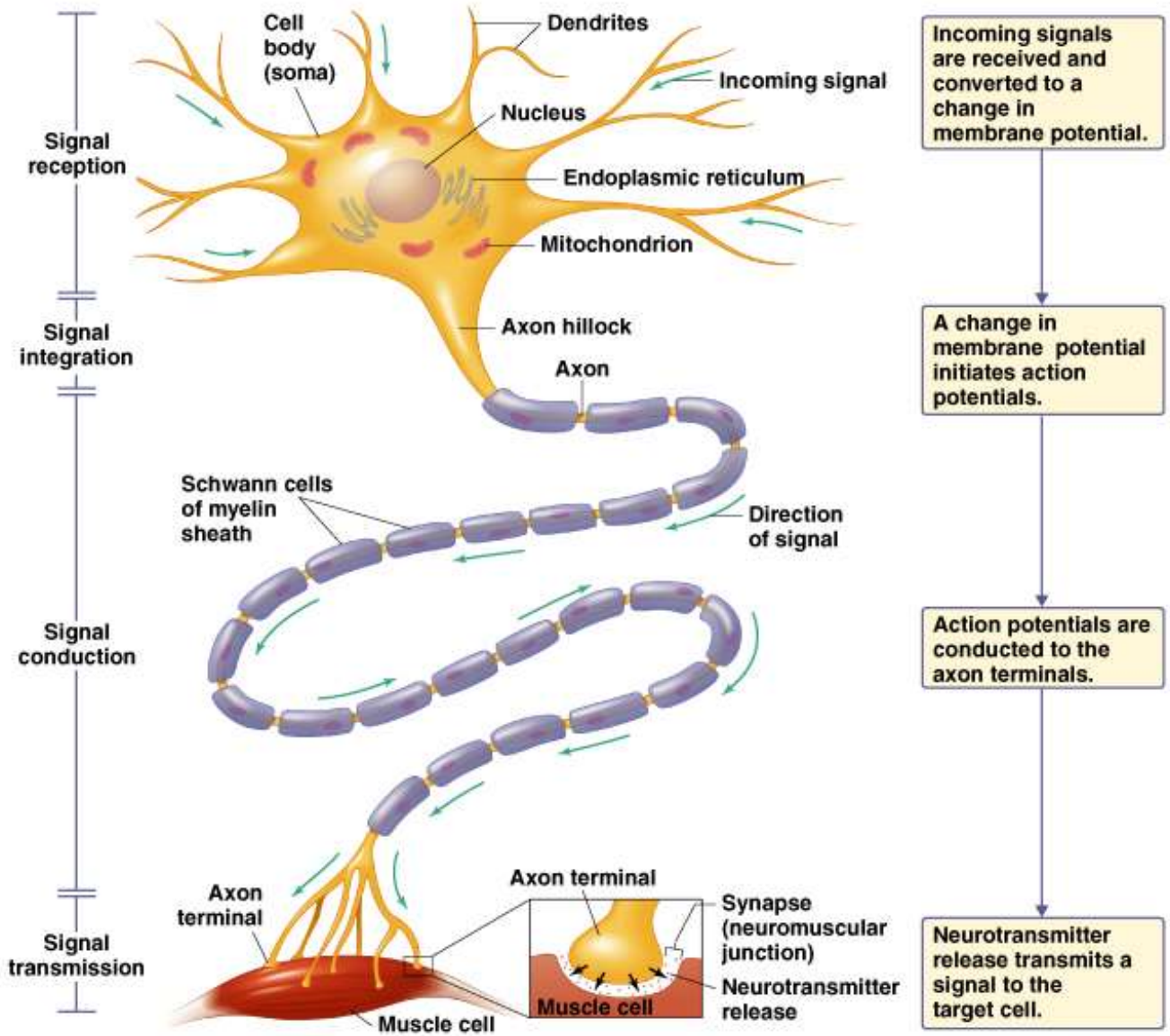
Excitable Tissue

- The nervous system coordinates the activities of many other organ systems. The nervous system
- activates muscles for movement,
- controls the secretion of hormones from glands,
- regulates the rate and depth of breathing, and
- is involved in modulating and regulating a multitude of other physiological processes.

- To perform these functions, it relies on neurons, which are designed for the rapid transmission of information from one cell to another by conducting electrical impulses and secreting chemical neurotransmitters.
- The electrical impulses travel along the length of nerve fiber processes to their terminals
- Here, they initiate a series of events that cause the release of chemical neurotransmitters.
- Release of neurotransmitters occurs at sites of synaptic contact between two nerve cells.

- Released neurotransmitters bind with their receptors on the postsynaptic cell membrane
- Activation of receptors either excites or inhibits the postsynaptic neuron.
- The propagation of action potentials,
- The release of neurotransmitters, and
- The activation of receptors constitute the means whereby nerve cells communicate and transmit information to one another and to non-neuronal tissues.

- Neurons communicate by a combination of electrical and chemical signaling.
- Generally, information is integrated and transmitted along the processes of a single neuron electrically and then transmitted to a target cell chemically.
- The chemical signal then initiates an electrical change in the target cell.
- Electrical signals that depend on the passive properties of the neuronal cell membrane spread electrotonically over short distances.
- These potentials are initiated by local current flow and decay with distance from their site of initiation.


Signal reception
Signal integration
Signal conduction
Signal transmission
Cell body (soma)
Dendrites
Incoming signal
Nucleus
Endoplasmic reticulum
Mitochondrion
Axon hillock
Axon
Schwann cells of myelin sheath
Direction of signal
Axon terminal
Axon terminal
Synapse (neuromuscular junction)
Neurotransmitter release
Muscle cell
Muscle cell
Incoming signals are received and converted to a change in membrane potential.
A change in membrane potential initiates action potentials.
Action potentials are conducted to the axon terminals.
Neurotransmitter release transmits a signal to the target cell.

- Alternatively, an action potential is an electrical signal that propagates over a long distance without a change in amplitude.
- Action potentials depend on a regenerative wave of channel openings and closings in the membrane

- The shape of a nerve cell is highly specialized for reception and transmission of information.
- One region of the neuron is designed to receive and process incoming information; another is designed to conduct and transmit information to other cells.
- The type of information that is processed and transmitted by a neuron depends on its location in the nervous system.
- For example:
- Nerve cells associated with visual pathways convey information about the external environment, such as light and dark, to the brain;

- Neurons associated with motor pathways convey information to control the contraction and relaxation of muscles for walking.

- Regardless of the type of information transmitted by neurons, they transduce and transmit this information via similar mechanisms.
- The mechanisms depend mostly on the specialized structures of the neuron and the electrical properties of their membranes.
- Emerging from the soma (cell body) of a neuron are processes called dendrites and axons

- Many neurons in the central nervous system (CNS) also have knob-like structures called dendritic spines that extend from the dendrites.
- The dendritic spines, dendrites, and soma receive information from other nerve cells.
- The axon conducts and transmits information and may also receive information.
- Some axons are coated with myelin, a lipid structure formed by glial cells (oligodendrocytes in the CNS or Schwann cells in the peripheral nervous system, the PNS).
- Regular intermittent gaps in the myelin sheath are called nodes of Ranvier.

- The speed with which an axon conducts information is directly proportional to the size of the axon and the thickness of the myelin sheath.
- The end of the axon, the axon terminal, contains small vesicles packed with neurotransmitter molecules.

- The site of contact between a neuron and its target cell is called a synapse.
- When a neuron is activated, an action potential is generated in the axon hillock (or initial segment) and conducted along the axon.
- The action potential causes the release of a neurotransmitter from the terminal.
- These neurotransmitter molecules bind to receptors located on target cells.

- The binding of a NT to its receptor typically causes a flow of ions across the membrane of the postsynaptic cell.
- This temporary redistribution of ionic charge can lead to the generation of an action potential, which itself is mediated by the flow of specific ions across the membrane.
- These electrical charges, critical for the transmission of information, are the result of ions moving through ion channels in the plasma membrane

Channels Allow Ions to Flow Through the Nerve Cell Membrane

- Ions can flow across the nerve cell membrane through three types of ion channels:
- nongated (leakage), ligand-gated, and voltage-gated
- Non-gated ion channels are always open.
- They are responsible for the influx of Na and efflux of K when the neuron is in its resting state.
- Ligand-gated ion channels are directly or indirectly activated by chemical neurotransmitters binding to membrane receptors.
- In this type of channel, the receptor itself forms part of the ion channel or may be coupled to the channel via a G protein and a 2^{nd} messenger.

- When chemical transmitters bind to their receptors, the associated ion channels can either open or close to permit or block the movement of specific ions across the cell membrane.
- Voltage-gated ion channels are sensitive to the voltage difference across the membrane.
- In their initial resting state, these channels are typically closed; they open when a critical voltage level is reached

- Each type of ion channel has a unique distribution on the nerve cell membrane.
- Non-gated ion channels, important for the establishment of the resting membrane potential, are found throughout the neuron.
- Ligand-gated channels, located at sites of synaptic contact, are found predominantly on dendritic spines, dendrites, and somata.
- Voltage-gated channels, required for the initiation and propagation of action potentials or for neurotransmitter release, are found predominantly on axons and axon terminals

- Next slide gives the approximate concentrations of important electrolytes and other substances in the *extracellular fluid* and *intracellular fluid*
- Note that ECF contains a lot of Na^+ small amount of K^+
- Opposite is true of the intracellular fluid lots of K^+ and less Na^+

Concentration of important ions

ECF

Cations:

Na^+ ($142_{mmol/L}$)

K^+ (4.2)

Mg^{2+} (0.8)

Anions:

Cl^- (108)

HCO_3^- (24)

Nutrients:

O_2, glucose, fatty acids, & amino acids.

Wastes:

CO_2, Urea, uric acid, excess water, & ions.

ICF

Cations:

Na^+ (14)

K^+ (140)

Mg^{2+} (20)

Anions:

Cl^- (4)

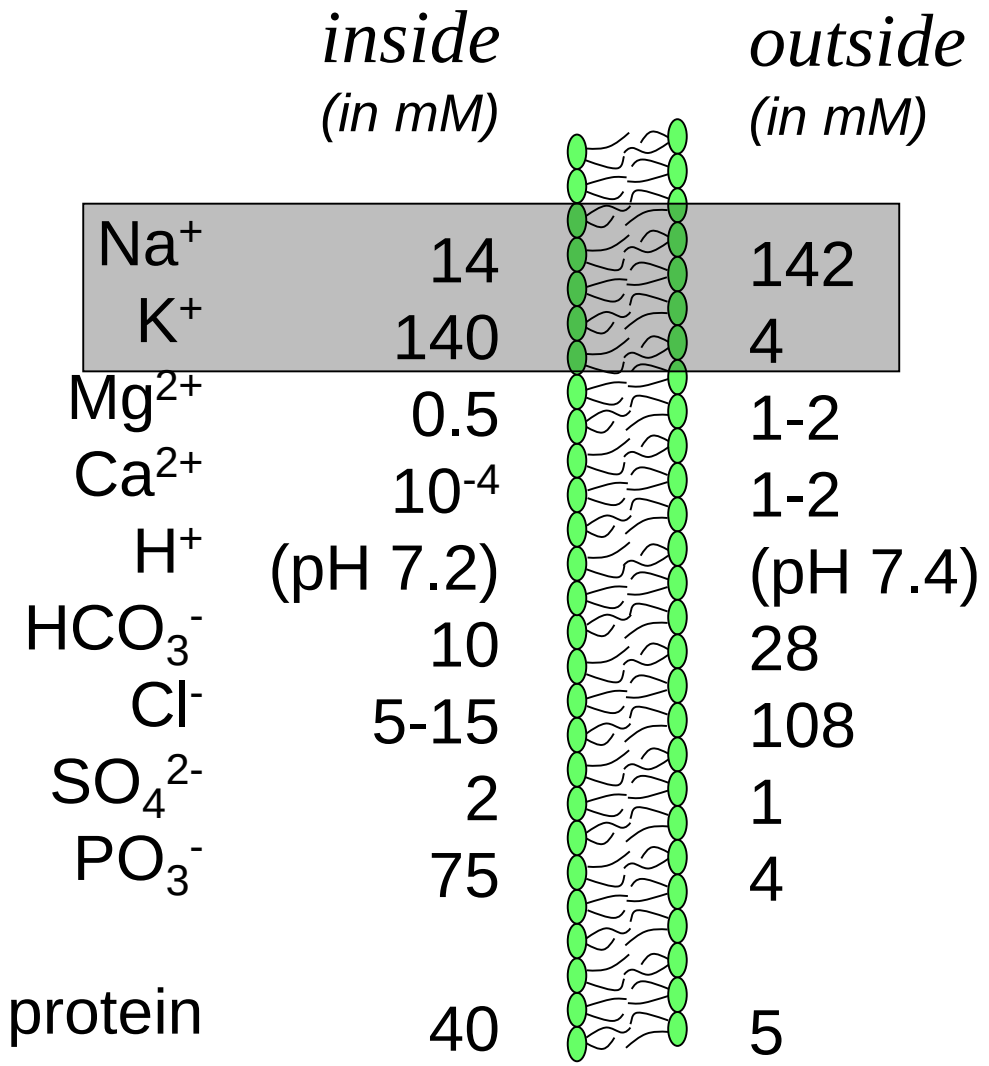
HCO_3^- (10)

Phosphate ions

Nutrients:

High concentrations of proteins.

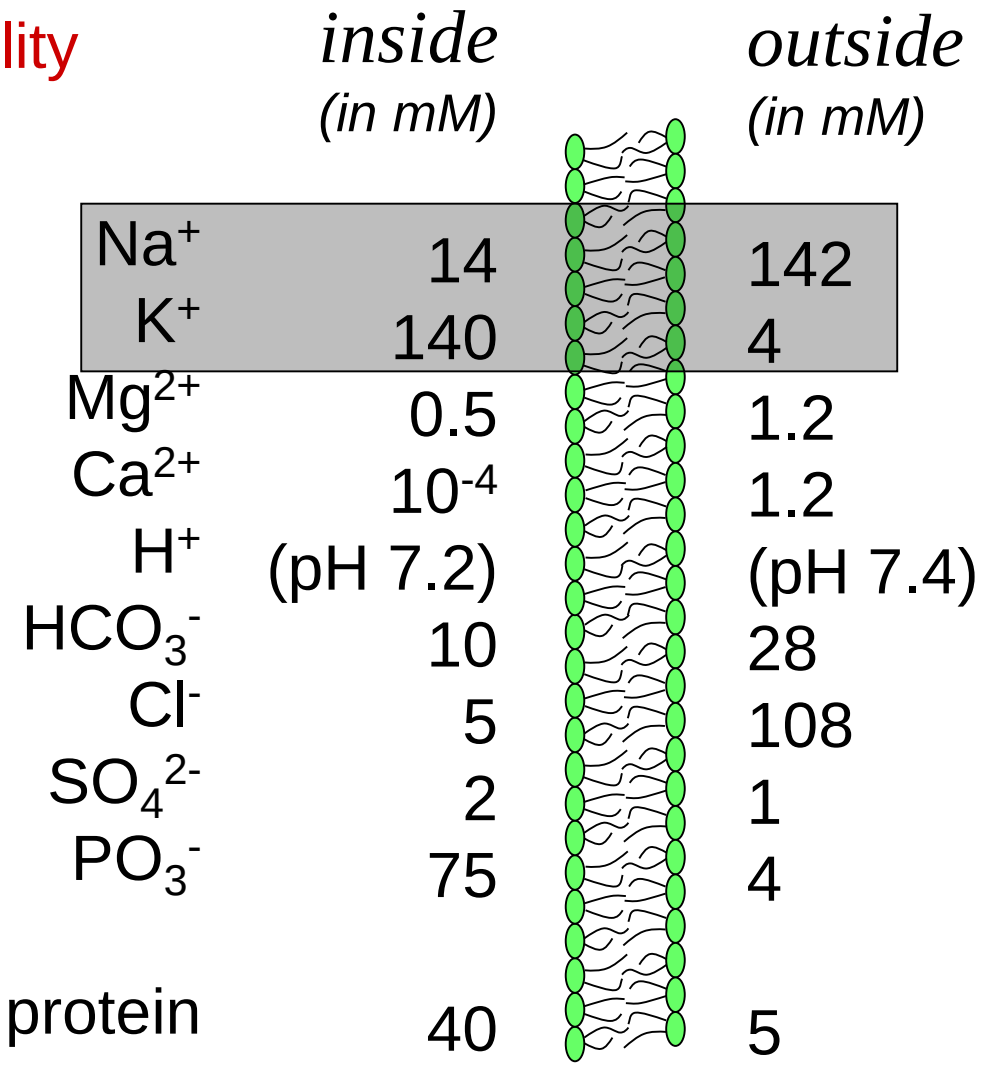
- ECF also has lots Cl^- ions whereas ICF has lots of Phosphates and proteins.
- Differences are extremely important to the life of the cell.


inside
(in mM)
outside
(in mM)
Na+
K+
Mg2+
Ca2+
H+
HCO3-
Cl-
SO42-
PO3-
protein
14
140
0.5
10-4
(pH 7.2)
10
5-15
2
75
40
142
4
1-2
1-2
(pH 7.4)
28
108
1
4
5

“Sidedness” of the membrane and some reasons why

Different permeability
Pumps
Protein channels

Remember to ask:
Is there a gradient?
Can it diffuse?
If allowed to diffuse, which way would it go?



Membrane potential caused by Diffusion

- K^+ conc'n is high inside a nerve fiber membrane and low outside
- Assume that membrane only permeable to K^+ only but no other ions
- Due to high conc'n gradient of K^+ from inside to outside, there is a strong tendency for extra no. of K^+ ions to diffuse outwards through the membrane
- As they do so, they carry +ve electrical charge to the outside , creating electropositivity to the outside and electronegativity to the inside because of the –ve anions that remain behind and do not diffuse with the K^+

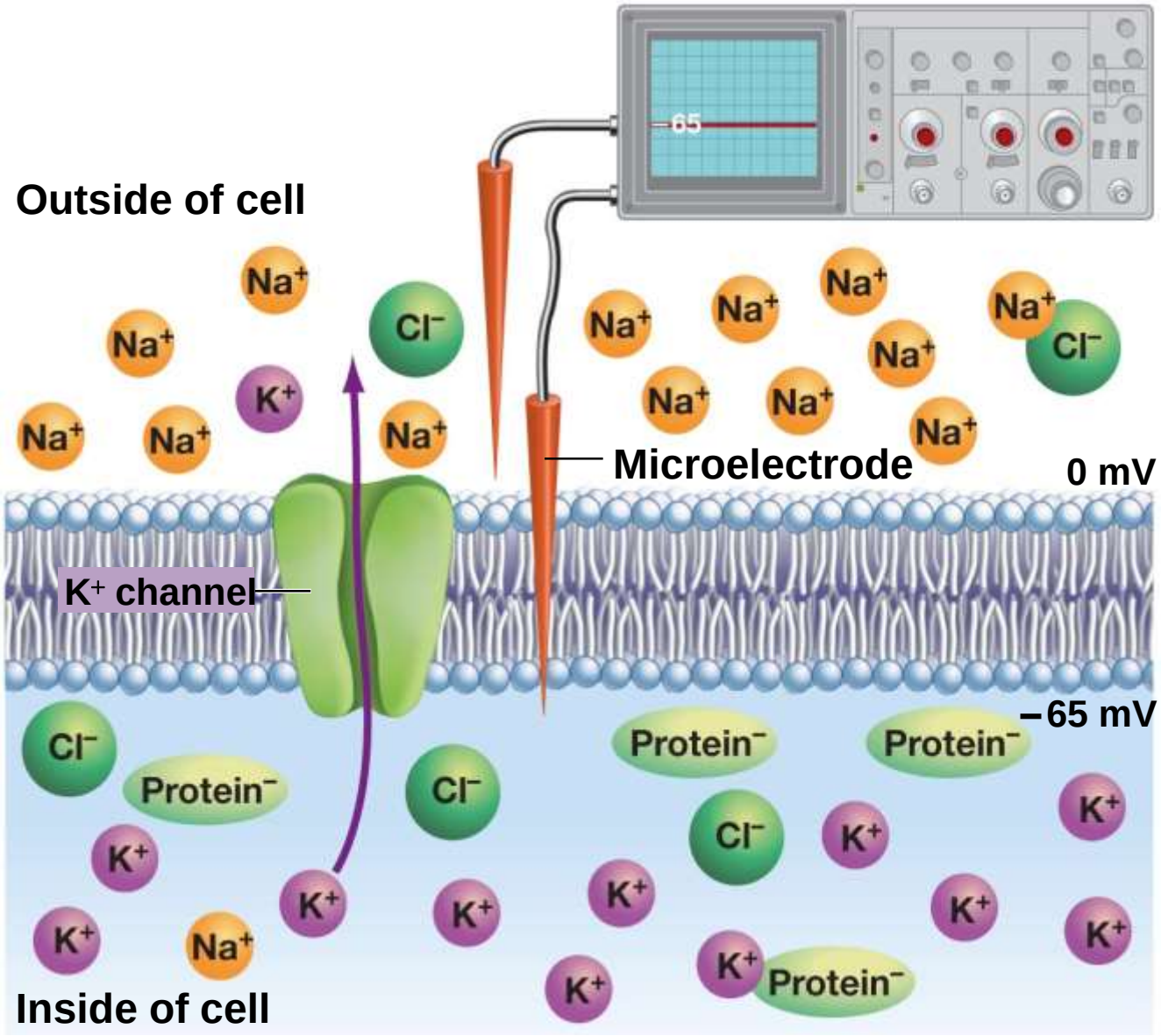
- As K leaves the cell, it takes a positive charge outside with it, so the inside is more negative.
- However, as the inside of the cell is becoming more negative, the outside of the cell is becoming more positive, the positive charges will want to flow back inside of the cell since they are attracted to the negative charges.
- 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.

- This is electrical potential that counters Net diffusion of K.
- In the normal mammalian nerve fiber, the potential difference required is about 94 millivolts, with negativity inside the fiber membrane.
- The electrical potential that counters net diffusion of K^+ is called the K^+ equilibrium potential (E_K).
- The equilibrium potential of K^+ is minus 94 mV
- So, if the membrane were permeable only to K+, Vm would be -94 mV (cell death from equilibrium)

Increasing [K+] outside the neuron

Equilibrium!

Increasingly negative charge inside the neuron

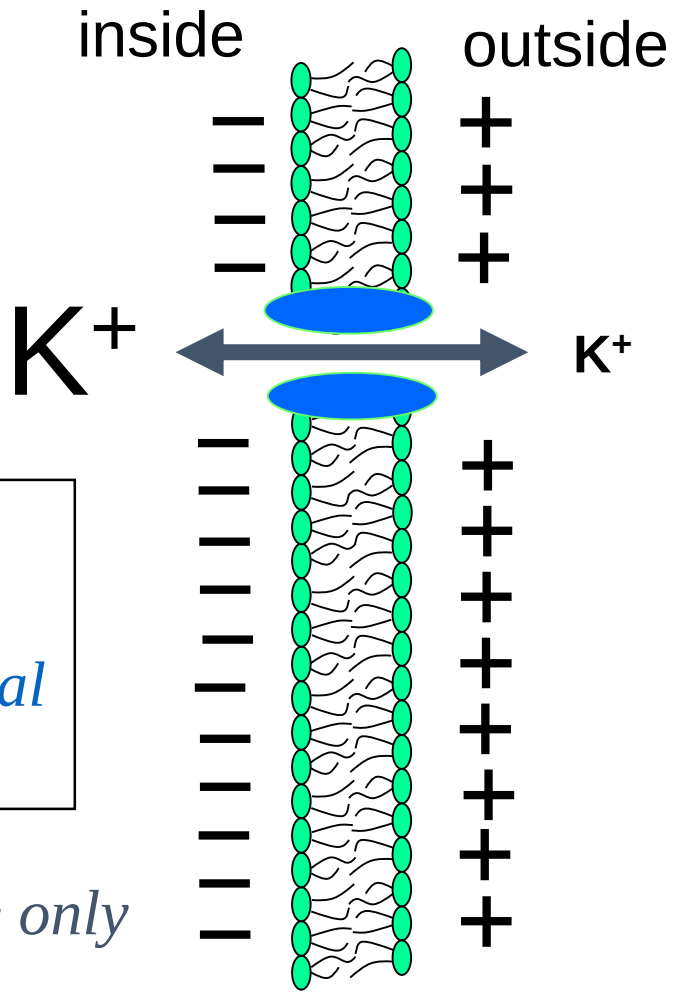


- The diffusion potential level across a membrane that exactly opposes the net diffusion of a particular ion through the membrane is called the Nernst potential for that ion.

$$\text{EMF (millivolts)} = \pm 61 \log \frac{\text{Concentration inside}}{\text{Concentration outside}}$$

Simplest Case Scenario:

If a membrane were permeable to only K^+ then…



The electrical potential that counters net diffusion of K^+ is called the K^+ equilibrium potential (E_K).

So, if the membrane were permeable only to K+, Vm would be -94 mV

- In case membrane only permeable to Na^+, then the reverse would occur with the Na^+ moving to the inside due to conc'n gradient carrying +ve charges to the inside hence leaving the outside more electronegative and the inside more electropositive.
- Again the membrane potential rises high within milliseconds to block further diffusion of Na^+ ions to the interior.
- The potential is about 61 mv with positive inside fiber.

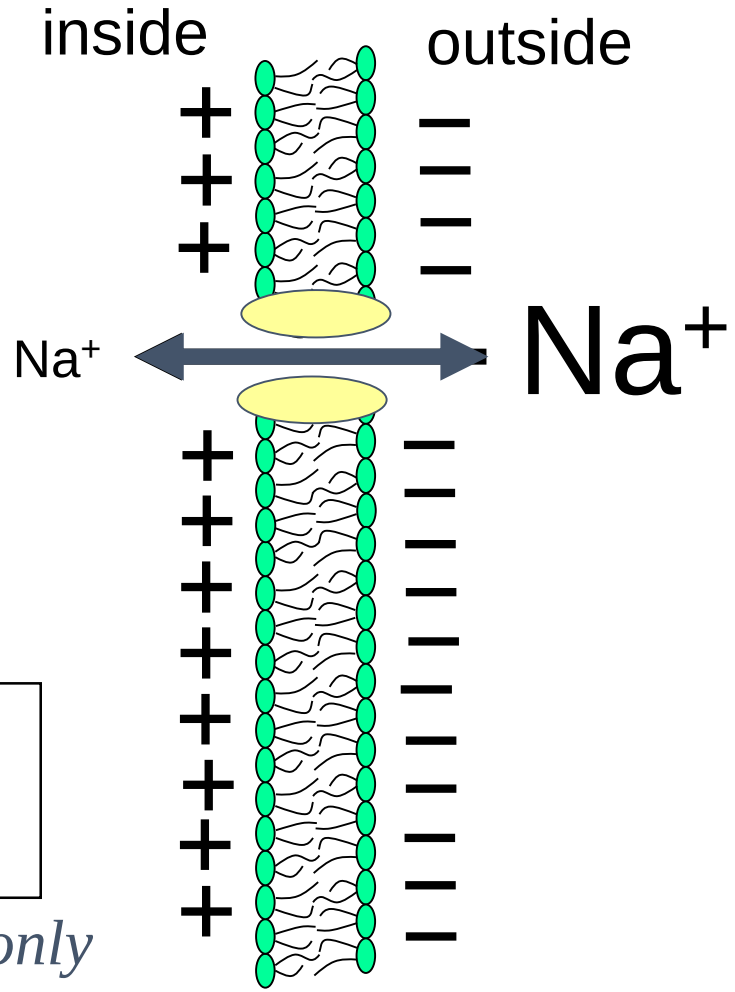
Simplest Case Scenario: 21st

If a membrane were permeable to only Na^+ then…

Na^+ would diffuse down its concentration gradient until potential across the membrane countered diffusion.

The electrical potential that counters net diffusion of Na^+ is called the Na^+ equilibrium potential (E_{Na}).

So, if the membrane were permeable only to Na^+, Vm would be +61 mV



- When a membrane is permeable to several different ions, the diffusion potential that develops depends on three factors:
- (1) the polarity of the electrical charge of each ion,
- (2) the permeability of the membrane (P) to each ion,
- (3) the concentrations (C) of the respective ions on the inside (i) and outside (o) of the membrane.
- Thus, the following formula, called the Goldman-Hodgkin-Katz equation, gives the calculated membrane potential on the inside of the membrane when two univalent positive ions, sodium (Na^+) and potassium (K^+), and one univalent negative ion, chloride ($Cl^–$), are involved.

$$\text{EMF (millivolts)} = -61 \cdot \log \frac{C_{\mathrm{Na}^+{}_i} P_{\mathrm{Na}^+} + C_{\mathrm{K}^+{}_i} P_{\mathrm{K}^+} + C_{\mathrm{Cl}^-{}_o} P_{\mathrm{Cl}^-}}{C_{\mathrm{Na}^+{}_o} P_{\mathrm{Na}^+} + C_{\mathrm{K}^-{}_o} P_{\mathrm{K}^+} + C_{\mathrm{Cl}^-{}_i} P_{\mathrm{Cl}^-}}$$

- Na^+, K^+ & Cl^- ions most important in development of membrane potential in nerves and muscle cells.
- Their conc'n gradient across the membrane helps determine the voltage of the membrane potential
- Degree of importance for each ion in determining voltage depends on permeability to it
- If zero permeability to K^+ & Cl^-, then membrane potential will be dependent of Na^+ only hence resulting potential will be equal to Nernst potential for Na^+
- Same holds for the other ions if membrane would be selectively permeable for either one of them alone

- +ve ion conc’n gradient to the outside causes electronegativity to the inside
- -ve ion gradient from the outside to the inside causes electronegativity to the inside since –vely charged Cl^- ions move to the inside leaving the non diffusible +ve ions to the outside
- The permeability of the K & Na channels undergoes rapid changes during transmission of an impulse whereas that to Cl^- does not change much.
- As such, rapid changes in Na and K permeability is primarily responsible for signal transmission in nerves as explained later

Resting Membrane Potential

- In the unstimulated state, nerve cells exhibit a resting membrane potential that is approximately -90 mV relative to the ECF
- The resting membrane potential reflects a steady state that can be described by the Goldman equation
- One should remember that the ECF conc'n of Na+ is much greater than for K+.
- Moreover, the permeability of the membrane to K+ (PK) is much greater than the permeability to Na (PNa) because there are many more leakage (non-gated) channels in the membrane for K+ than in the membrane for Na+
- As such, the RMP is much closer to the equilibrium potential for potassium (EK) than it is for sodium
- Because Na is far from its equilibrium potential, there is a large driving force on sodium, so Na+ ions move readily whenever a voltage-gated or ligand-gated Na+ channel opens in the membrane

The Resting Membrane Potential.

- Polarity. On the inner surface of the membrane resting potential is electronegative in respect of "zero" of the Earth.
- In other words, the outer surface of the membrane is charged positively, and internal - negatively.
- Sustainability of magnitude. Value of the RP for a particular structures (nerve fiber, muscle cells, neurons) are constant.
- Absolute value.
- RMP has the following meanings:
- Nerve fibers - -90 mV,
- Skeletal muscle fibers - -90 mV,
- Smooth muscle - -50-60 mV,
- Neurons of the central nervous system - -40-60 mV.

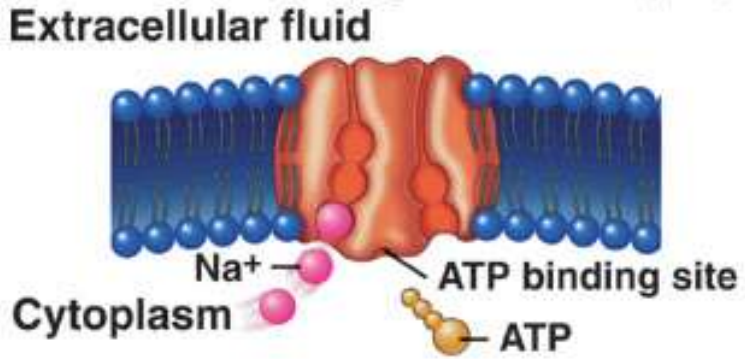
Resting Membrane Potential

- Normal RMP of large nerves at when not transmitting is -90mv
- Explained by the following

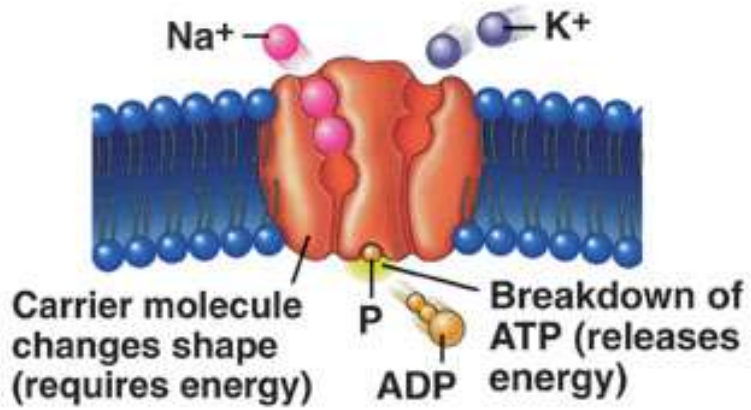
Transport properties of resting membrane

- Sodium Potassium (Na^+-K^+) Pump
- Continuously pumps Na^+ ions outside the cell and K^+ ions inside
- Is an electrogenic pump pumping 3 Na^+ ions outside for each 2 K^+ ions pumped inside
- Leaves net deficit of -ve ions on the inside causing –ve potential inside the cell membrane

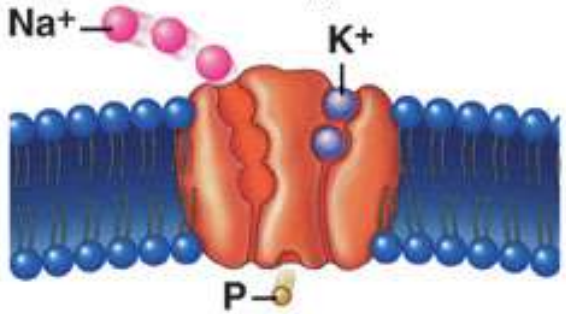
Sodium-Potassium Exchange Pump



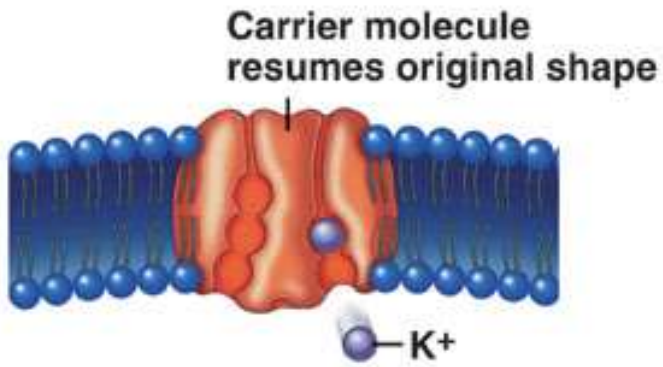
1. Three Na^+ and ATP bind to the carrier molecule.



2. The ATP breaks down to ADP and phosphate and releases energy. The carrier molecule changes shape, and Na^+ are transported across the membrane.

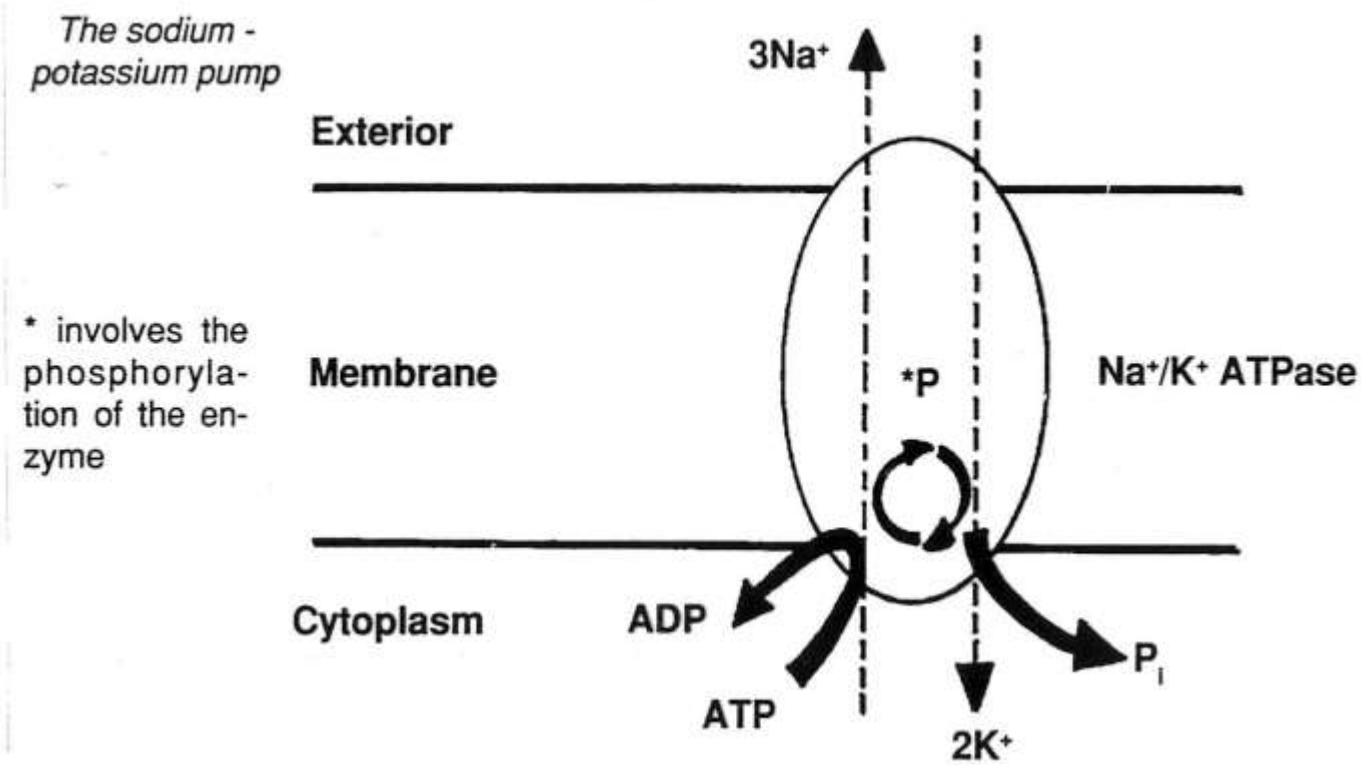


3. Na^+ diffuse away from the carrier molecule, two K^+ bind to the carrier molecule, and the phosphate is released.



4. The carrier molecule resumes original shape, transporting K^+ across the membrane, and K^+ diffuse away from the carrier molecule. The carrier molecule can again bind to Na^+ and ATP.

Na^+- K^+ pump


The sodium - potassium pump
* involves the phosphorylation of the enzyme
3Na+
Exterior
Membrane
*P
Na+/K+ ATPase
Cytoplasm
ADP
ATP
Pi
2K+

- This pump causes conc'n gradient for Na and k ions across the resting nervous membrane as below

	Inside	Outside
Sodium	14mEq/L	142mEq/L
Potassium	140mEq/L	4mEq/L

The ratios for the respective 2 ions from inside to outside are

Na^+ inside/Na^+outside = 0.1

K^+ inside/K^+outside = 35

Leak channels

- Leak channels are the passive channels, which maintain the resting membrane potential by allowing movement of positive ions (Na+ and K+) across the cell membrane.
- 3 important ions, sodium, chloride and potassium are unequally distributed across the cell membrane.
- Na+ and Cl– are more outside and K+ is more to the inside.
- Cl– channels are mostly closed in resting conditions Cl– are retained outside the cell.
- Na+ is actively out of cell and K+ is actively transported into the cell.
- Due to concentration gradient, Na+ diffuses back into the cell through Na+ leak channels and K+ diffuses out via K+ leak channels.

- In resting conditions, almost all the K+ leak channels are opened but most of the Na+ leak channels are closed.
- Due to this, K+, which are transported actively into the cell, can diffuse back out of the cell in an attempt to maintain the conc'n equilibrium.
- Among the Na+, which are transported actively out of the cell, only a small amount can diffuse back into the cell.
- That means, in resting conditions, the passive K+ efflux is much greater than the passive Na+ influx.
- It helps in establishing and maintaining the resting membrane potential.

- After establishment of RMP, (i.e. inside negativity and outside positivity), the efflux of K+ stops in spite of concentration gradient.
- This is due to:
- i. Positivity outside the cell repels positive K+ and prevents further efflux of these ions
- ii. Negativity inside the cell attracts positive K+ and prevents further leakage of these ions outside.

Factors determining RMP

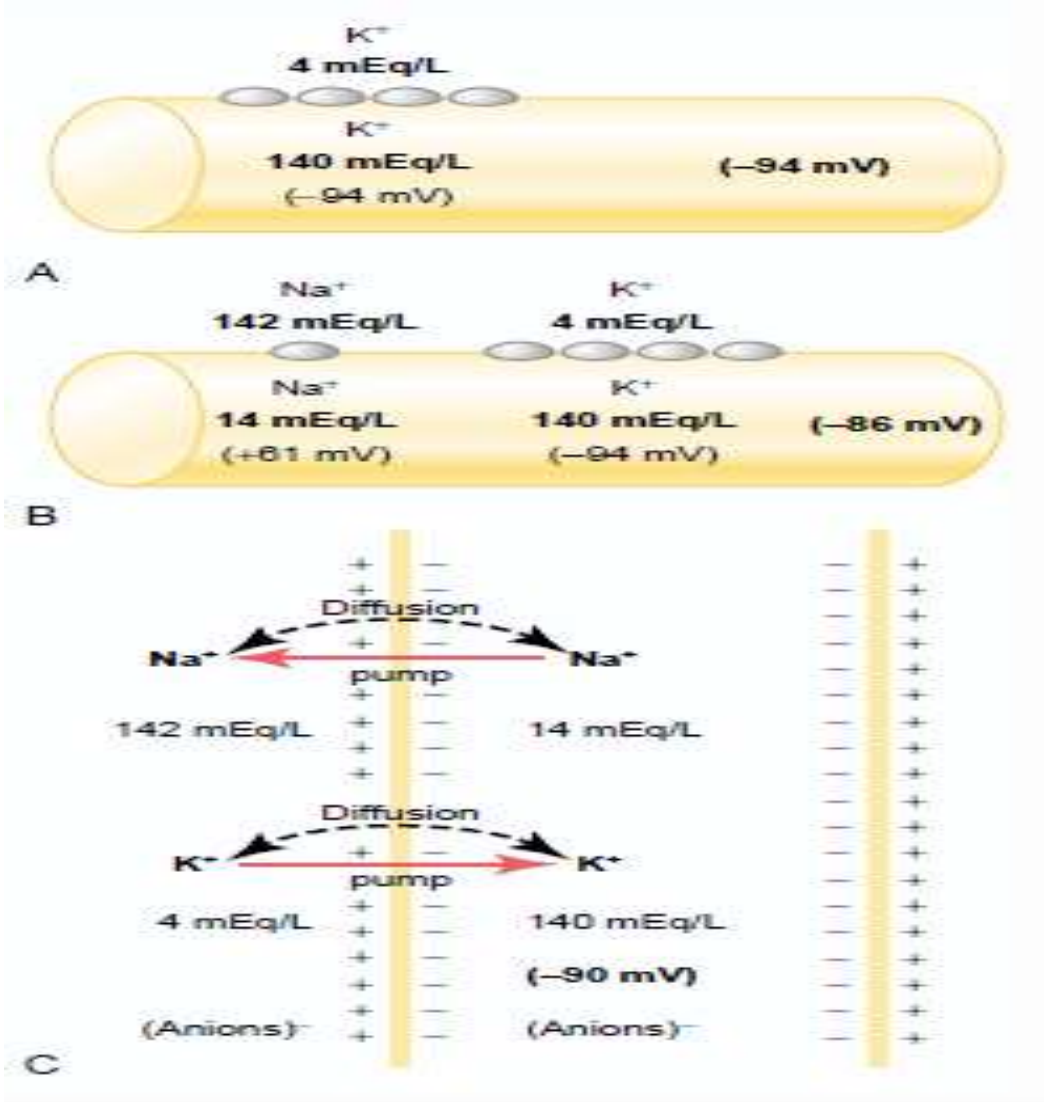
- Nernst potential for K^+, -94mv (-61*log 140/4)
- Nernst potential for Na^+, +61mv (-61log 14/140)

Net effect determined by Goldman equation as membrane much more permeable to K^+ through the leak channels. This net potential comes to -86mv

- The Na^+ -K^+ Pumps more Na^+ outside than K^+ hence more –ve inside membrane. This contributes additional -4 mv to membrane potential
- When all this factors operating at same time, then normal resting potential about -90mv

- K^+ and Na^+ diffusion alone causes a membrane potential of about -86 mv
- Na^+ - k^+ pump contributes about -4mv
- Total Membrane Resting Potential normally -90mv

Origin of the Normal Resting Membrane Potential



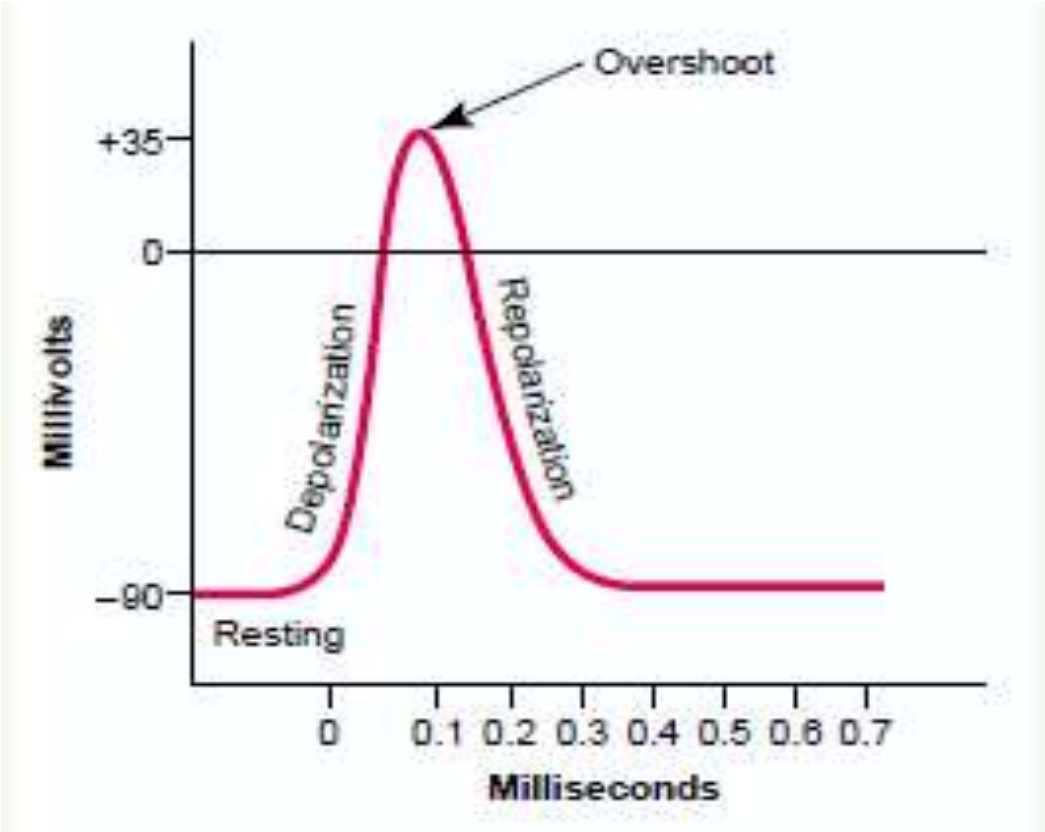
Contribution of the Na+-K+ Pump

- The Na+-K+ pump is shown to provide an additional contribution to the resting potential.
- There is continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane.
- The fact that more sodium ions are being pumped to the outside than potassium to the inside causes continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about –4 millivolts additional) on the inside beyond that which can be accounted for by diffusion alone.
- Therefore, the net membrane potential with all these factors operative at the same time is about –90 mV.

Action Potential

- Are rapid changes in membrane potential that spread rapidly along a nerve fibre
- Begins with rapid change in RMP to a positive potential ending with an almost rapid change to the negative potential.
- To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the nerves end

Action potentials are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane.



- Shows changes occurring in membrane during AP
- Explosive onset of AP and equally rapid recovery to the –ve potential

Stages of AP

I. Resting stage
II. Depolarization
III. Repolarization stage

Resting Stage

This is the resting membrane potential before the action potential begins.

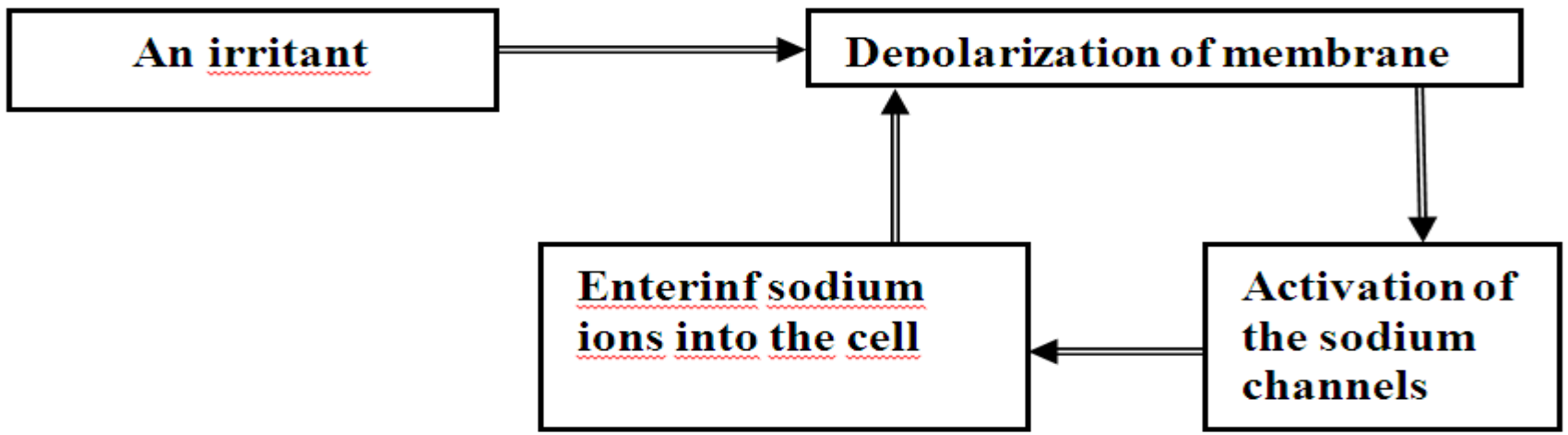
The membrane is said to be “polarized” during this stage because of the –90 millivolts negative membrane potential that is present.

Depolarization stage

At this time, the membrane suddenly becomes very permeable to Na+ ions, allowing tremendous numbers of positively charged Na 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.

This is called *depolarization.*


An irritant
Depolarization of membrane
Activation of the sodium channels
Enterinf sodium ions into the cell

Repolarization Stage

Within a few 10,000ths of a second after the membrane becomes highly permeable to Na ions, the Na channels begin to close and the K+ channels open more than normal.

Then, rapid diffusion of K+ ions to the exterior re-establishes the normal negative resting membrane potential.

This is called *repolarization* of the membrane.

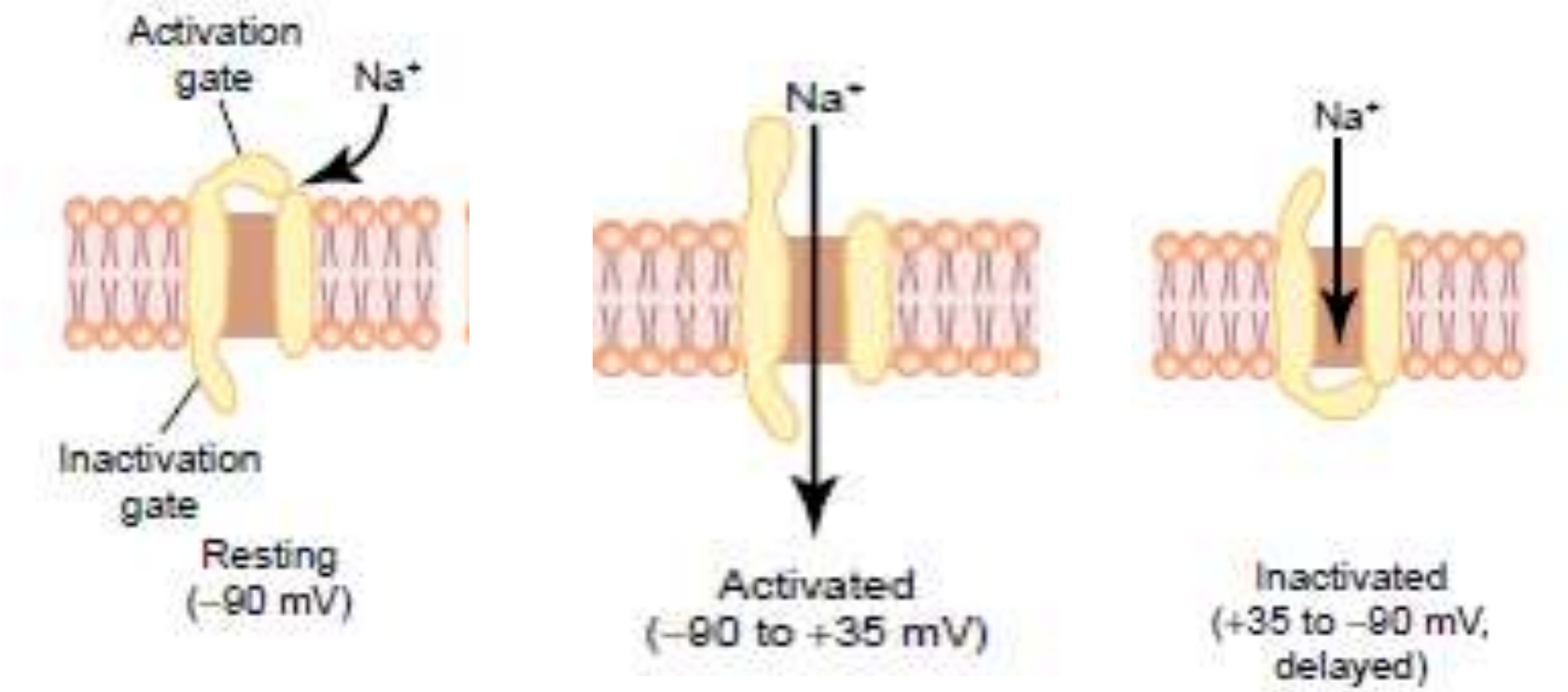
- In the absence of an action potential, a stimulus applied to the neuronal membrane results in a local potential change that decreases with distance away from the point of stimulation.
- The stimulus is the particular one which the nerve reacts to eg- if taste, then it is a chemical which stimulates that receptor and cause the local potential change. For salty taste, Na+ ions open specific Na channels which cause the change in potential which may lead to the AP
- The voltage change at any point is a function of current and resistance as defined by Ohm's law.
- If a ligand-gated channel opens briefly and allows +ve ions to enter the neuron, the electrical potential derived from that current will be greatest near the channels that opened, and the voltage change will steadily decline with increasing distance away from that point.

- The reason for the decline in voltage change with distance is that some of the ions backleak out of the membrane because it is not a perfect insulator, and less charge reaches more distant sites.
- Since membrane resistance is a stable property of the membrane, the diminished current with distance away from the source results in a diminished voltage change.
- An action potential depends on the presence of voltage-gated sodium and potassium channels that open when the neuronal membrane is depolarized.

Voltage gated sodium and potassium channels

- These channels play important part in depolarization and repolarization of the nerve membrane during AP
- Has 2 gates, a an activation gate near the outside and an inactivation gate near the inside
- At rest (-90mv) the inactivation gate is open with activation gate closed preventing entry of Na into the nerve

Voltage-Gated Sodium Channels



Activation

- When membrane becomes less –tive than during resting potential rising from -90 towards 0, it finally reaches a voltage (mostly between -70 to -50 mv depending on the nerve) that causes conformational changes in the activation gate causing it to open
- This is the activated state during which Na ions pour into the cell with membrane permeability to sodium increased to 500 -5000 fold

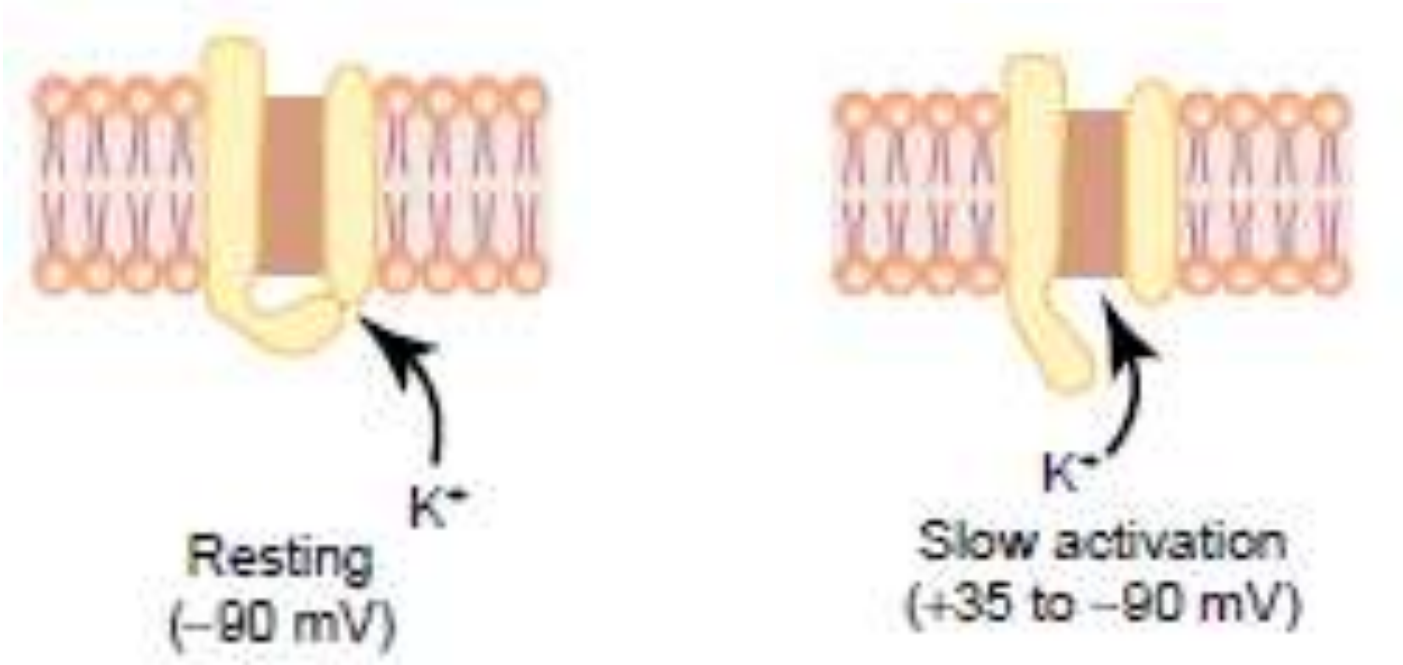
Inactivation

- Same voltage increase that opens activation gate also closes the inactivation gate
- However, this gate closes several 10,000ths of a second after the opening after activation gates
- The conformation change that closes the inactivation gate is a slower process than the conformational change that opens the activation gate
- No more Na can enter the cell
- The inactivation gate does not open again until the potential returns to near the RMP

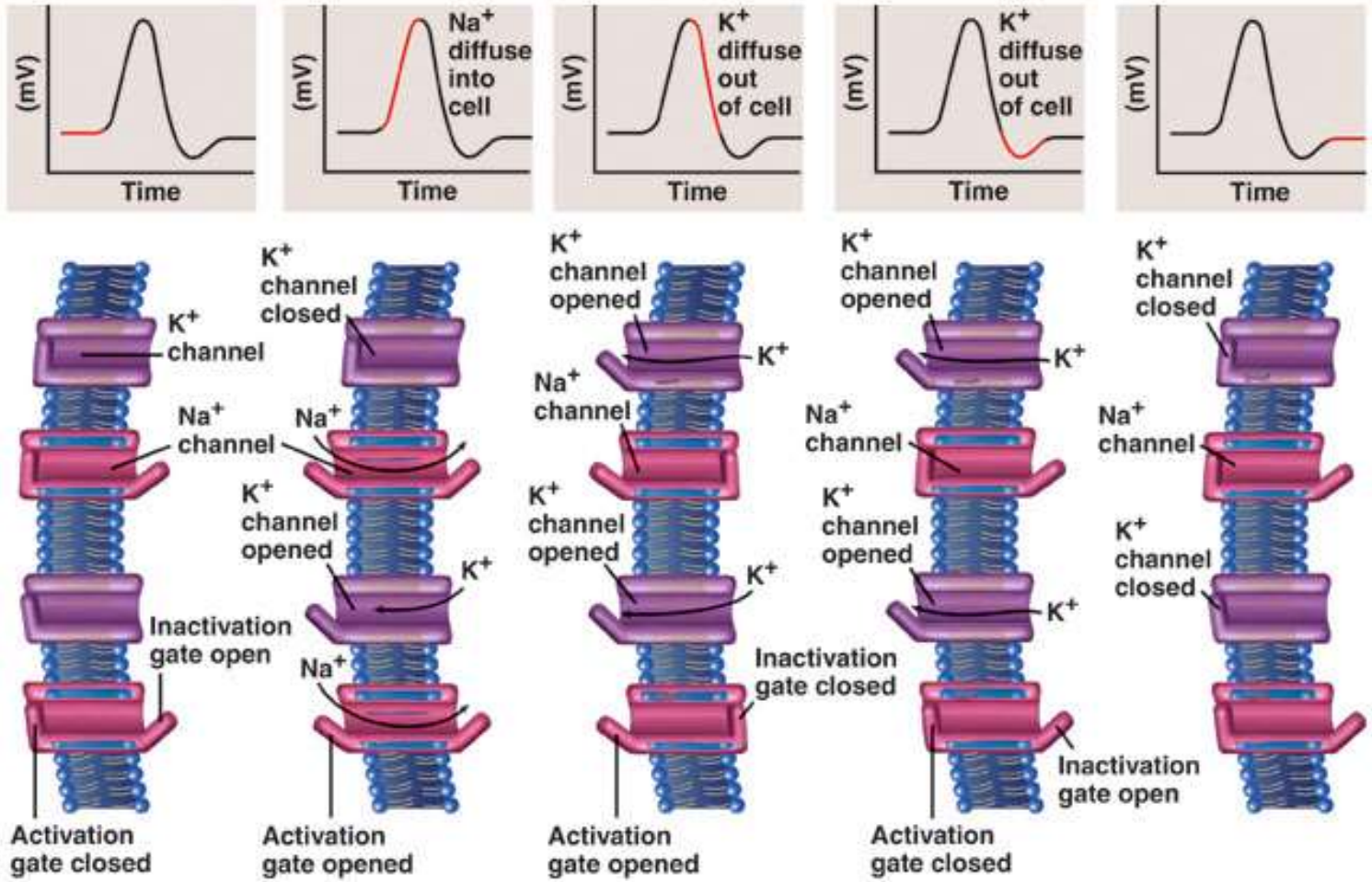
Voltage gated potassium channels

- At rest voltage gated potassium channels closed.
- When membrane potential rises from -90mv towards 0, a conformational change occurs allowing this channels to open with K^+ ions diffusing to the outside
- However, there is a delay in opening o f this channel with it opening just as the Na channels are beginning to close due to inactivation
- Thus, decrease in sodium entry to the cell and simultaneous increase in K^+ exit from the cell combine to speed the repolarization process leading to full recovery of membrane potential within another few 10,000th of a second

Voltage-Gated Potassium Channel



Action Potential



Initiation of the Action Potential: 28th Sept

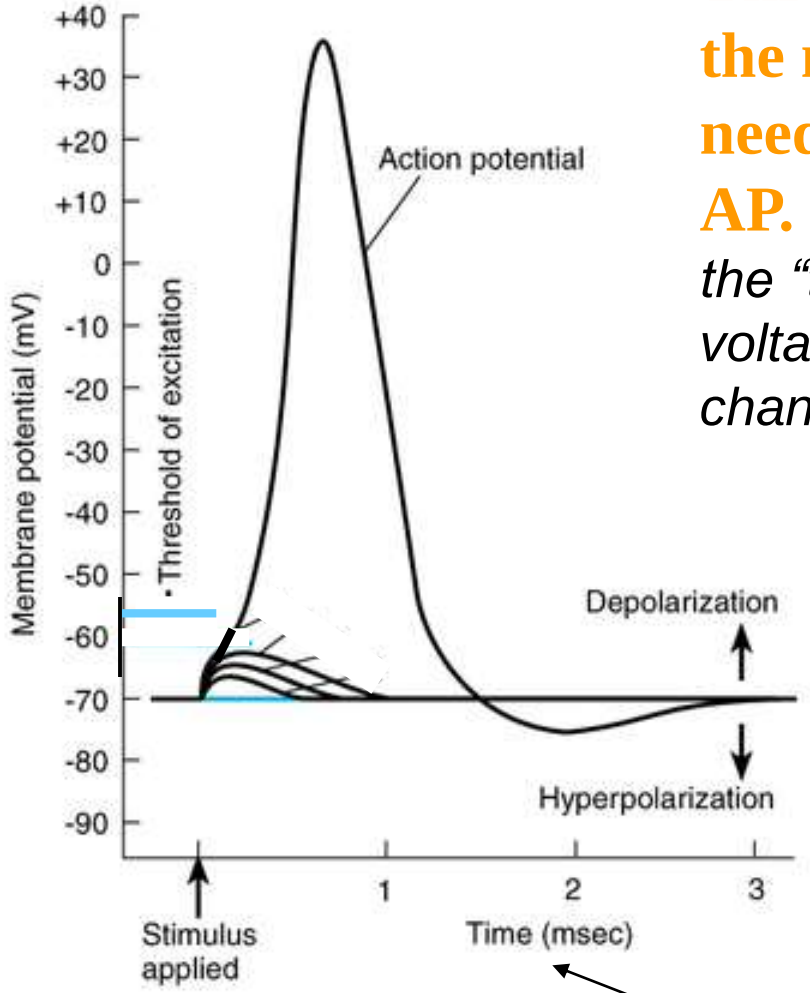
- As long as nerve fibers membrane remains undisturbed, no AP occurs
- If an event occurs to change potential from the -90mv towards 0, this rise cause many voltage gated Na channels to begin opening allowing rapid inflow of Na ions which causes further rise in membrane potential.
- This opens still more voltage gated Na channels and more ions streaming into the interior of fiber.

- This is a vicious +ve feedback cycle that, once the feedback is strong enough, continues till all voltage gated Na channels have become opened
- Then within another ms, the rising potential causes the na channels to close as well as opening the K channels and the action potential soon terminates

Threshold for Action potential

- An AP will not occur until the initial rise in potential is great enough to create the vicious cycle
- This occurs when the number of Na ions become higher than the number of K leaving the cell
- A sudden rise of about 15 – 30 mv often required
- Therefore a sudden increase in potential from -90 to about -65 mv usually causes the the explosive development of an action potential
- This level of -65 mv is said to be the threshold for stimulation

► **Action Potential as Seen on an Oscilloscope Screen**



Definition:

Threshold voltage is the minimum voltage needed to trigger an AP. *not a number, rather the "trigger" to open voltage operated channels*

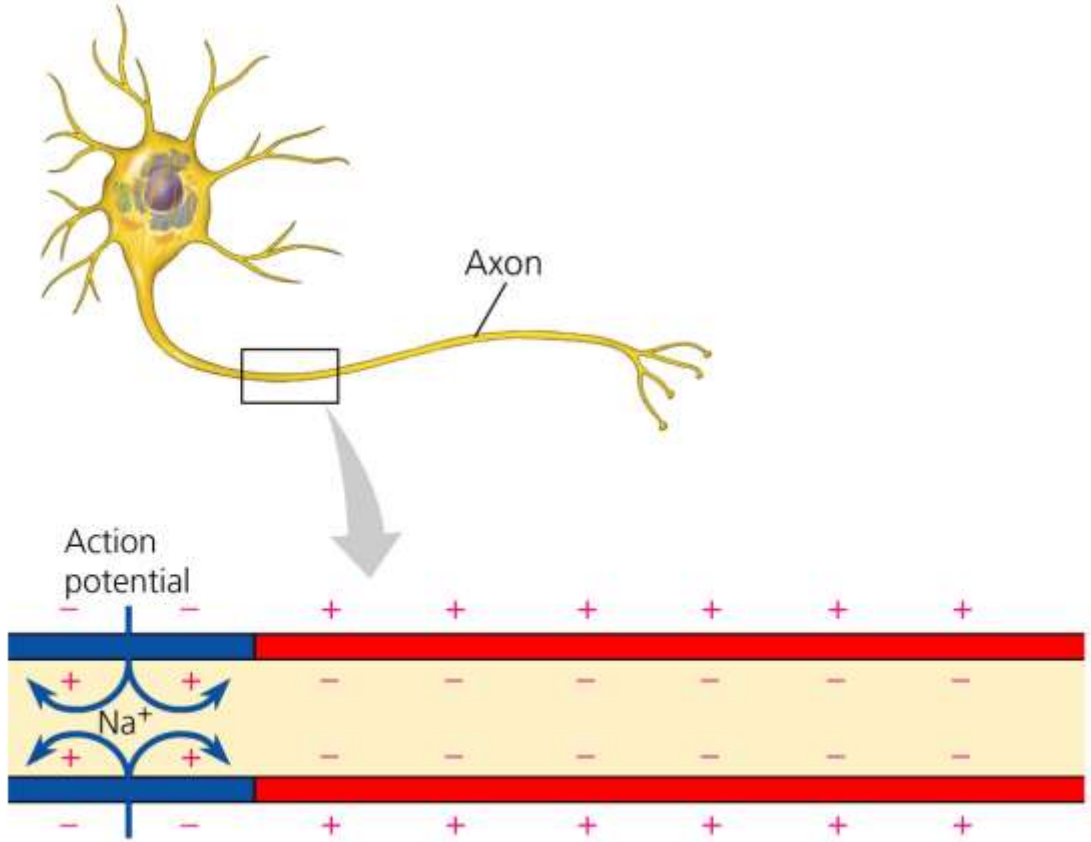
Note the timeframe for one AP

Propagation of the Action Potential

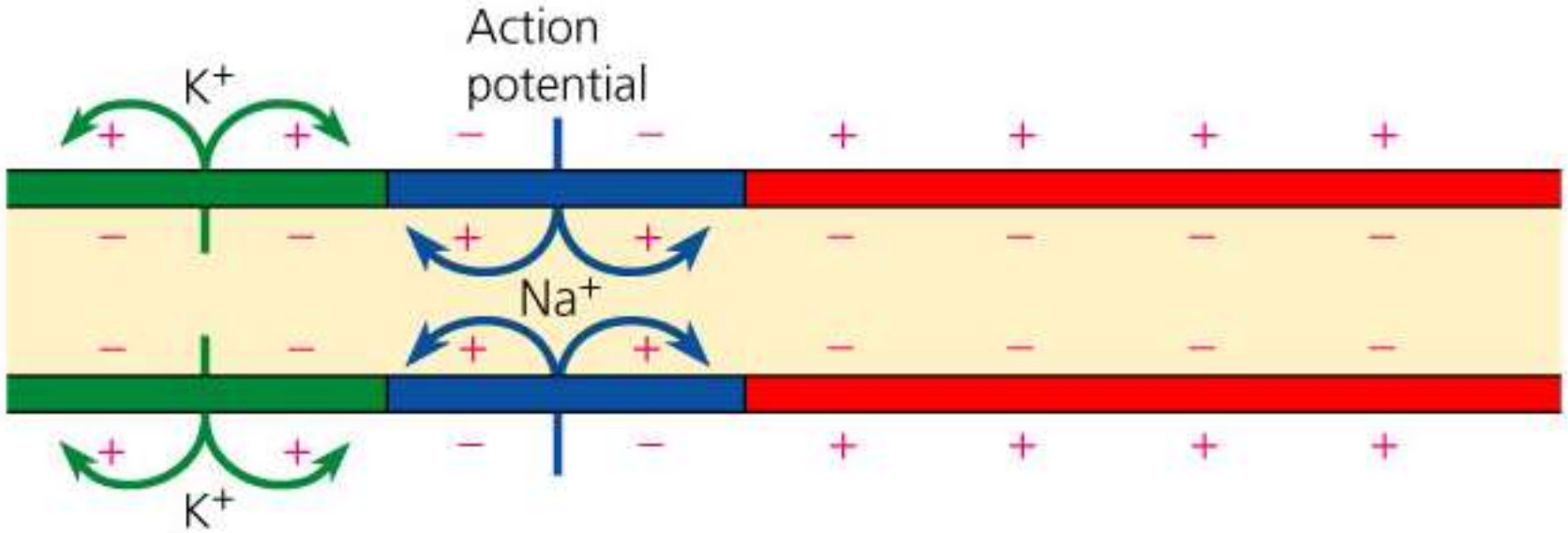
- An AP elicited at any one point of an excitable membrane usually excites adjacent parts of the membrane resulting in propagation of the AP along the membrane
- The +ve electrical charges are carried by the inward diffusing Na ions through the depolarizing membrane and then for several mm along the nerve fiber in both directions along the core of the axon.
- This +ve charges increase the voltage for a distance of 1-3mm inside the fiber to above threshold voltage for initiation of AP

- Therefore, Na channels in these new areas open and the explosive AP spreads
- These newly depolarized areas produce still more local circuits of current flow further along the membrane causing progressively more and more depolarization
- The depolarization process travels along the entire length of fiber
- This transmission of the depolarization process along a nerve or muscle fiber is called a nerve or muscle impulse

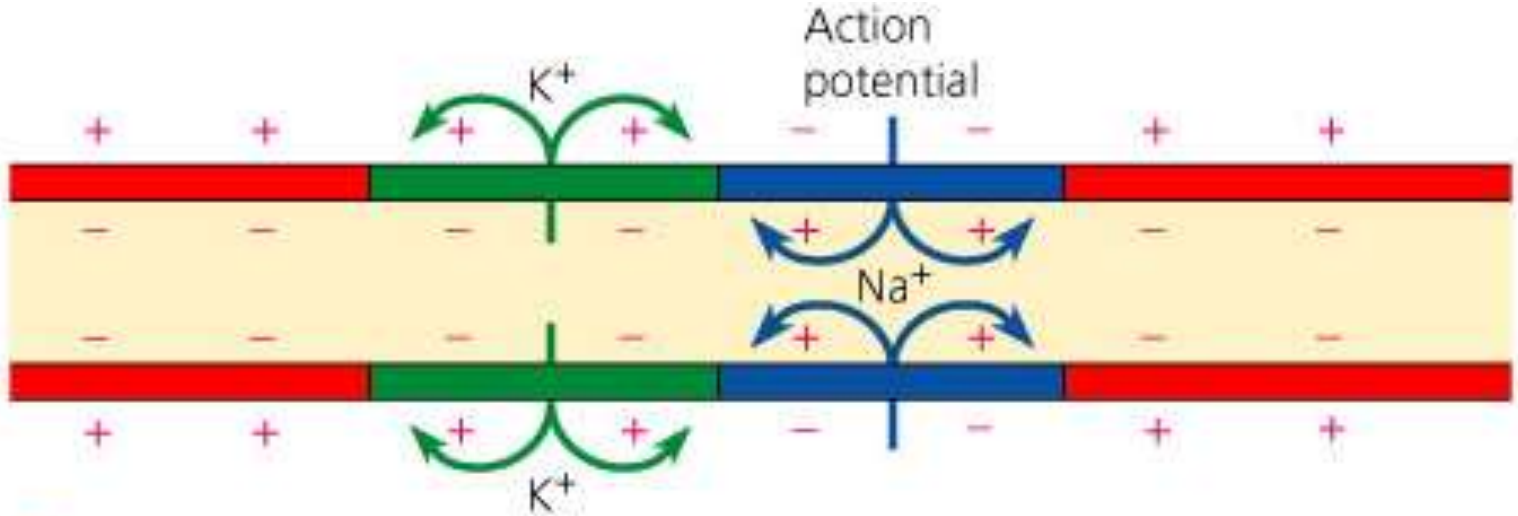
- Propagation and Speed of the Action Potential.
- After an AP is generated, it propagates along the axon toward the axon terminal; it is conducted along the axon with no decrement in amplitude.
- The mode in which AP’s propagate and the speed with which they are conducted along an axon depend on whether the axon is myelinated.
- The diameter of the axon also influences the speed of AP conduction: larger-diameter axons have faster AP potential conduction velocities than smaller-diameter axons.



1 An action potential is generated as Na^+ flows inward across the membrane at one location.



2 The depolarization of the action potential spreads to the neighboring region of the membrane, re-initiating the action potential there. To the left of this region, the membrane is repolarizing as K^+ flows outward.



3 The depolarization-repolarization process is repeated in the next region of the membrane. In this way, local currents of ions *across* the plasma membrane cause the action potential to be propagated *along* the length of the axon.

Step 1

- Adequate stimulus is applied to a neuron, then the **stimulus-gated Na+ channels** at the point of stimulus open, **Na+ diffuses rapidly into the cell** producing a **local depolarization**

Step 2

- If the magnitude of the depolarization surpasses a limit termed **THRESHOLD POTENTIAL (about -65 mV),** the **voltage-gated Na+ are stimulated to open**

Step 3

- As more Na+ rushes into the cell, the membrane **moves toward 0 mV, then continues to a peak of +30 mV** (the + indicates that there is an excess of +ions inside the membrane
  - If the local depolarization **fails to cross -65 mV the voltage-gated Na+ do not open** and the membrane simply recovers back to the resting potential of **-90 mV without producing an action potential**

Step 4

- **Voltage-gated Na+ stays open for only about 1 ms before automatically closing**. This means that once they are stimulated the Na+ always allow sodium to rush in. therefore the ***action potential is an all-or-nothing response***

Step 5

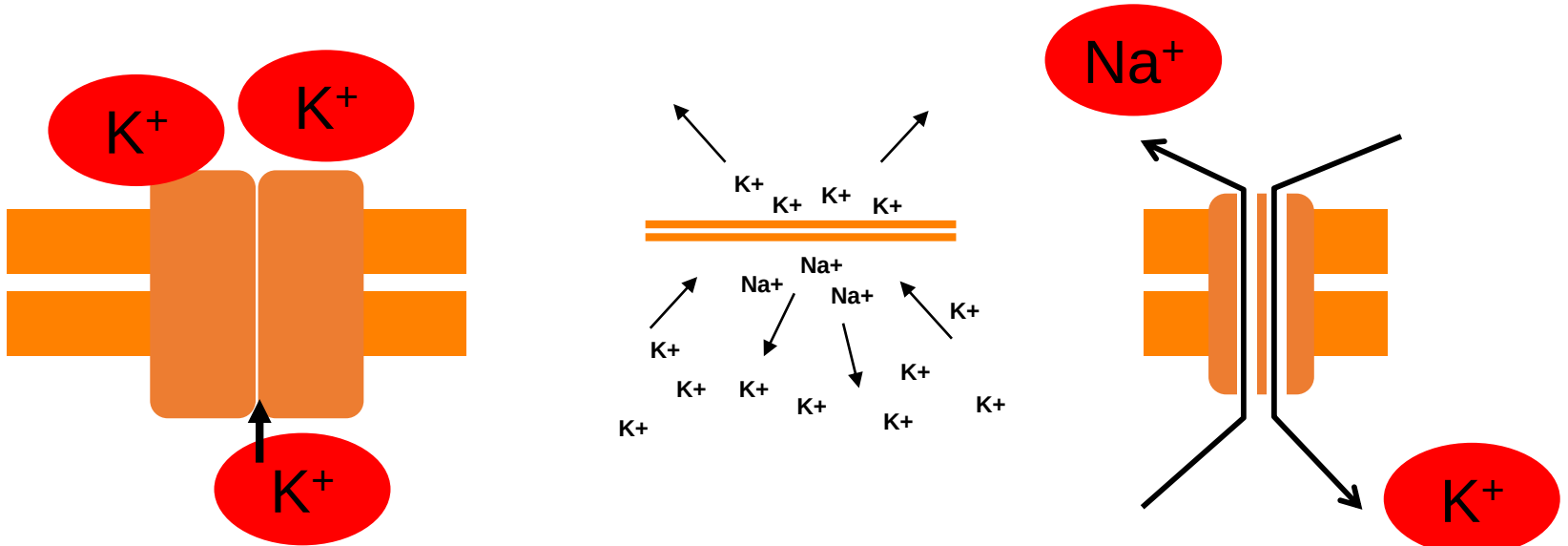
- Once the peak is reached the membrane potential begins to move back toward the resting potential termed REPOLARIZATION
- Surpassing the threshold not only triggers the opening of voltage-gated Na+ but also the voltage-gated K+ BUT these are slow to respond, however, and thus do not begin opening until the inward diffusion of Na+ has caused the membrane potential to reach +30 mV once the K+ are open it rapidly diffuses out of the cell.
- The outward rush of K+ restores the original excess of + ions on the outside of the membrane, thus repolarizing the membrane

Step 6

- Because the K+ channels remain open as the membrane reaches its resting potential, too many K+ may rush out of the cell.
- This causes a brief period of hyperpolarization before the resting potential is restored by the action of the Na+-K+ pump and the return of ion channels to their resting state

Action potentials: Resuming the Resting Potential

- Potassium channels close.
- Repolarization resets sodium ion channels.
- Ions diffuse away from the area.
- Sodium-potassium transporter maintains polarization.
- The membrane is now ready to “fire” again.



All-or Nothing Principle

- Once an AP has been elicited at any one point in the membrane, the depolarization process travels over the entire membrane if conditions are right or it will not travel at all
- This is the all or nothing principle
- At times, the AP reaches a point on the membrane where it does not generate sufficient voltage to stimulate the next area of the membrane.

- When this occurs, spread of depolarization stops
- For continued propagation of impulse, the ratio of AP to threshold fro excitation must be greater than 1
- This greater than 1 ratio is called the safety factor for propagation

ALL OR NONE RESPONSE

- The action potential doesn’t occur in a nerve if the stimulus is sub-threshold. If the stimulus is threshold and above, the action potential produced will be of same amplitude, regardless of intensity of stimulus.
- * The frequency of action potential increases with the increasing intensity of stimulus.

- Propagation of an action potential in an unmyelinated axon.
- The initiation of an action potential in one segment of the axon depolarizes the immediately adjacent section, bringing it to threshold and generating an action potential.
- The propagation of an action potential in a myelinated axon.
- The initiation of an action potential in one node of Ranvier depolarizes the next node.
- Jumping from one node to the next is called saltatory conduction.

Refractory Periods

- After the start of an action potential, there are periods when
- i. The initiation of additional action potentials requires a greater degree of depolarization and
- II. When action potentials cannot be initiated at all.
- These are called the relative and absolute refractory periods, respectively
- The inability of a neuronal membrane to generate an AP during absolute refractory period is due to the state of the voltage-gated Na channel.
- After the inactivation gate closes during the repolarization phase of an AP, it remains closed for some time; therefore, another action potential cannot be generated no matter how much the membrane is depolarized.

- The importance of the absolute refractory period is that it limits the rate of firing of AP’s
- The absolute refractory period also prevents AP’s from traveling in the wrong direction along the axon

- In the relative refractory period, the inactivation gate of a portion of the voltage-gated Na+ channels is open.
- Since these channels have returned to their initial resting state, they can now respond to depolarizations of the membrane.
- Consequently, when the membrane is depolarized, many of the channels open their activation gates and permit the influx of Na+ ions.
- However, since only a portion of the Na+ channels have returned to the resting state, depolarization of the membrane to the original threshold level activates an insufficient number of channels to initiate an AP

- With greater levels of depolarization, more channels are activated, until eventually an action potential is generated.
- The K+ channels are maintained in the open state during the relative refractory period, leading to membrane hyperpolarization.
- By these two mechanisms, the AP threshold is increased during the relative refractory period

Refractory period

- During the AP, a 2nd stimulus, no matter how strong, will not produce a second AP
- The membrane is said to be in its absolute refractory period.
- Occurs since the voltage-gated Na channels enter a closed, inactive state at the peak of the AP
- Membrane must repolarize before the Na channel can be open.
- After absolute refractory period, there is an interval during which a second action potential can be produced, but only if the stimulus strength is considerably greater than usual.
- Is the relative refractory period, and lasts 10 to 15 ms or longer in neurons
- Occurs during hyperpolarization.

- If a depolarization exceeds the increased threshold or outlasts the relative refractory period, additional action potentials will be fired.
- The refractory periods limit the number of AP’s that can be produced by an excitable membrane in a given period of time.
- Also increase reliability of neural signaling because they help limit extra impulses.
- Most nerve cells respond at frequencies of up to 100 AP’s per sec

GRADED POTENTIAL: 5th Oct

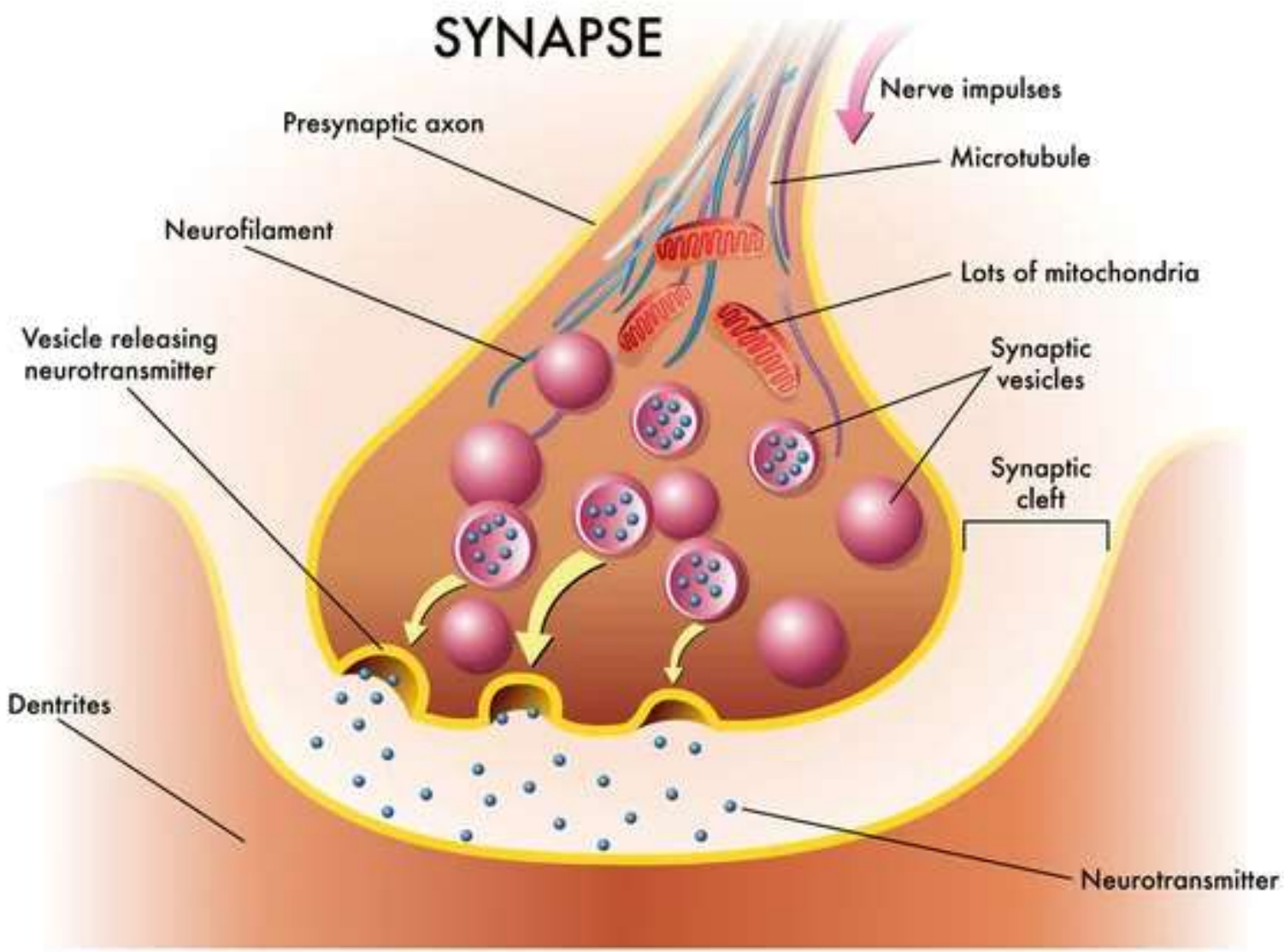
- Graded potential is a mild local change in the membrane potential that develops in receptors, synapse or neuromuscular junction when stimulated.
- Also called graded membrane potential or local potential.
- It is non-propagative and characterized by mild depolarization or hyperpolarization.
- In most of cases, graded potential is responsible for the generation of AP
- In some cases it hyper-polarizes the membrane potential (more negativity than resting membrane potential) and inhibits the generation of AP

Action Potential vs Graded potential

Action Potential	Graded potential
Propagative	Non-Propagative
Long-distance signal	Short-distance signal
Both depolarization and repolarization	Only depolarization or hyperpolarization
Obeys all or none law	Does not obey all or none law
Summation is not possible	Summation is possible
Has refractory period	Has no refractory period

Synaptic transmission

- There are 2 types of synapses: electric and chemical.
- At electric synapses, the plasma membranes of the pre- and postsynaptic cells are joined by gap junctions
- These allow the local currents resulting from arriving AP's to flow directly across the junction through the connecting channels in either direction from one neuron to the neuron on the other side of the junction, depolarizing the membrane to threshold thus initiating an AP in the 2^{nd}.
- Electric synapses rare in the mammalian nervous system and mostly found in cardiac and smooth muscles
- Most common are chemical synapses


SYNAPSE
Nerve impulses
Presynaptic axon
Microtubule
Neurofilament
Lots of mitochondria
Vesicle releasing neurotransmitter
Synaptic vesicles
Synaptic cleft
Dentrites
Neurotransmitter

Synapses

FUNCTIONS OF SYNAPSE

Main function of the synapse is to transmit the impulses, i.e. action potential from one neuron to another.

However, some of the synapses inhibit these Impulses hence impulses are not transmitted to the postsynaptic neuron.

On the basis of functions, synapses are divided into two types:

1. Excitatory synapses, which transmit the impulses (excitatory function)
2. Inhibitory synapses, which inhibit the transmission of impulses (inhibitory function).

EXCITATORY FUNCTION

- Excitatory Postsynaptic Potential
- Excitatory postsynaptic potential (EPSP) is the non-propagated electrical potential that develops during the process of synaptic transmission.
- When the action potential reaches the presynaptic axon terminal, the Voltage gated calcium channels at the presynaptic membrane are opened

- .The calcium ions enter the axon terminal from ECF
- Calcium ions cause the release of neurotransmitter substance from the vesicles by means of exocytosis.
- Neurotransmitter, which is excitatory in function (excitatory neurotransmitter) passes through presynaptic membrane and synaptic cleft and reaches the postsynaptic membrane

CONT…

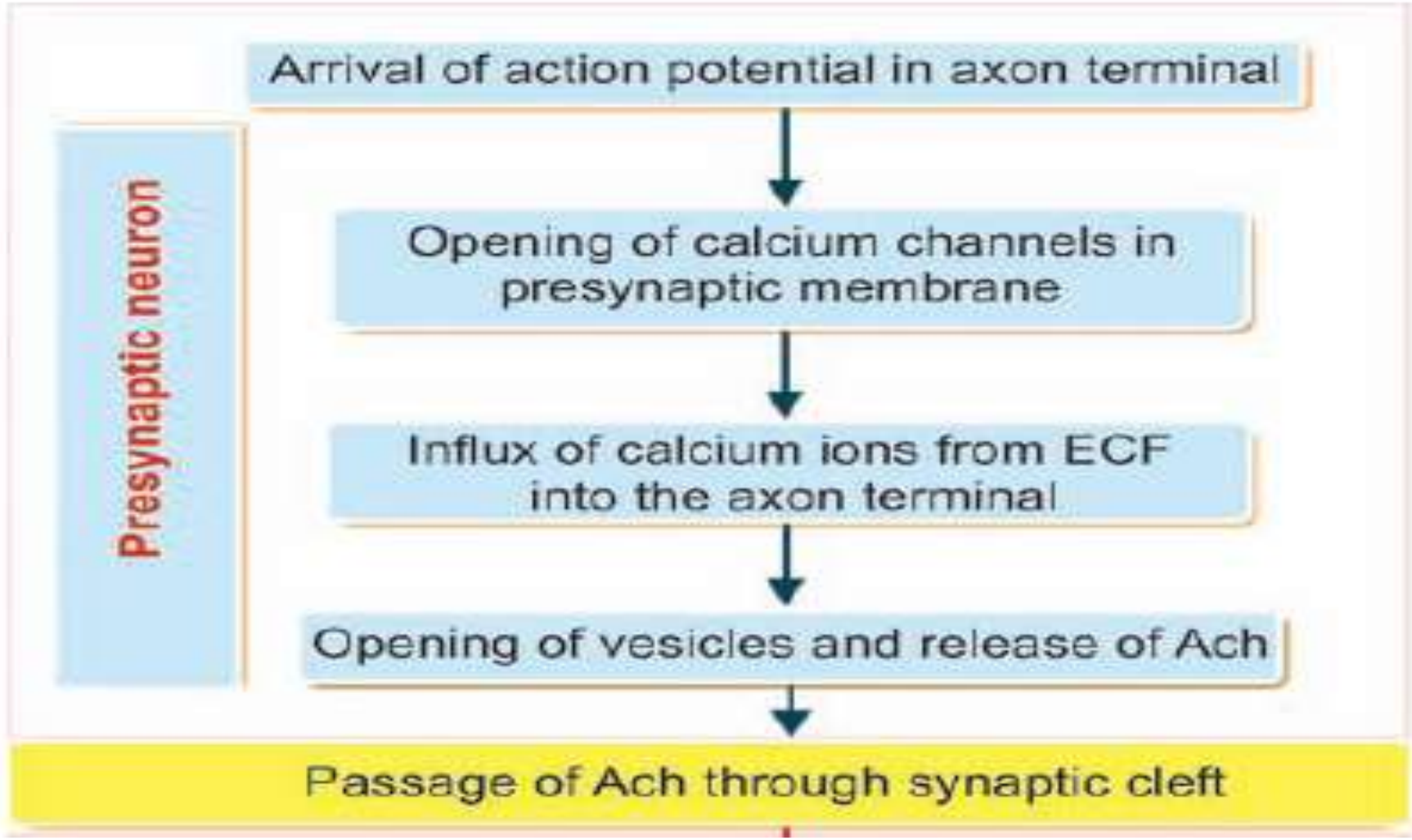
- .The neurotransmitter binds with receptor protein present in postsynaptic membrane to form neurotransmitter-receptor complex.
- Neurotransmitter receptor complex causes production of a non-propagated EPSP.
- Common excitatory neurotransmitter in a synapse is acetylcholine.

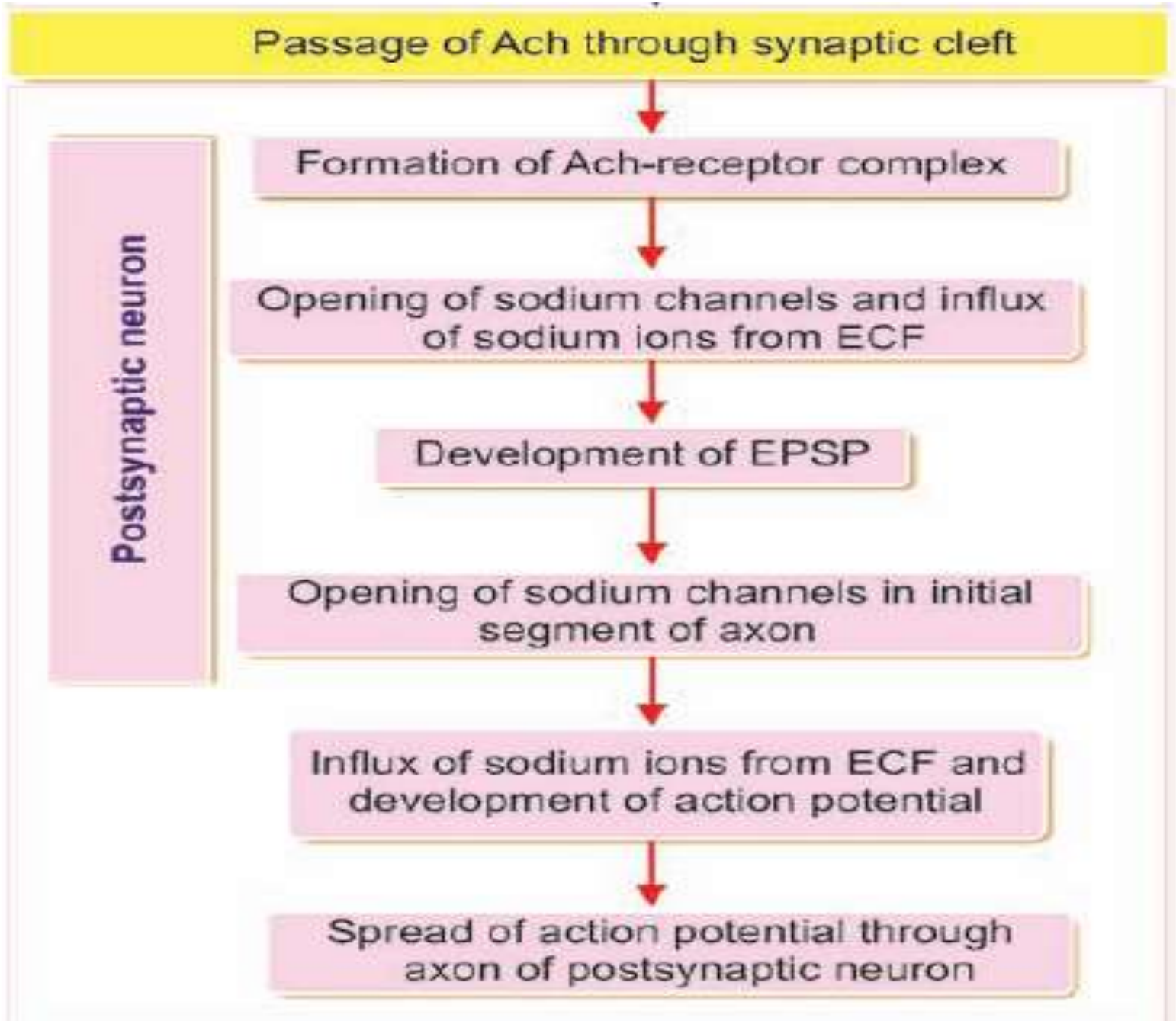
Mechanism of Development of EPSP

- Neurotransmitter-receptor complex causes opening of ligand gated Na+ channels.
- The Na+ ions from ECF enter the cell body of postsynaptic neuron.
- As the sodium ions are positively charged, RMP inside the cell body is altered and mild depolarization develops.
- This type of mild depolarization is called EPSP.
- It is a local potential (response) in the synapse.

Mechanism of Development of EPSP

Neurotransmitter-receptor complex causes opening of ligand-gated **sodium channels**. Now, the **sodium ions**




Passage of Ach through synaptic cleft
Postsynaptic neuron
Formation of Ach-receptor complex
Opening of sodium channels and influx of sodium ions from ECF
Development of EPSP
Opening of sodium channels in initial segment of axon
Influx of sodium ions from ECF and development of action potential
Spread of action potential through axon of postsynaptic neuron

Properties of EPSP

- EPSP is confined only to the synapse.
- It is a graded potential similar to receptor potential.
- EPSP has two properties:
- 1. It is non propagated
- 2. It does not obey all or none law

Significance of EPSP

- EPSP is not transmitted into the axon of postsynaptic neuron.
- However, it causes development of action potential in the axon.
- When EPSP strong enough, causes the opening of voltage gated sodium channels in the initial segment of axon.
- Due to the entrance of sodium ions, the depolarization occurs in the initial segment of axon and thus, the AP develops.
- From here, the AP spreads to other segment of the axon.

Inhibitory Function

Postsynaptic or Direct Inhibition

- Postsynaptic inhibition is the type of synaptic inhibition that occurs due to the release of an inhibitory neurotransmitter from presynaptic terminal instead of an excitatory neurotransmitter substance.
- Also called direct inhibition.
- Inhibitory neurotransmitters are gamma aminobutyric acid (GABA), dopamine and glycine.

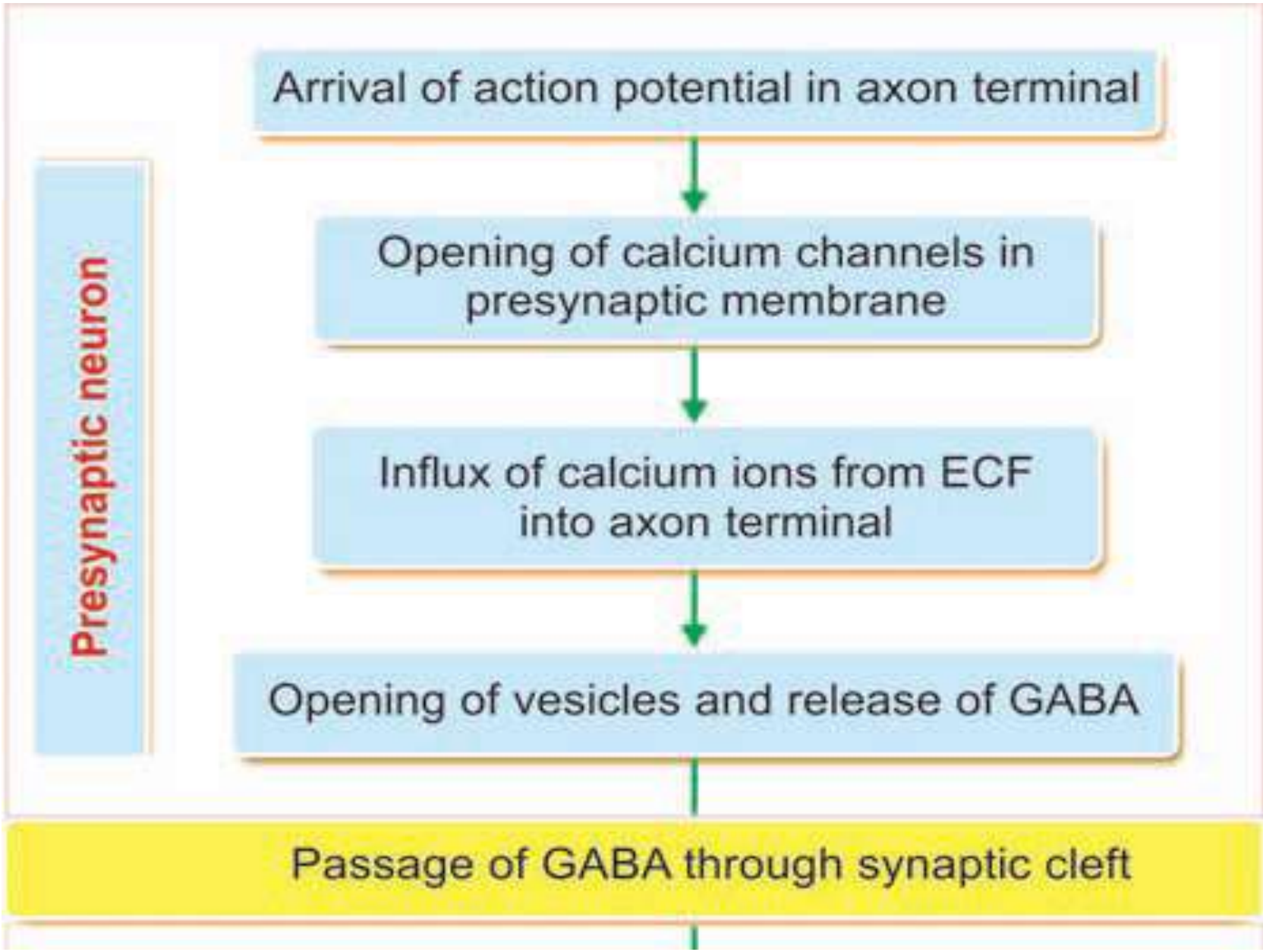
Action of GABA

Development of inhibitory postsynaptic potential

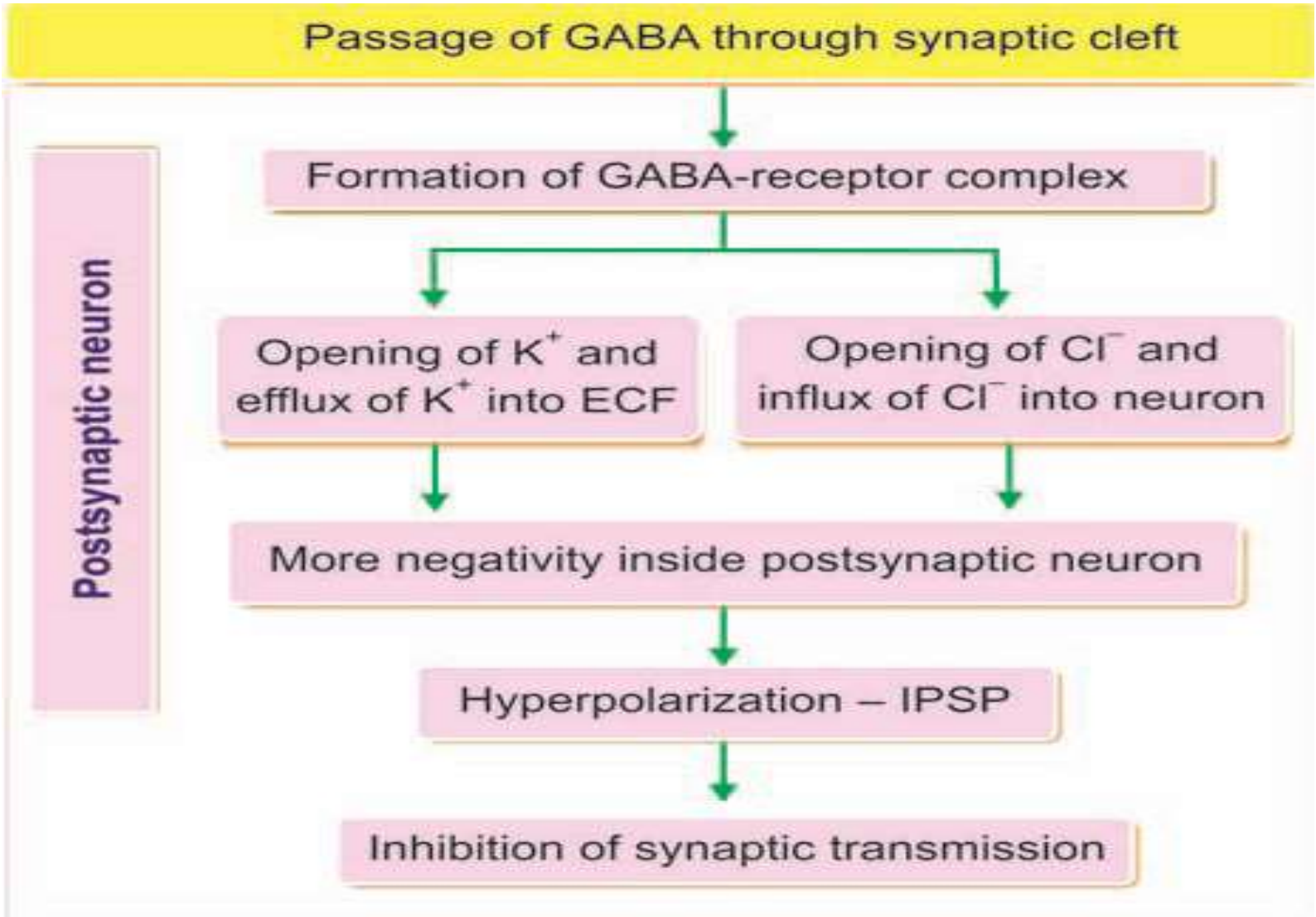
- Inhibitory postsynaptic potential (IPSP) is the electrical potential in the form of hyperpolarization that develops during postsynaptic inhibition.
- Inhibitory neurotransmitter substance acts on postsynaptic membrane by binding with receptor.
- Transmitter receptor complex opens the ligand gated potassium channels instead of sodium channels.

CONT…

- The K+ ions, which are available in plenty in the cell body of postsynaptic neuron move to ECF.
- Simultaneously, chloride channels also open and chloride ions (which are more in ECF) move inside the cell body of postsynaptic neuron.
- The exit of potassium ions and influx of chloride ions cause more negativity inside, leading to hyperpolarization.
- Hyperpolarized state of the synapse inhibits synaptic transmission


Presynaptic neuron
Arrival of action potential in axon terminal
Opening of calcium channels in presynaptic membrane
Influx of calcium ions from ECF into axon terminal
Opening of vesicles and release of GABA
Passage of GABA through synaptic cleft

CONT…


Passage of GABA through synaptic cleft
Postsynaptic neuron
Formation of GABA-receptor complex
Opening of K^+ and efflux of K^+ into ECF
Opening of Cl^- and influx of Cl^- into neuron
More negativity inside postsynaptic neuron
Hyperpolarization – IPSP
Inhibition of synaptic transmission

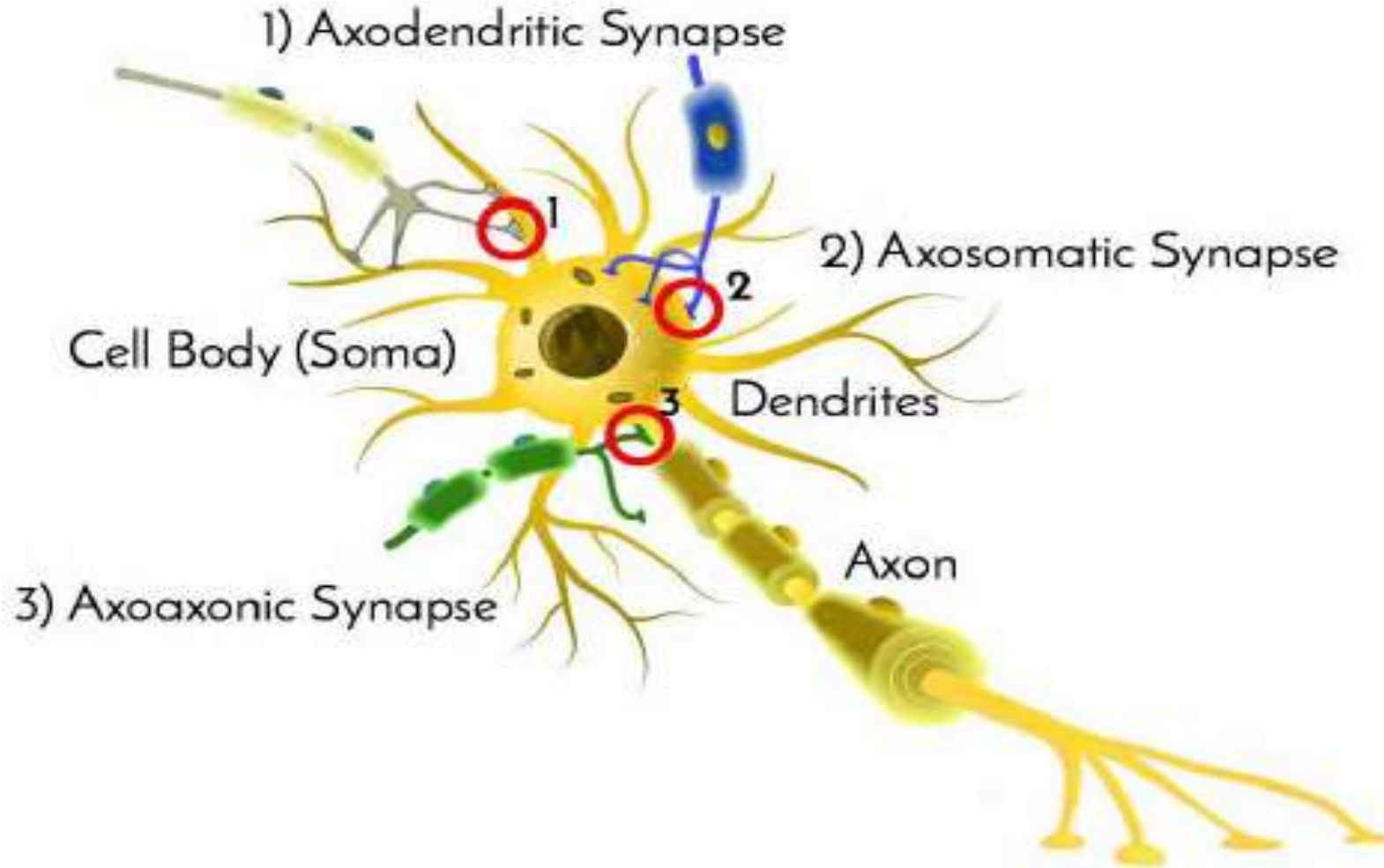
Refractory period

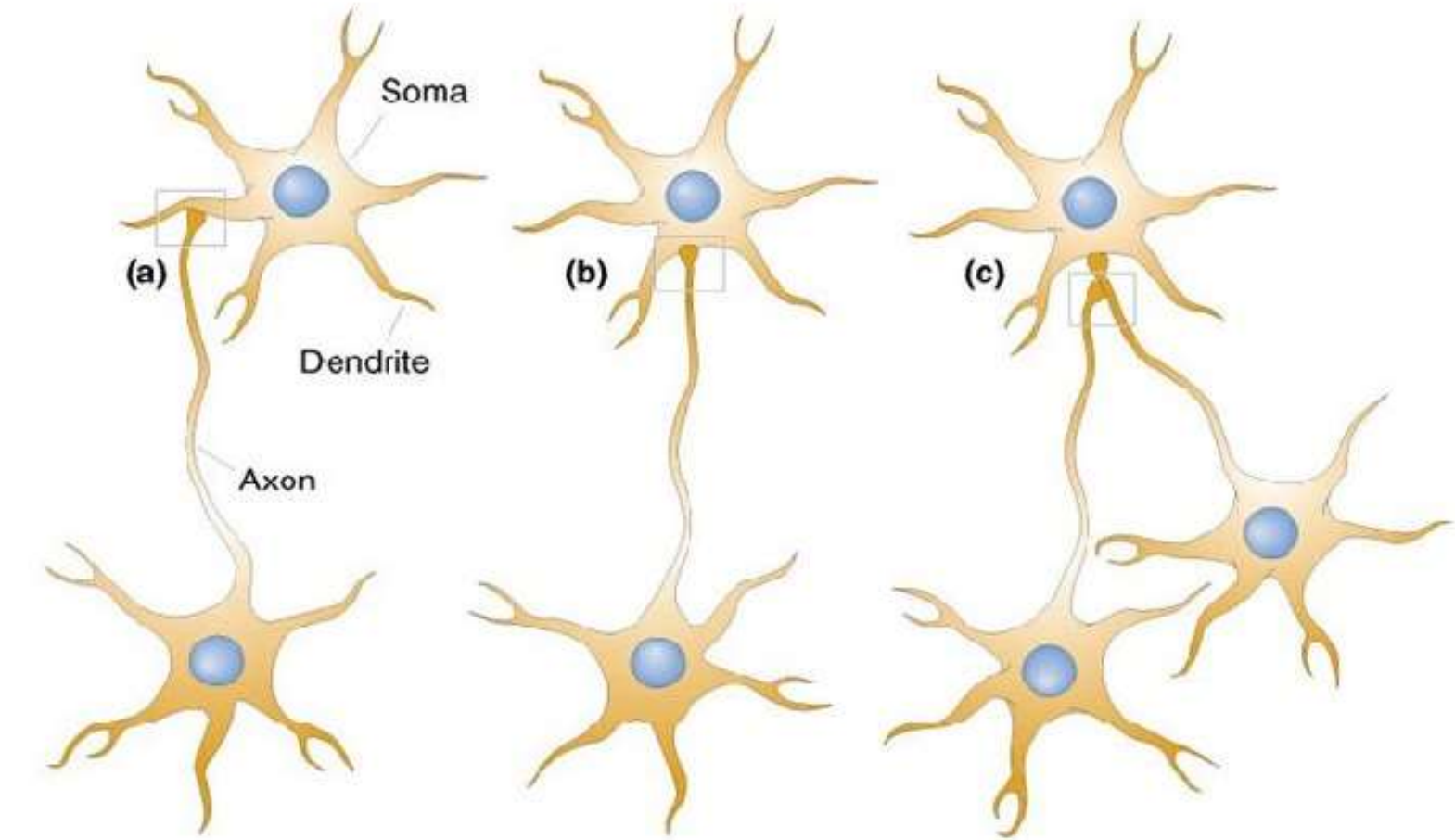
- During the AP, a 2nd stimulus, no matter how strong, will not produce a second AP
- The membrane is said to be in its absolute refractory period.
- Occurs since the voltage-gated Na channels enter a closed, inactive state at the peak of the AP
- Membrane must repolarize before the Na channel can be open.
- After absolute refractory period, there is an interval during which a second action potential can be produced, but only if the stimulus strength is considerably greater than usual.
- Is the relative refractory period, and lasts 10 to 15 ms or longer in neurons
- Occurs during hyperpolarization.

- If a depolarization exceeds the increased threshold or outlasts the relative refractory period, additional action potentials will be fired.
- The refractory periods limit the number of AP’s that can be produced by an excitable membrane in a given period of time.
- Also increase reliability of neural signaling because they help limit extra impulses.
- Most nerve cells respond at frequencies of up to 100 AP’s per sec

Presynaptic or Indirect Inhibition:

- Presynaptic inhibition occurs due to the failure of presynaptic axon terminal to release sufficient quantity of excitatory neurotransmitter substance.
- It is also called indirect inhibition.
- Presynaptic inhibition is mediated by axoaxonal synapses.
- Prominent in spinal cord and regulates propagation of information to higher centers in brain.


1) Axodendritic Synapse
1
2) Axosomatic Synapse
2
Cell Body (Soma)
3
Dendrites
Axon
3) Axoaxonic Synapse



Axodendritic Axosomatic Axoaxonic

CONT…

- Normally, during synaptic transmission, action potential reaching the presynaptic neuron causes development of EPSP’s in the postsynaptic neuron.
- But, in spinal cord, a modulatory neuron called presynaptic inhibitory neuron forms an axoaxonic synapse with the presynaptic neuron
- This inhibitory neuron inhibits the presynaptic neuron and decreases the magnitude of action potential in presynaptic neuron.

- The smaller action potential reduces calcium influx.
- This in turn decreases the quantity of neurotransmitter released by presynaptic neuron.
- The magnitude of EPSP in postsynaptic neuron is decreased resulting in synaptic inhibition

Spatial summation

- Excitation of a single presynaptic terminal on the surface of a neuron almost never excites the neuron
- Because single terminal causes EPSP of only about 0.5 – 1mv instead of the 20 – 30 required to reach threshold
- Many synapses usually stimulated at same time and this effects summate to reach threshold

Temporal summation

- Each time a presynaptic terminal fires, the released transmitter substance opens the membrane channels for at most a millisecond or so.
- This changed postsynaptic potential lasts up to 15 milliseconds after the synaptic membrane channels have already closed.
- A second opening of the same channels can increase the postsynaptic potential to a still greater level

- The more rapid the rate of stimulation, the greater the postsynaptic potential becomes.
- Thus, successive discharges from a single presynaptic terminal, if they occur rapidly enough, can add to one another; that is, they can “summate.”
- This is temporal summation

Fatigue of Synaptic Transmission

- When excitatory synapses are repetitively stimulated at a rapid rate, no. of discharges by postsynaptic neuron very high at first, but rate becomes progressively less in succeeding milliseconds or seconds.
- This is fatigue
- Important as in case of epileptic seizures where fatigue subdues the seizures finally
- Is protective mechanism against excess neuronal activity

- Mainly due to exhaustion of transmitter substance pre-synaptically
- Could also be due to:
- (1) progressive inactivation of many of the postsynaptic membrane receptors
- (2) slow development of abnormal concentrations of ions inside the postsynaptic neuronal cell.

Effect of Acidosis or Alkalosis

- PH affects neuronal transmission highly
- Alkalosis increases excitability highly
- PH of 7.8 – 8 often causes seizures
- Acidosis decreases excitability
- In very severe diabetic patients, coma will develop

Effect of Hypoxia

- Neuronal excitability highly dependent on an adequate oxygen supply.
- Cessation of oxygen for only a few seconds can cause complete in-excitability of some neurons.
- Observed when the brain’s blood flow is temporarily interrupted, because within 3 to 7 seconds the person becomes unconscious

Effect of Drugs

- Many drugs increase or decrease the excitability of neurons
- Caffeine, theophylline, and theobromine, found in coffee, tea, and cocoa respectively, all increase neuronal excitability mostly by decreasing threshold
- Most anesthetics increase threshold for excitation thus decreasing synaptic transmission at many points in the nervous system

Synaptic delay

- During transmission of a neuronal signal from a presynaptic neuron to a postsynaptic neuron, a certain amount of time is consumed in the process of
- (1) discharge of the transmitter substance by the presynaptic
- terminal,
- (2) diffusion of the transmitter to the postsynaptic neuronal membrane,
- (3) action of the transmitter on the membrane receptor,

- (4) action of the receptor to increase the membrane permeability, and
- (5) inward diffusion of sodium to raise the excitatory postsynaptic potential to a high enough level to elicit an action potential.
- The minimal period of time required for all these events to take place, even when large numbers of excitatory synapses are stimulated simultaneously, is about 0.5 millisecond.
- This is synaptic delay.

NEUROTROPHINS

- For trophic support of neurons
- Some proteins, referred to as neurotrophins, have been found to be necessary for survival and growth of neurons
- Some are products of the muscles or other structures that the neurons innervate whereas others are produced by astrocytes.
- They bind to receptors at the endings of a neuron,, are then internalized and then transported by retrograde transport to the neuronal cell body
- Here cause production of proteins associated with neuronal development, growth, and survival.

- Other neurotrophins are produced in neurons and transported anterogradely to the nerve ending, where they maintain the integrity of the postsynaptic neuron.
- The neurons have receptors for the neutrophils for the uptake into neuron
- One of the most important is the **Nerve Growth Factor**

Nerve growth factor

- It is a protein growth factor necessary for the growth and maintenance of sympathetic neurons and some sensory neurons.
- Made up of two α, two β, and two γ subunits.
- It is picked up by neurons in the extracerebral organs they innervate
- Transported in retrograde fashion from the endings of the neurons to their cell bodies.

- NGF also present in the brain
- Appears to be responsible for the growth and maintenance of cholinergic neurons in the basal forebrain and striatum.
- Injection of antiserum against NGF in newborn animals leads to near total destruction of the sympathetic ganglia
- there is evidence that the maintenance of neurons by NGF is due to a reduction in apoptosis (programmed cell death)

- Others include Brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), NT-4/5 which again help in reduction of apoptosis among other effects
- Schwann cells and astrocytes produce ciliary neurotrophic factor (CNTF).
- It promotes the survival of damaged and embryonic spinal cord neurons
- May prove to be of value in treating human diseases in which motor neurons degenerate

Chemical transmission at synapse

- Nerve endings have been called biological transducers that convert electrical energy into chemical energy.
- This conversion process involves

i. The synthesis of the transmitter agents,

ii. The storage of neurotransmiter in synaptic vesicles, and

iii. The release of NT by the nerve impulses into the synaptic cleft.

iv. The NT acting on appropriate receptors on postsynaptic membrane

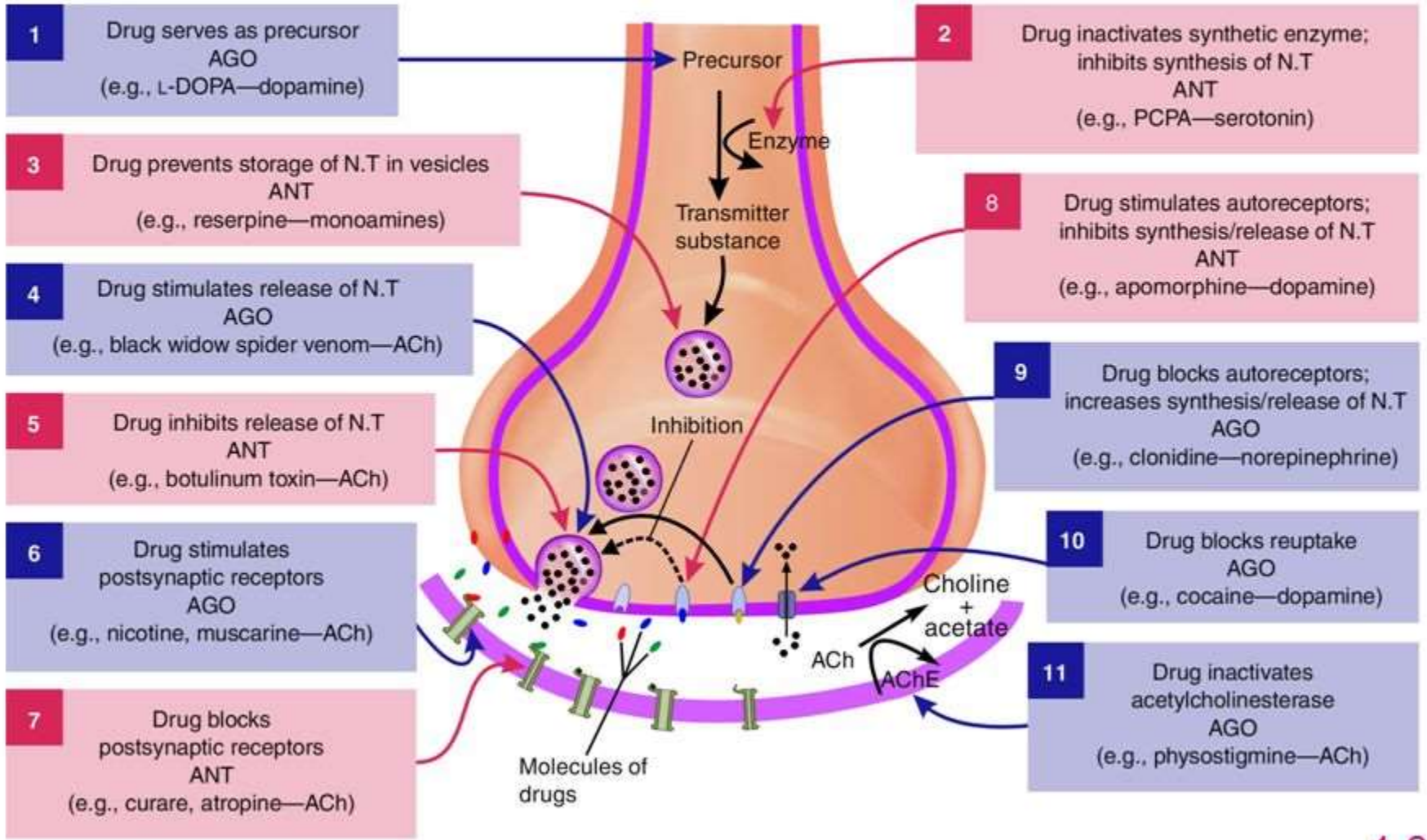
v. Rapid removal of the NT the synaptic cleft.

- All these processes, plus the postreceptor events in the postsynaptic neuron, are regulated by many physiologic factors and can be altered by drugs.
- Therefore, interventions can be done to alter nerve function in any one of the steps involved in synaptic transmission as we will find out later

- A great majority of drugs that act on the nervous system do so by altering synaptic mechanisms and thus synaptic effectiveness.
- All the synaptic mechanisms in earlier slide are vulnerable.
- Long-term effects of drugs are sometimes difficult to predict because the imbalances produced by the initial drug action are soon counteracted by feedback mechanisms that normally regulate the processes.
- EG: If a drug interferes with the action of a NT by inhibiting its synthesis, the neurons may respond by increasing the rate of precursor transport into the axon terminals to maximize the use of any enzyme that is available.

- Drugs that bind to a receptor and produce a response similar to the normal activation of that receptor are called agonists, and drugs that bind to the receptor but are unable to activate it are antagonists.
- By occupying the receptors, antagonists prevent binding of the normal neurotransmitter when it is released at the synapse.
- Specific agonists and antagonists can affect receptors on both pre- and postsynaptic membranes.
- Diseases can also affect synaptic mechanisms.

Drug Action on Synaptic Transmission



Antagonist drugs are in red, Agonists are in blue

Neurotransmiters

- Acetylcholine Acetylcholine (ACh) is synthesized from choline and acetyl coenzyme A in the cytoplasm of synaptic terminals and stored in synaptic vesicles.
- After release, activates receptors on the postsynaptic membrane
- Inactivated (metabolized) by the enzyme acetylcholinesterase located on the pre- and postsynaptic membranes
- Choline released during inactivation taken up into presynaptic axon for synthesis of new ACh.
- The ACh concentration at the receptors is also reduced by simple diffusion away from the site

- Found in both peripheral and CNS
- Receptors in brain are important in cognitive functions.
- Some play major role in attention, learning, and memory by reinforcing the ability to detect and respond to meaningful stimuli.
- Degeneration of this neurons common in people with Alzheimer’s disease, a brain disease that is usually age-related and is the most common cause of declining intellectual function in late life, affecting 10 to 15 percent of people over age 65, and 50 percent of people over age 85.

- Because of the degeneration of cholinergic neurons, this disease is associated with a decreased amount of ACh in certain areas of the brain and even the loss of the postsynaptic neurons that would have responded to it.
- These defects and those in other neurotransmitter systems that are affected in this disease are related to the declining language and perceptual abilities, confusion, and memory loss that characterize Alzheimer’s victims.
- The exact causes of this degeneration are unknown

Biogenic Amines

- Are neurotransmitters that are synthesized from amino acids and contain an amino group (R–NH2).
- Most common are dopamine, norepinephrine, serotonin, and histamine and epinephrine
- Catecholamines
- Dopamine, norepinephrine (NE), and epinephrine referred to as catecholamines.
- Formed from amino acid tyrosine and share the same basic synthetic pathway
- Synthesis and release from the presynaptic terminals strongly modulated by autoreceptors on the presynaptic terminals.

- After activation of the receptors on the postsynaptic cell, the NT is decreased by
- Active transport into the presynaptic axon terminal.
- Metabolism by enzymes at terminal mostly by monoamine oxidase and Catechol –o- methyl transferase
- Monoamine oxidase inhibitors, which increase the brain extracellular concentration of the catecholamine neurotransmitters, are used in the treatment of diseases such as depression
- In the CNS play essential roles in states of consciousness, mood, motivation, directed attention, movement, blood-pressure regulation among others

Serotonin

- Produced from amino acid tryptophan
- Its effects generally have a slow onset, indicating that it works as a neuromodulator.
- Serotonin releasing neurons innervate virtually every structure in the brain and spinal cord and operate via at least 16 different receptor types.
- In general, it has an excitatory effect on pathways that are involved in the control of muscles, and an inhibitory effect on pathways that mediate sensations.

- The activity of serotonergic neurons is lowest or absent during sleep and highest during states of alert wakefulness.
- In addition to their contributions to motor activity and sleep also involved in
- Regulation of food intake (depresses appetite),
- Reproductive behavior (activation reduces sexual behavior), and
- Emotional states such as mood and anxiety (low levels associated with emotional disorders).

Amino Acid Neurotransmitters

- Several amino acids function as neurotransmitters.
- Are by far the most prevalent neurotransmitters in CNS
- EXCITATORY AMINO ACID NT's
- Glutamate and aspartate, serve as neurotransmitters at most of excitatory synapses in the CNS
- In fact, most excitatory synapses in the brain release glutamate.
- The excitatory amino acids function in learning, memory, and neural development.
- Also implicated in epilepsy, Alzheimer's and Parkinson's diseases, and the neural damage that follows strokes, brain trauma, and other conditions of low oxygen availability

- INHIBITORY Amino Acid NT’s
- GABA (gamma-aminobutyric acid) and Glycine are the major inhibitory neurotransmitters in the CNS
- Drugs such as Valium that reduce anxiety, guard against seizures, and induce sleep enhance the action of GABA.