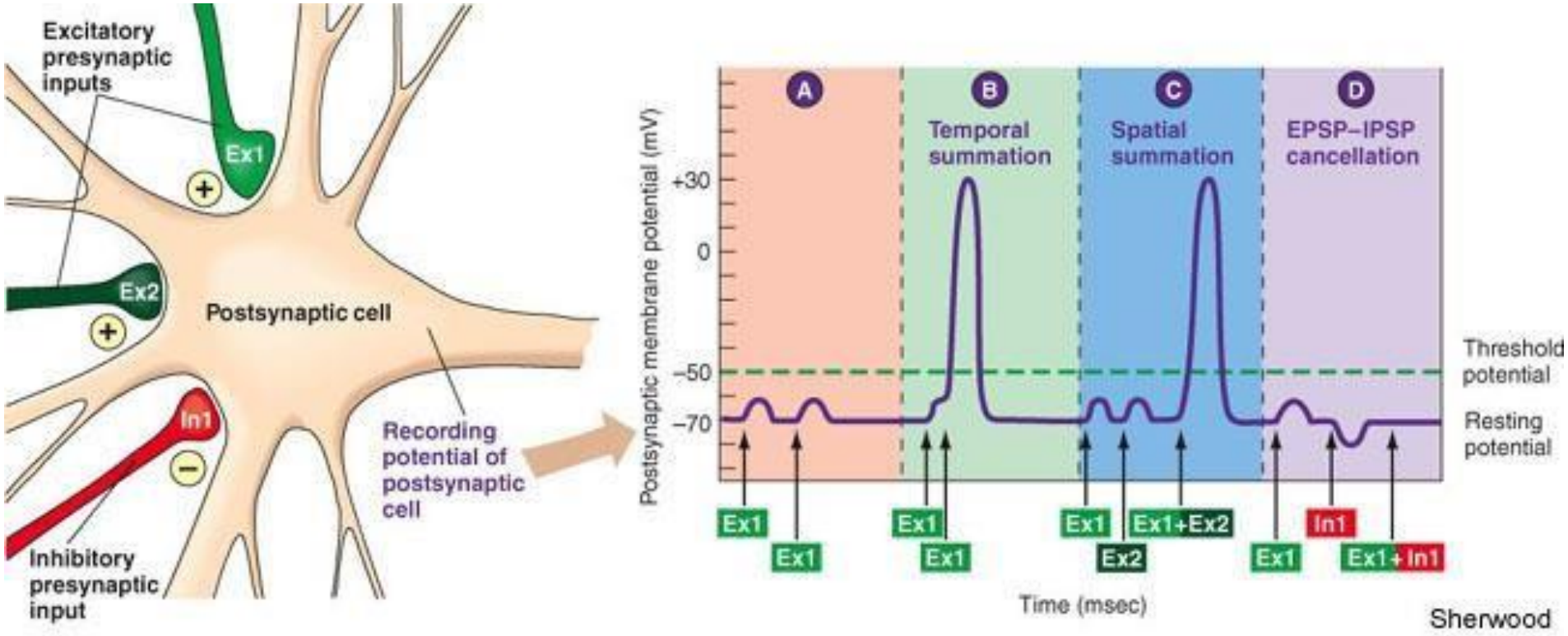


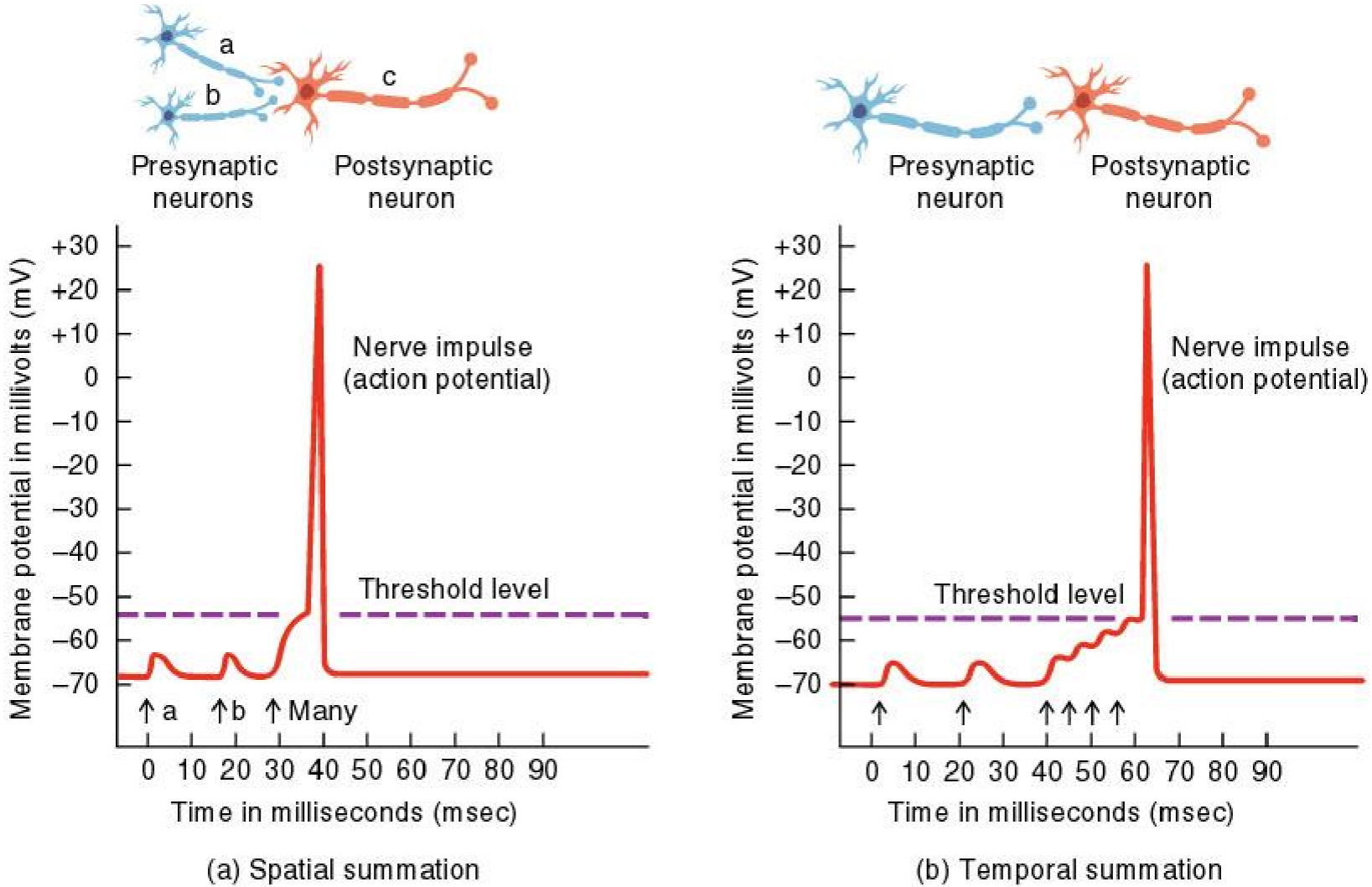
(a) Hyperpolarizing graded potential

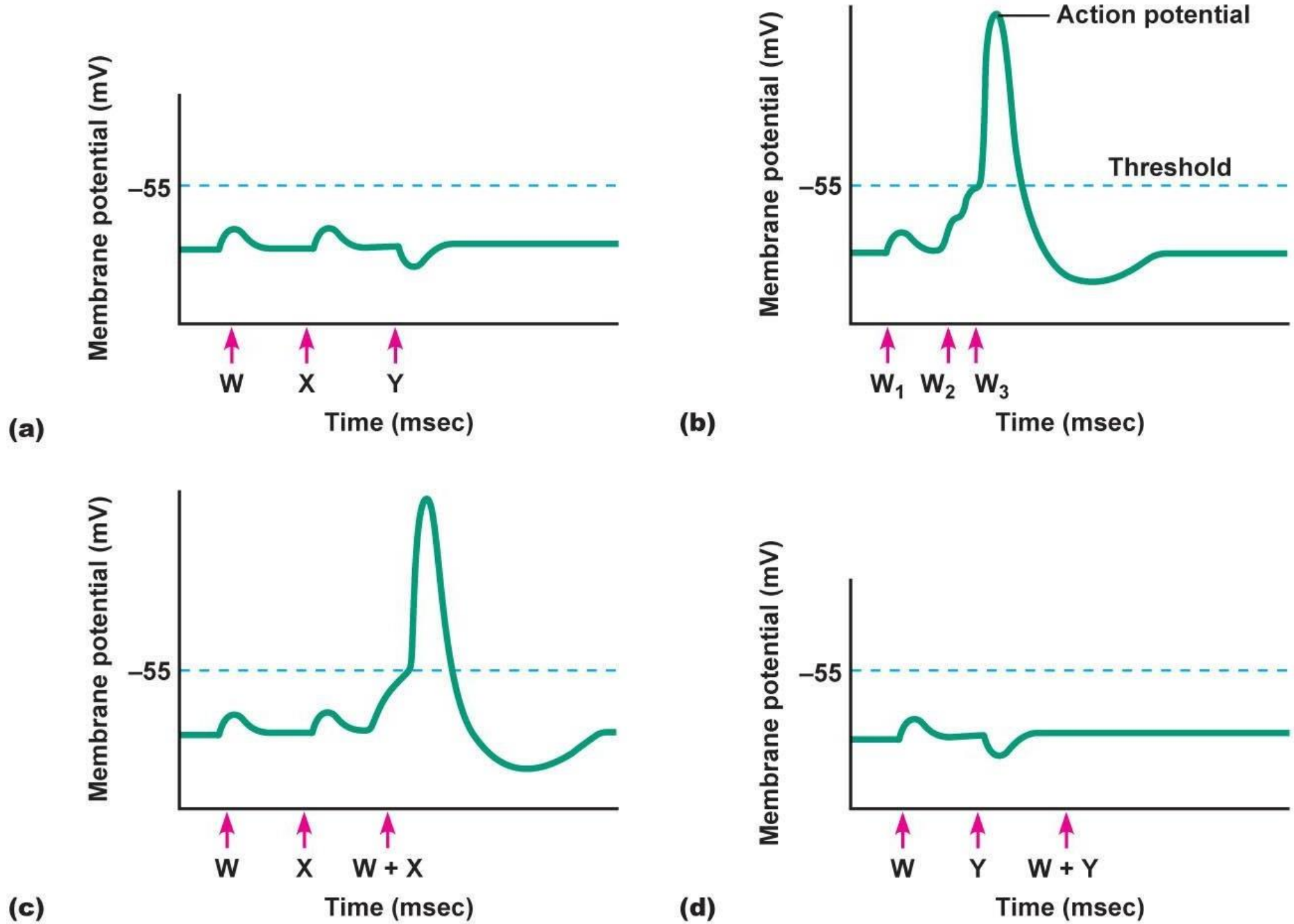


(b) Depolarizing graded potential

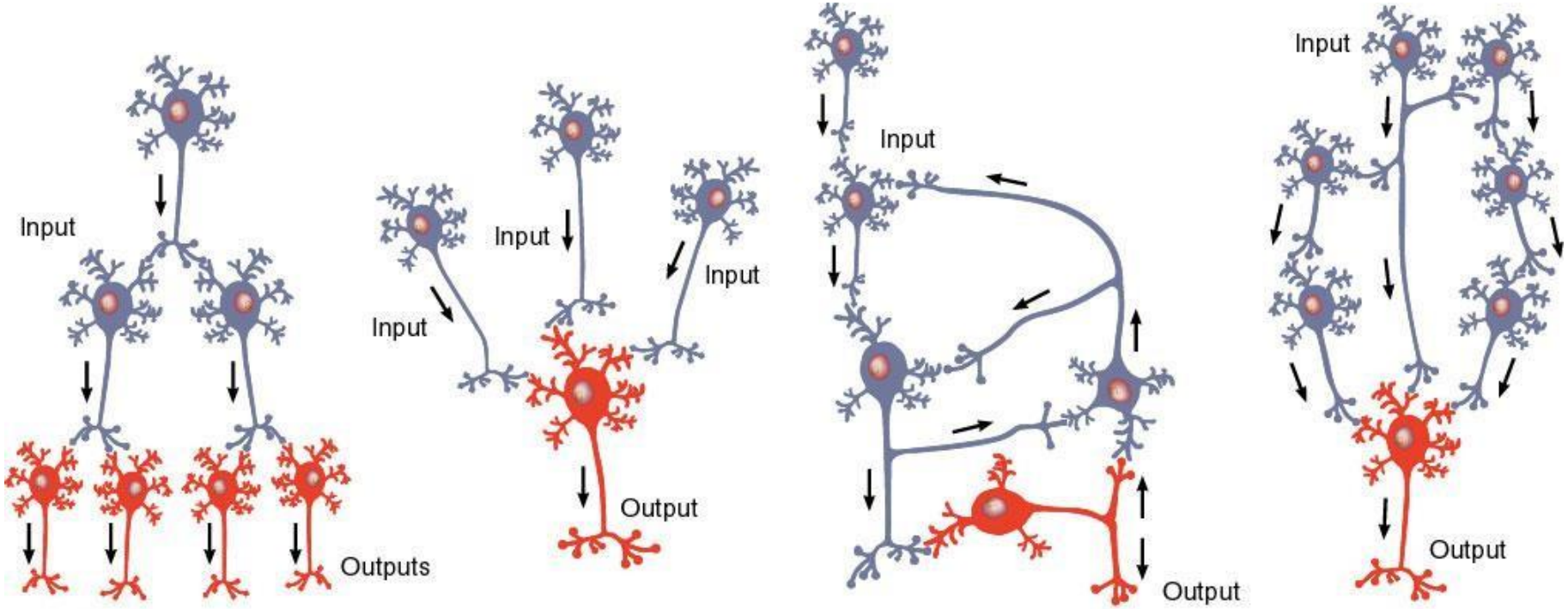
Summation of postsynaptic potentials




a
b
c
Presynaptic neurons
Postsynaptic neuron
Membrane potential in millivolts (mV)
+30
+20
+10
0
–10
–20
–30
–40
–50
–60
–70
Nerve impulse (action potential)
Threshold level
↑a
↑b
↑Many
0 10 20 30 40 50 60 70 80 90
Time in milliseconds (msec)
(a) Spatial summation
Presynaptic neuron
Postsynaptic neuron
Membrane potential in millivolts (mV)
Nerve impulse (action potential)
Threshold level
Time in milliseconds (msec)
(b) Temporal summation



Synaptic organization



(a) Diverging circuit (b) Converging circuit (c) Reverberating circuit (d) Parallel after-discharge circuit

12.16

DR.'S HANDOUT

University of Jordan Faculty of Medicine
Department of Physiology & Biochemistry
Medical students,

Review: Membrane physiology and the basis of excitability

Ref: Guyton, 14th ed. 63-76, Jordan and 13th ed. pp: 61-71. 12th ed. pp: **57-69**,

MEMBRANE POTENTIALS AND ACTION POTENTIALS:

MEMBRANE POTENTIAL:

If we assume that a cellular membrane is permeable **only** to K+, which is found in a very high concentration inside the cell. 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 the membrane (positive outside and negative inside). Creation of this potential difference will oppose diffusion of K+ to the outside at a certain concentration difference. When you reach a point at which diffusion of K+ is completely opposed by the potential difference created across the membrane and the net diffusion for K+ is zero even though you still have a concentration gradient, you have reached the equilibrium potential for K+ (E_K). The equilibrium potential for any univalent ion at normal temperature can be calculated by Nernest equation:

E (mV) = - 61.log (Ci/Co)

E = equilibrium potential for a univalent ion Ci = concentration inside the cell.
Co = concentration outside the cell.

When more ions are involved in creating the potential, we can calculate the potential according to Goldman-Hodgkin-Katz equation.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{Na+}[Na^+]_o + P_{K+}[K^+]_o + P_{Cl-}[Cl^-]_i}{P_{Na+}[Na^+]_i + P_{K+}[K^+]_i + P_{Cl-}[Cl^-]_o} \right)$$

P = permeability of the membrane to that ion.

In this equation, Goldman and his colleagues considered that these ions are mostly involved in the development of membrane potential.

According to this equation, the permeability of the membrane to an ion is very important in determining the membrane potential. If the membrane is permeable only to K+ and not permeable to Cl- and Na+, the membrane potential will be equal to E_{K+}.

Resting membrane potential:

In excitable cells the membrane potential is not constant. When the cell is stimulated, the membrane potential is changing. These changes in membrane potential are due to changes in permeability of plasma membrane to different ions. For example, when a neuron is stimulated, this will result in increased permeability to Na+. This will bring the membrane potential closely to E_{Na}. The recorded membrane potential for a cell under resting conditions when no stimulus is involved is known as **resting membrane potential**. For neurons, the recorded resting membrane potential is about (– 90 mV). This represents a potential difference between the inside to the outside when the neuron is not active.

Origin of resting membrane potential:

Contribution of K+ diffusion:

As mentioned earlier, if the membrane is permeable only for K+ the calculated E_{K+} is about (-94mV).

Co_{K+} = 4meq/l , Ci_{K+} = 140meq/l E_{K+} = -61. log 140/4 = -94mV

Which is not far from the recorded membrane potential but not exactly.

The contribution of Na+ diffusion:

Membrane is also permeable to Na+. The permeability of the plasma membrane for Na+ is much less than that of K+. If the membrane is permeable only to Na+, the calculated E_{Na+} = + 61mV.

…….. (Co_{Na+} = 142meq/l , Ci_{Na+} = 14meq/l).

Because of the permeability of the membrane for the two ions, the E would be between (-94mV and +61mV). The calculated E for the two ions is –86mV, which is not far from the E_{K+} because of the higher permeability of membrane for K+ than for Na+ (100 times more).

So the Na+ contribution in resting potential is by bringing the membrane potential to a lower value than the calculated E_{K+}.

Contribution of Na+ - K+ pump:

As mentioned earlier, this pump is electrogenic. It moves more positive charges outside the cell (3 for 2). This will induce loss of positive charges from the cell and bring the membrane potential to a higher negativity (about –4mV additional negativity).

Therefore all these factors, during **rest**, will give a net membrane potential of –90mV (called **Resting Membrane Potential**).

ACTION POTENTIAL:

As we have seen, the plasma membrane is **polarized** (has ability to separate opposite charges) during resting state. When the membrane potential decreases (becomes less negative), the membrane is in **depolarization** stage. While the change in membrane potential in opposite direction (becomes more negative than resting potential) is known as **hyperpolarization**.

When a cell is depolarizing, it reaches a maximum according to stimulus, then the membrane potential returns to its resting state. The phase of returning from depolarized state to resting state is known as **repolarization**. These changes in membrane potential can be recorded by placing one electrode inside the cell and the other outside the cell. By recording of whole action potential in this way, we will obtain a **monophasic action potential**.

Let us consider the changes in membrane potential of an excitable cell to understand the events that appear during changes of membrane
potential. To induce a change, a stimulus must be applied to change activity of channels at the membrane. Any increase in permeability of membrane to Na+ will result in diffusion of (+) charges inward. This event will decrease the membrane potential (becomes less negative). And
conversely any increase in K+ diffusion (movement outward) will result in an increase in membrane potential (becomes more negative). The diffusion of these ions depends on the activity of Na+ and K+ channels that are found on the membrane. Activation of Na+ channels will induce depolarization, while activation of K+ channels will increase the potential difference across membrane.

Action potential and the role of Na+ channels:

On the membrane, most Na+ channels during resting state are inactive (closed). According to channel type, these channels can be activated by a chemical stimulus (in case of chemical gated channels), electrical stimulus (in case of voltage gated channels), or mechanical stimulus. In the case of chemical gated channels, binding of ligand to its receptor will induce activation of chemical gated Na+ channels. Once activated, the membrane potential will decrease (becomes less negative). Which means that the membrane depolarizes. The voltage changes in the membrane will cause the other type of channels (Na+ voltage gated channels) to be activated. Activation of these channels will cause more changes in membrane potential (more depolarization). More and more depolarization will occur in the membrane by a positive feed back mechanism. If we reach a point at which most voltage gated Na+ channels are activated, this will cause a sudden increase in Na+ permeability. This increase in Na+ permeability will even reverse the membrane potential (becomes positive inside and negative outside) (this is known as the **overshot** in the action potential), because Na+ is trying to approach its equilibrium potential (E_{Na}). At this point, the membrane has reached maximal changes in membrane potential (a peak of an action potential).

As we have seen, during depolarization there is a point at which a sudden increase in Na+ influx which induces rapid and maximal change in membrane potential. This point is known as the **threshold** of an action potential. The rapid change in membrane potential during the raising phase of an action potential is known as **firing stage**. When a stimulus causes a depolarization that brings the membrane potential to the threshold, the membrane will respond by the firing stage of an action potential. If depolarization in the membrane has not reached threshold, the membrane will not enter firing stage, and instead, the potential returns to its resting level. Therefore, the response in the membrane will be either by an action potential when threshold is achieved or no appearance of an action potential when the membrane potential has not reached threshold. For that reason, induction of an action potential in excitable cells follows the **NONE OR ALL PRINCIPLE**.

The voltage changes in membrane potential not only activate voltage dependent Na+ channels, but also inactivate these channels at certain potential difference. This inactivation appears because channels have changed their state from opened channels to closed channels due to voltage changes. The closing event of Na+ channels does not make these

channels as the only responsible for bringing membrane potential to its resting level. But also, activation of voltage dependent K+ channels is the main player in returning the membrane potential to its resting level.

Action potential and K+ channels:

Although there is some leakage of K+ during resting state, which maintains the resting membrane potential close to $E_{K+,}$ depolarization causes activation of voltage gated K+ channels. The activation of these channels is much slower than activation of Na+ channels. This results in a delay in the maximal activation of K+ channels.

The delayed activation of K+ channels combined with inactivation of Na+ channels will result in a rapid returning of the membrane potential to its resting level, causing the **falling phase** in the action potential. The membrane potential may go for a while to more negative potential than during resting potential, which is known as **positive afterpotential** (**after hyperpolarization**). Followed by full recovery in the membrane potential (returns completely to its resting level). The positive after potential is probably due to an excess in K+ efflux, which causes more deficit of positive ions inside the cell.

Action potential and Ca++:

As discussed before, the raising phase of an action potential results by fast activation of Na+ channels. These are called *fast channels*. In some excitable cells, like cardiac muscle and uterine muscle, cells are equipped with another type of channels known as *slow* Na+ – Ca++ *channels*. These channels are activated at slower rate than Na+ channels. The slow and prolonged opening of slow channels will cause mainly Ca++ to enter the cell and prevents the rapid fall induced by activation of K+ channels, and the membrane potential is maintained for a while then the potential falls to its resting level. This is known as a **plateau** in action potential. The presence of plateau in this type of cell is important in prolonging the time of an action potential, giving more time for the cell to be able to respond to another stimulus, because the cell remains longer time in **refractory period**.

Refractory periods of an action potential:

During an action potential, the cell is not able to respond to another stimulus. From the firing stage to the end of the first third of falling phase the cell will not respond at all even by a stronger stimulus. In this stage the cell is said to be in **absolute refractory period**. From the beginning of the second phase until the resting membrane potential is achieved, the cell cannot respond to the usual stimulus, but a stronger stimulus can

change the membrane potential. In this period, the cell is in **relative refractory period**.

The periods depend on the activity of Na+ channels. These channels pass three states during action potential. During resting potential, Na+ channels are **closed but capable for opening** when stimulated. During the raising phase (firing), almost all Na+ channels are **opened**. And any other stimulus (even stronger one) will not cause activation of more Na+ channels. During this period, the membrane is in absolute refractory period.

In the third state, when voltage dependent Na+ channels become closed after the membrane potential has reached positive values. At this state, Na+ channels are not capable for opening. During all the falling phase of an action potential, these channels remain **closed and not capable for opening**. They can pass to the first state (closed and capable for opening) when the membrane potential returns to its normal level or to a more negative potential than resting potential. During this period, the membrane is in relative refractory period. This means that a stronger (suprathreshold) stimulus may activate the closed channels that are not capable for opening by normal stimulation. In addition to the role of voltage gated Na+ channels in establishing the relative refractory period, the presence of widely opened K+ channels during falling phase, which cause excess flow of positive charges to the outside, may also play a role by opposing stimulating signals.

Na+ -K+ pump and action potential:

This pump has **no** role in the electrical activity that are taking place during action potential. But it plays an important role in restoring ionic composition that has been altered during action potential. This role is important in maintaining the ionic composition of the intra- and the extra- cellular fluids.

Nerve Cells (Neurons)

The nervous system is formed of neurons and supportive cells. A neuron, typically consists of 3 basics parts: **cell body, dendrites, and axon** (or nerve fiber). Dendrites are short projections from the cell body, which receive inputs from neighboring neurons. Axon is a long tubular like structure which projects from cone-shaped elevation in the cell body known as **axon hillock** (means small hill). The impulse begins at the junction between axon hillock and the initial segment of axon. Axon ends

into fine processes called axon terminals. Some of these terminals end with a bulb-shape structure called **synaptic end bulb (synaptic knob)**, where neurotransmitter is stored in vesicles and ready for the release.

Many classifications for neurons are known, according to shape, function, neurotransmitter they release, myelination, location…etc.

Supportive cells and function (NEUROGLIA):

Many types of supportive cells around neurons have been described (at least 6). Microglia, Astrtocytes, oligodendrogliocytes have been shown around neurons from the CNS. And glial cells which are similar to astrocytes from the CNS have been described in the neural network of the GI tract.

These cells perform the following functions:

*Maintenance of neural environment.

-uptake of K+ and neurotransmitters from the interstitial fluid around the neurons.

*Synthesize and release neurotrophic factors → maintain the survival and protection of neurons

* Other specialized supportive cells are responsible for myelination of axons. In the CNS these cells are oligodendrogliocytes. In the peripheral nervous system, these cells are known as **Schwan cells**. These cells wrap around axon segments and secrete myelin sheath (a protein lipid complex that insulates nerve fiber). There are gaps in myelin sheaths known as **nodes of Ranvier**, which appear at intervals along axon. These gaps are used for transmission of impulse along myelinated nerve fiber.

TANSMISSION OF ACTION POTENTIAL ALONG NERVE FIBERS:

Once an action potential is generated at the axon hillock, no more triggering events are needed to activate the whole nerve fiber (axon). The generated impulse is conducted along the nerve fiber by one of the followings 2 methods of propagation:

1. Continuous conduction (conduction by local current flow):
   occurs in unmyelinated fibers. Local currents flow between the active area, which is at the peak of action potential and the inactive area, which is still in resting potential. This flow will cause activation of Na+ channels in the inactive area and reduce

the membrane potential to the threshold, which triggers an action potential in this area (that was previously inactive). This process is repeated all along the nerve fiber until the impulse has reached nerve terminals.

2. Saltatory conduction: In myelinated fibers, the impulse skips the myelinated regions in the axon and jumps from one node of Ranvier to the adjacent node. This process ensures faster propagation of an action potential along the myelinated axons (50 times faster than in unmyelinated fibers of the same size). The conduction also involves current flow between two adjacent nodes of Ranvier, which results in activation of Na+ channels in the adjacent node, which is still in resting potential. The process is repeated until the impulse activates the axon terminals.

Note: current flow in both types of conduction is from the **positively charged to the negatively charged regions at both sides of the membrane**, and the membrane has high resistance to the passage of current flow across it (**no** current flow can pass through the membrane).

Not only myelination can influence the velocity of conduction, but also the diameter of nerve fibers. Larger fibers conduct impulse with higher velocity.
Nerve fibers have been classified in (A, which includes as subtypes (α, β, γ, δ) fibers, B, C). The diameter and the velocity of conduction is the highest in Aα, and is the lowest in C fibers.

The importance of refractory periods in conduction:

The presence of refractory periods during action potential is very important in the conduction of impulse. The refractory periods ensure the **one-way (unidirectional)** propagation of action potential. Once an area has developed an action potential, the previous region is still under refractory period (unresponsive area). This area will not develop another action potential. But the following area that is at resting potential is capable to initiate an action potential.

SYNAPSES AND INTEGRATION OF RESPONSES:

Synapses:

Neuron may terminate at one of three structures: a neuron, a muscle, or a gland. The junction between 2 neurons is known as a synapse. The first neuron ends with end bulb (**synaptic knob**), where neurotransmitters are stored in vesicles and ready for the release. The membrane of the synaptic knob is known as **presynaptic membrane**. When secretory vesicles fuse with the presynaptic membrane, they release their content into a small space between two membranes known as the **synaptic cleft**. The released transmitters act on the second neurons by binding to their receptors at the second membrane, which is called **postsynaptic membrane** (**subsynaptic membrane**).

Synapses operate in one direction. Transmit signals from one neuron to an adjacent neuron. When the impulse from the presynaptic neuron reaches the synaptic knob, this will cause activation of voltage dependent Ca++ channels. This will result in Ca++ diffusion into the synaptic knob. The increase in Ca++ concentration inside the axon terminal will trigger the release of neurotransmitter from vesicles into synaptic cleft by a process of exocytosis. Inactivation of synaptic knob by inhibitory inputs that may synapse with the membrane at the nerve terminal may induce inhibition of the release of transmitter. This inhibition that appears at this site reduces the effectiveness of transmission in the synapse. This type of inhibition is known as presynaptic inhibition.

Once released, neurotransmitter binds to its receptor at the postsynaptic membrane. According to transmitter – receptor combination, this will induce either a decrease in membrane potential (depolarization) or increase in membrane potential (hyperpolarization). When there is a decrease in membrane potential, the developed postsynaptic potential is called **EPSPs** (**E**xcitatory **P**ost **S**ynaptic **P**otentials), while the increase in membrane potential is called **IPSPs** (**I**nhibitory **P**ost **S**ynaptic **P**otentials). After inducingthe appropriate response at the postsynaptic membrane, the transmitteris inactivated or removed, leaving the postsynaptic membrane ready to receive additional messages from the same presynaptic membrane. The inactivation of transmitter takes place by postsynaptic membrane bound enzymes. An example of these enzymes is *acetylcholine esterase*, which destroys acetylcholine (Ach) into acetyl and choline molecules, which then transported back to the synaptic knob, where they combine again to form new Ach molecules. Some types of transmitters are transported back, without inactivation, into

synaptic knob. Conditions that alter the activity of destroying enzyme, uptake of transmitter by nerve terminal, or induce release of high concentration of transmitter (presynaptic facilitation) alter the activity of synapse by prolonging the activation of receptors at the postsynaptic (subsynaptic) membrane. In addition to that, some drugs may combine with receptor and prevents binding of transmitter to its receptor. These drugs are known as **blockers**. An example of these is hexamethonium, which can bind to acetylcholine (Ach) receptor at postsynaptic membrane and prevents Ach from binding. This will inhibit transmission induced by Ach neurons.

The EPSPs are not action potentials. They are small depolarization (subthreshold potential) that can be induced by activation of few Na+ channels.

The IPSPs are usually induced by activation of K+ channels.

Which result in efflux of K+ and change in the membrane potential to more negative potential. Some transmitters activate Cl- channels, the activation of these channels will not induce hyperpolarization (during rest, neural cell is near the E_{cl}, and the opening of Cl- channels will not induce inward diffusion of Cl-). But this activation is inhibitory on neural activity. This inhibition is achieved by holding the membrane at its resting potential and preventing depolarization.

The time it takes for a signal from the first neuron to induce changes in membrane potential in the second neuron is known as **synaptic delay**.

Integration of responses at postsynaptic membrane:

Usually, the complexity of neural network connections permit synapsing of many axonal terminals from different neurons to one neural cell body (called **convergence**), and branching of one nerve fiber to many terminals that synapse to different neurons (**divergence**). This complexity results in converting the signal from one neuron to many postsynaptic neurons in the case of divergence, and many inputs from presynaptic neurons can be received by a single postsynaptic neuron in the case of convergence.

As mentioned before, one stimulus may induce depolarization or hyperpolarization at the postsynaptic membrane. The induced depolarization is not an action potential, but it is a subthreshold potential. The action potential will develop only when the threshold is achieved. In a neural network, to have subthreshold potentials eliciting an action potential, **summation** (two depolarizations can sum to elicit a higher

depolarization) must take place between responses at the postsynaptic membrane.

Two types of summation are known at the postsynaptic membrane.

Spatial summation appears when 2 or more responses from 2 or more different neurons have appeared simultaneously (at the same time) at the same site of postsynaptic membrane, which result in summing of these responses into a final response. This summation can take place between 2 or more IPSPs to elicit more hyperpolarization, two or more EPSPs to elicit more depolarization in the membrane, or between excitatory and inhibitory potentials which results in cancellation of potentials and induce postsynaptic inhibition.

The second type of summation is called **temporal summation**. Appears when 2 or more postsynaptic potentials, which were elicited by **one** presynaptic neuron at different times, sum to induce more depolarization in the membrane potential. In this case, the repetitive excitation of postsynaptic membrane from a single input induces a higher depolarization that may elicit an action potential at the postsynaptic membrane.

Recordings of action potential:

Recording of **monophasic action potential** is by placing one electrode inside the cell and the other electrode outside the cell. While a different configuration of an action potential can be obtained by placing the two electrodes outside the cell membrane. The later recording is known as **biphasic action potential**. Two waves are obtained in the recording of biphasic action potential, the first represents depolarization, and the second is in the reverse direction of the first and represents repolarization.

Additional Resources:

Reference Used:

1. Guyton and Hall Textbook of Medical Physiology, 13th Edition.
2. Dr.'s Lecture.
3. Dr.'s Handouts.

Extra References for the Reader to Use:

1. Ninja Nerd (Action Potential).

رسالة من الفريق العلمي:

عن أبي سعيد الخدري رضي الله عنه قال إنهم غزوا مع رسول الله ﷺ في رمضان، فكان منهم الصائم ومنهم المفطر، ولم يعب أحدٌ على أحد.

هذا المشهد وحده كافٍ ليعيد ترتيب أفكارنا.

في رمضان كانوا في ساحات القتال، في حرّ السفر، في مواجهة الخطر، ومع ذلك لم يكن الشهر عذرًا للتراجع ولا سببًا للكسل .كان رمضان يزيدهم قوةً وانضباطًا، لا شكوى وتذمّرًا.

أما اليوم ...نرى من يتأفف من دوامٍ مكيف، أو محاضرةٍ لساعتين، أو امتحانٍ يمكن تأجيله بالمذاكرة الجيدة .

وكأن رمضان أصبح موسم أعذار لا موسم إنجاز.

الحقيقة أن رمضان لا يُنقص من إنتاجيتنا، بل يباركها إذا صحّت النية .حين ينوي الإنسان دراسته لوجه الله، وأن يتقوّى بعلمه لخدمة دينه وأهله وناسه، تتحول ساعات المذاكرة إلى عبادة، ويصبح الجهد في ميزان الحسنات.

مزاحمة الطاعات لا تضيع الوقت، بل تزيده بركة .من جرّب تنظيم يومه بين صلاةٍ وذكرٍ ودراسة في رمضان، يعلم أن الإنجاز فيه يختلف، وأن التركيز فيه أصفى، وأن الشعور بالرضا أعمق.

رمضان مدرسة صبرٍ وانضباط، وليس شهر تعطيل للحياة .فمن استطاع أن يجاهد نفسه عن الطعام والشراب ساعاتٍ طويلة، فهو قادر أن يجاهدها عن الكسل والتسويف.

أسأل الله أن يعيننا و اياكم على استغلال كل ثانية في هذا الشهر لطاعته وإجتناب نواهيه ويبارك لنا فيه وأن يجعلنا من عتقاء هذا الشهر المبارك

واغفر لنا ولوالدينا ومن نحب، واجعل لنا في كل يومٍ من رمضان نصيبًا من الرحمة والمغفرة والبركة.

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