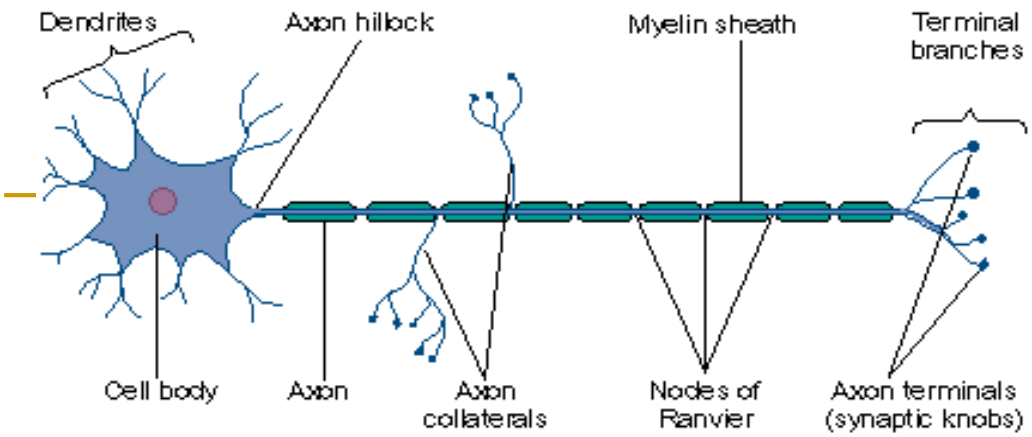
Nervous system



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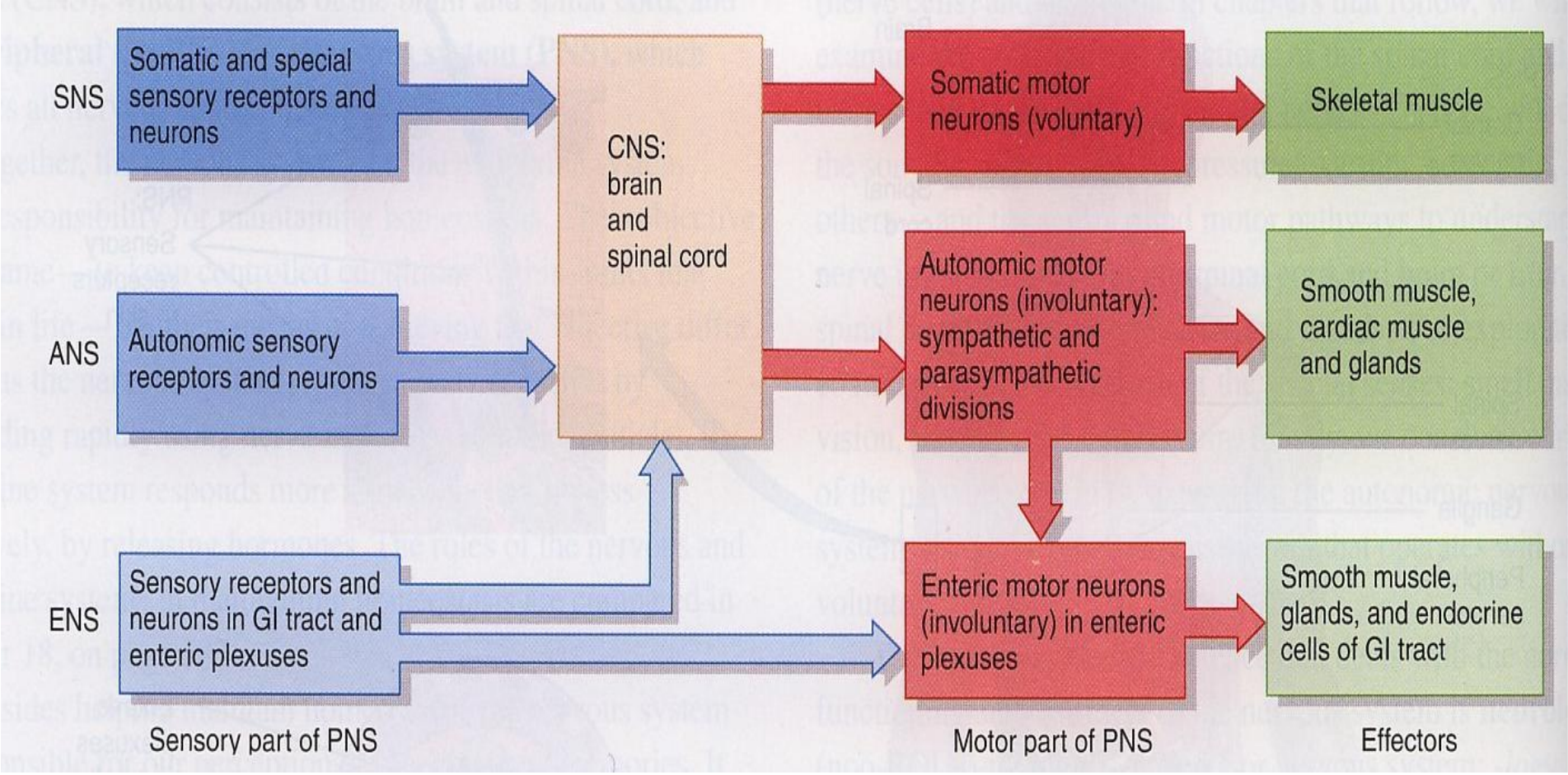
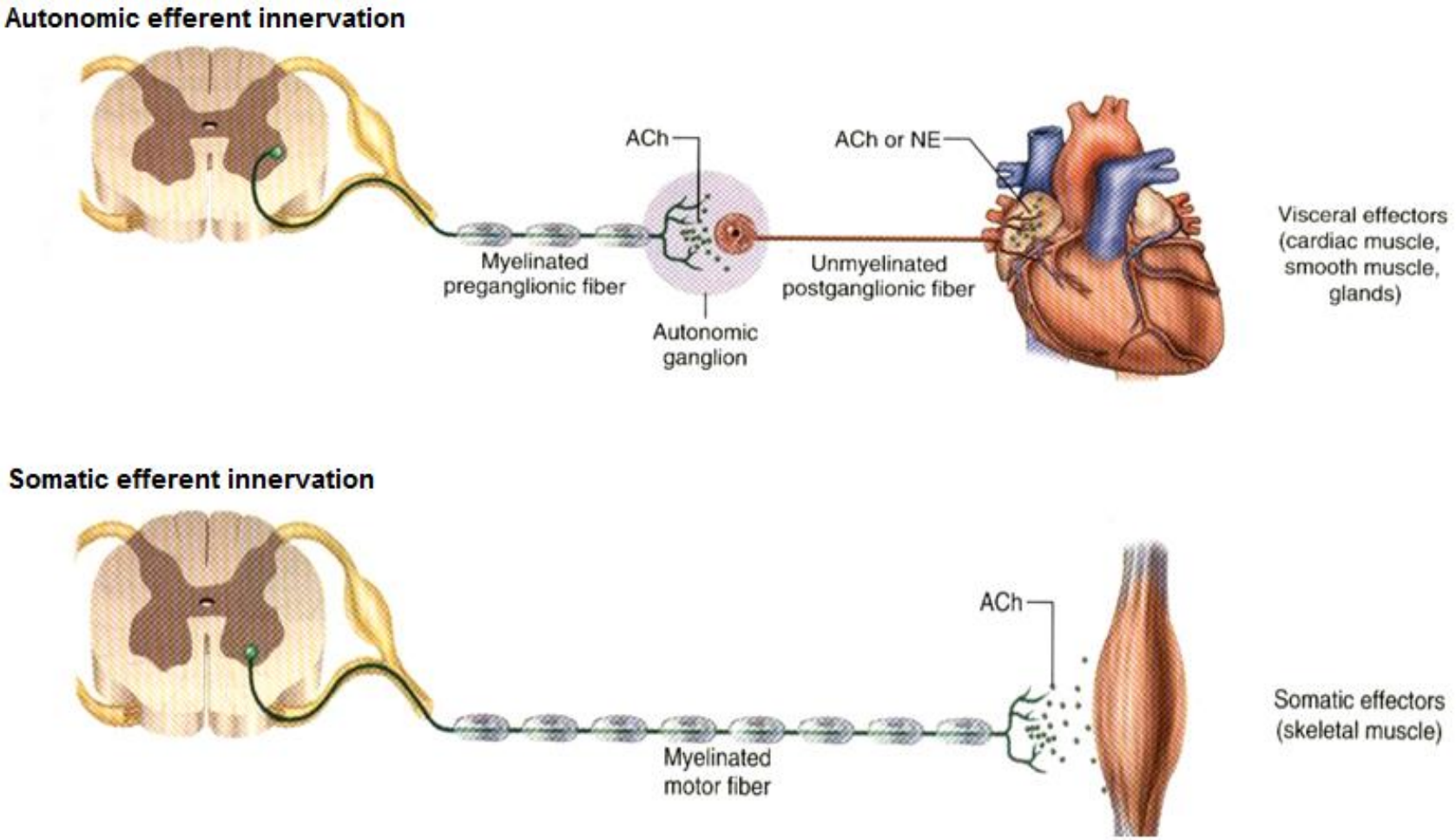
Dept. of Physiology, PUMS

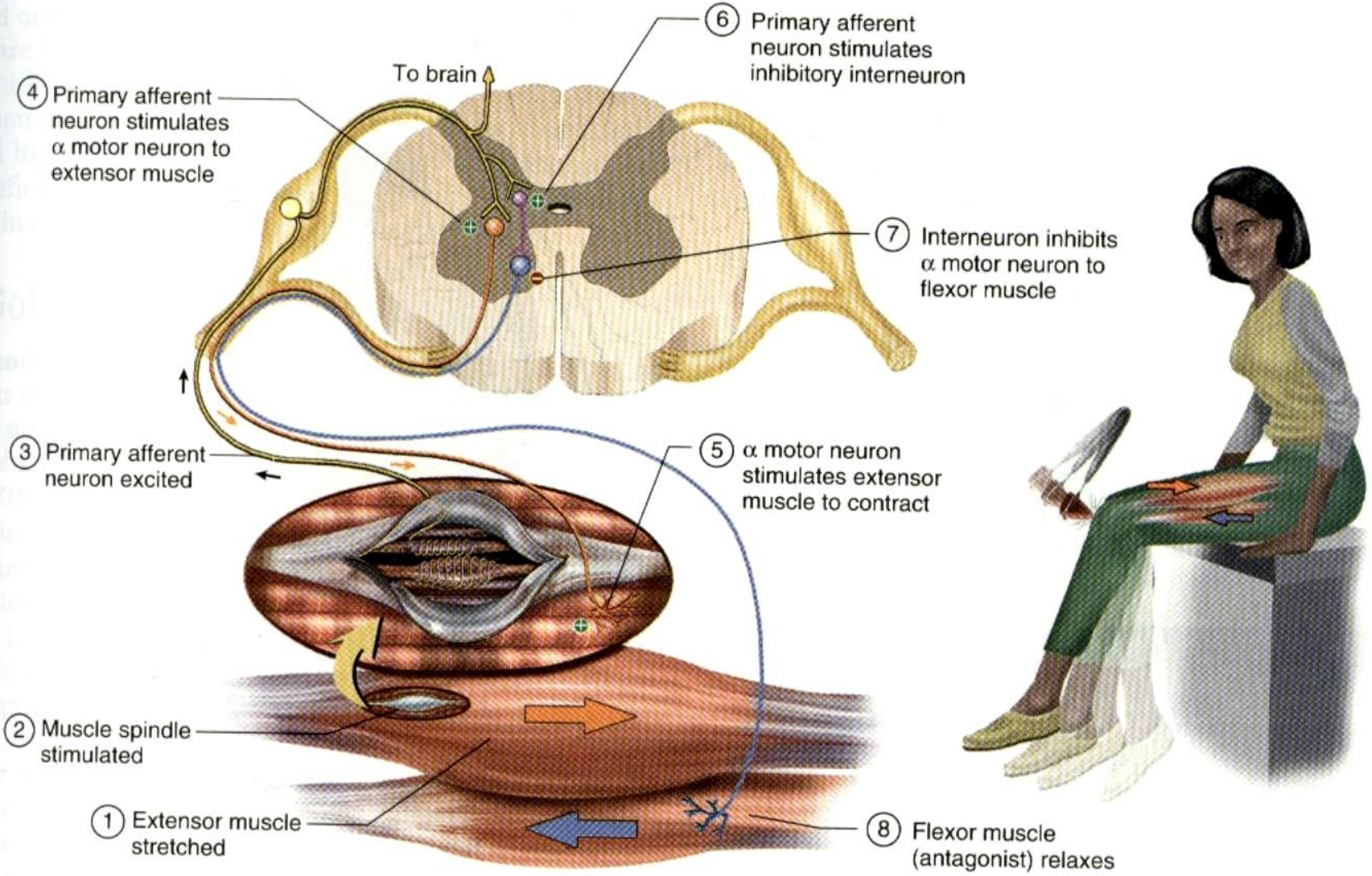
Organization of the nervous system



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 388, Figure 12.2

Autonomic and somatic efferent pathways

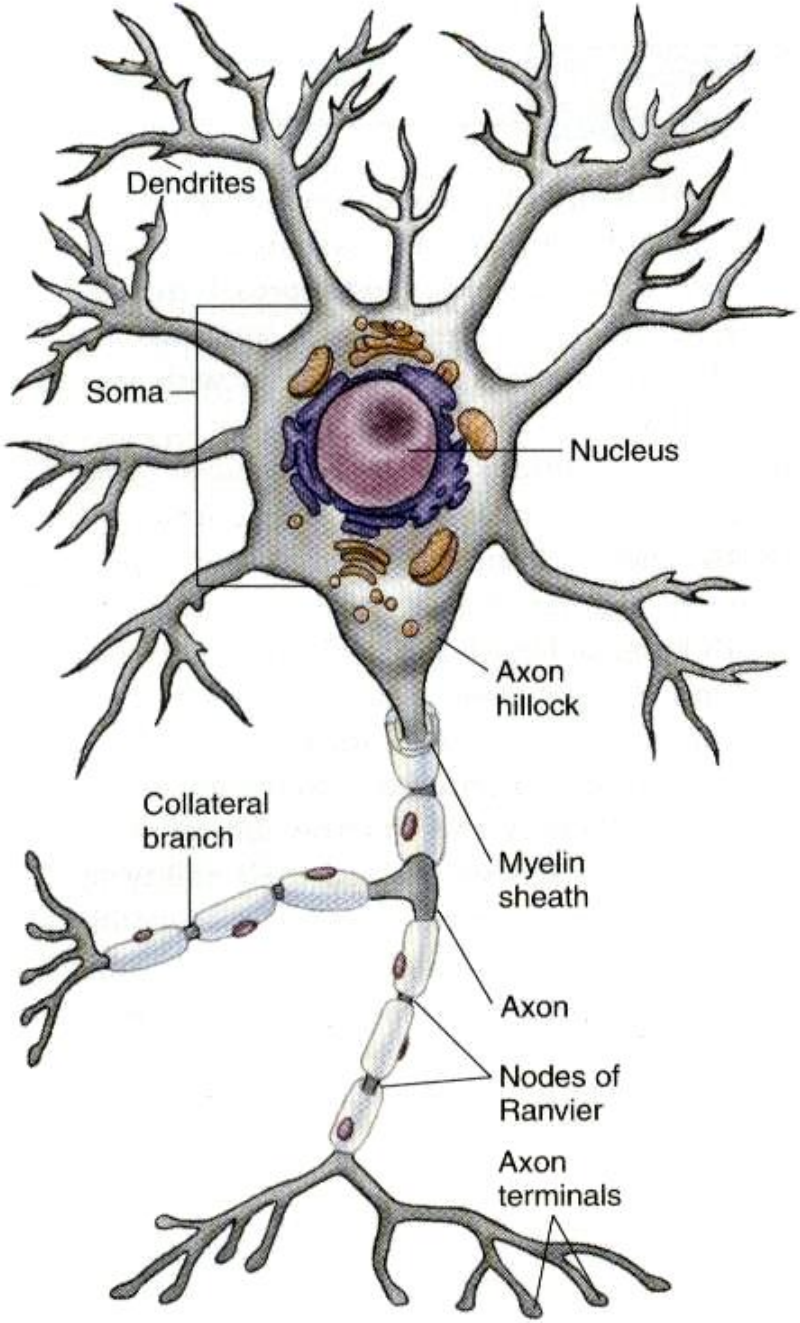


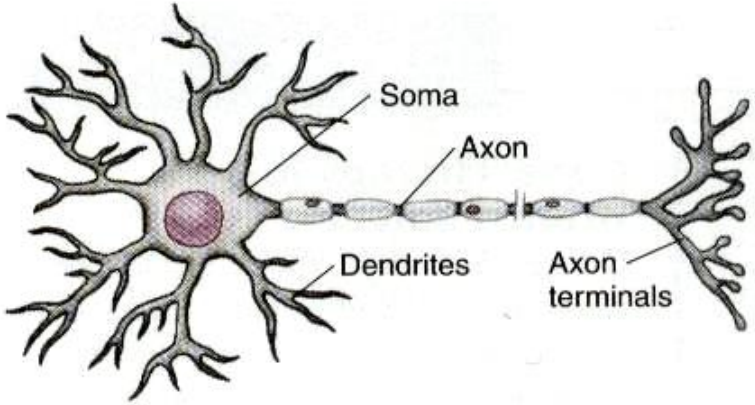


Reflex arc - a neural pathway that controls a reflex.

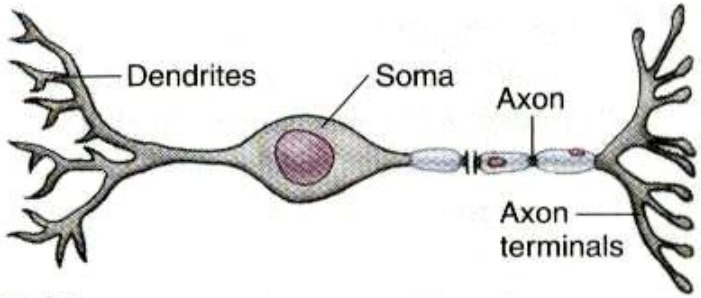
Anatomy review

Structure of neurons, excitability, ions distribution across cell membrane

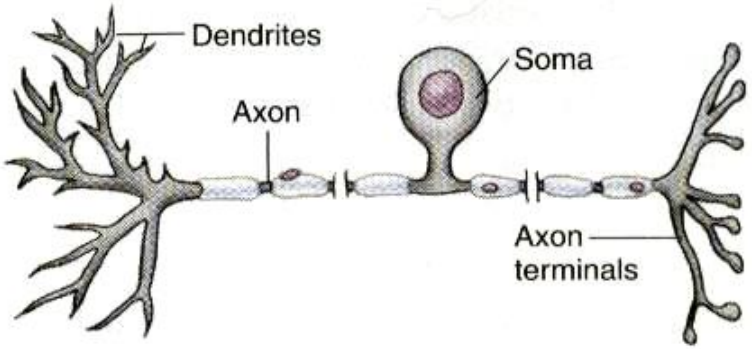




Multipolar



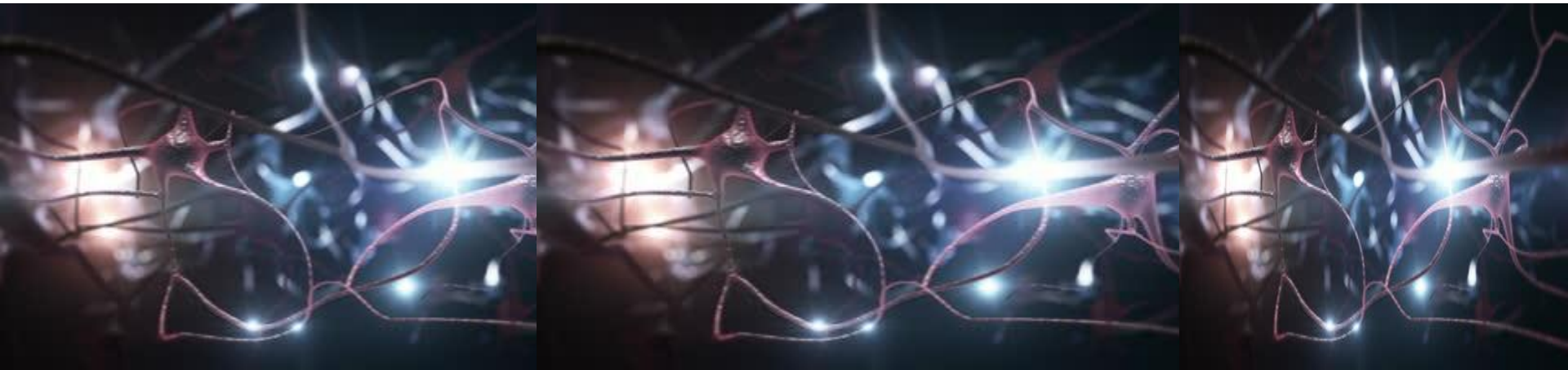
Bipolar



Pseudo-unipolar

Electrical excitability

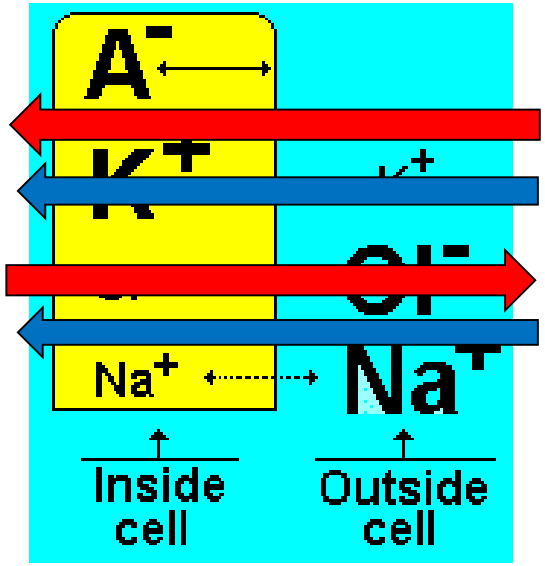
- Ability of nerve cell to respond to the applied stimulus by generating its own action potential
- Basic communication



Ion channels

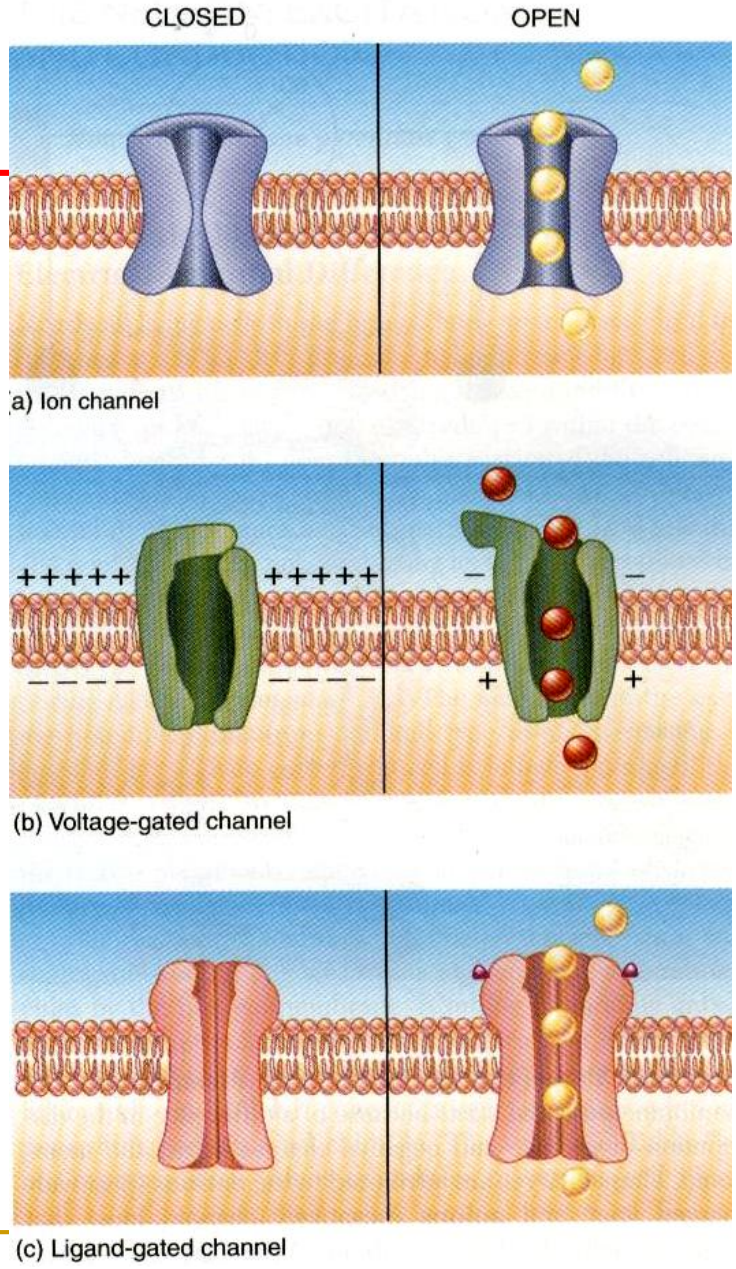
Nongated and gated ion channels – structure, function and localization

Relative concentration of ions inside and outside of cells

ICF		*ECF*
Na^+ 15		Na^+ 150
K^+ 150		K^+ 5
Cl^- 10		Cl^- 125
Protein anions		

Electrical signals in neurons

- Ion channels
  - Ion channels are selective.
  - Ion channels may be opened or closed.
  - Types of ion channels
    - A leakage channels
    - A voltage-gated channel
    - A ligand-gated channel
    - A mechanically gated channel

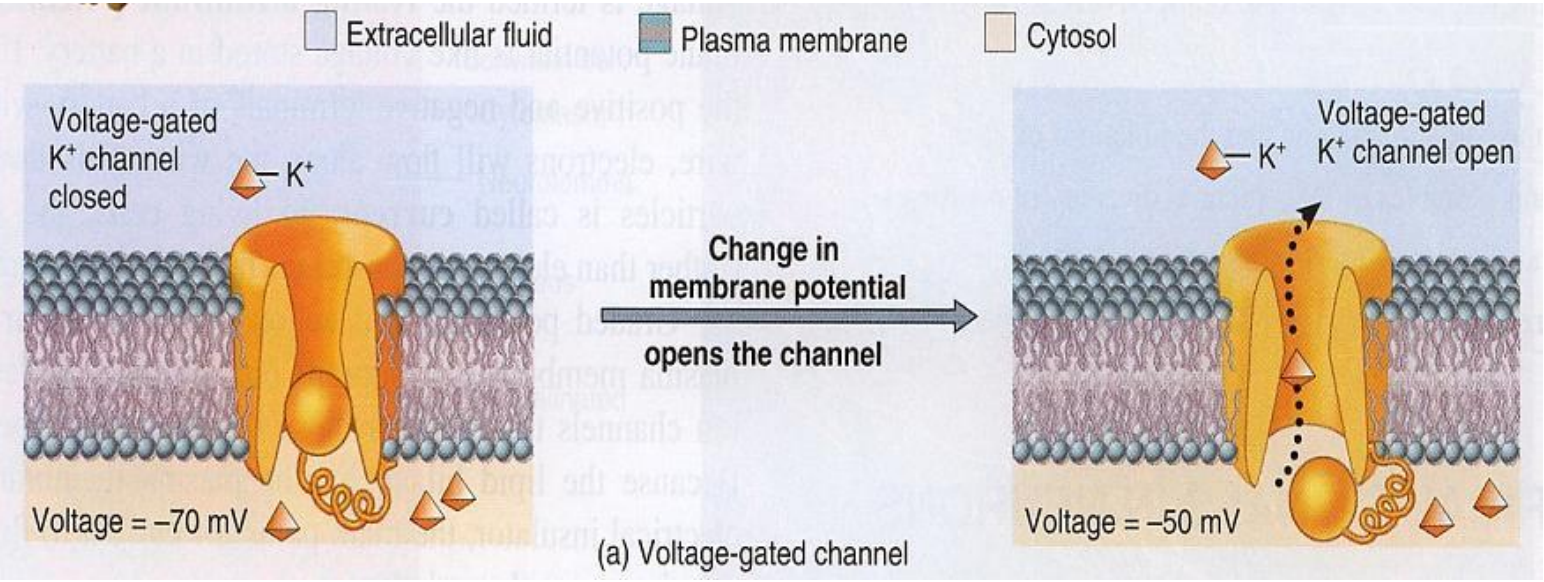


Leakage channels

- In leakage channels, the gates randomly alternate between open and closed position.
- Typically, plasma membranes have many more potassium ion (K^+) leakage channels than sodium ion (Na^+) leakage channels. Thus, the membranes permeability to K^+ is much higher than its permeability to Na^+.

Voltage-gated channels

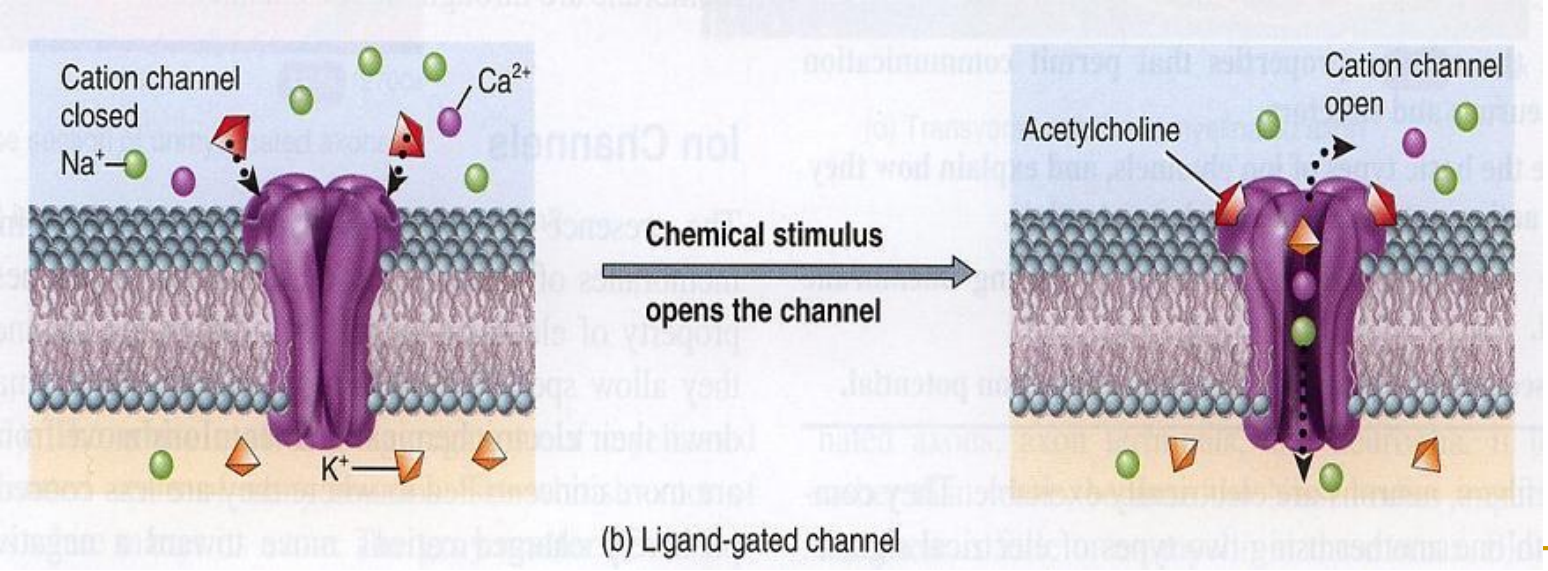
- A voltage-gated channel open in response to a change in membrane potential (voltage).
- Voltage-gated channels participate in the generation and conduction of action potential



Tortora & Grabowski – Principles of Anatomy & Physiology; Page 396, Figure 12.8

Ligand-gated channels

- A ligand-gated channel opens and closes in response to a specific chemical stimulus (neurotransmitters, hormones, and particular ions).
- The neurotransmitter acetylocholine, for example, opens cation-channels that allow Na^+ and Ca^{2+} to diffuse inward and K^+ to diffuse outward.

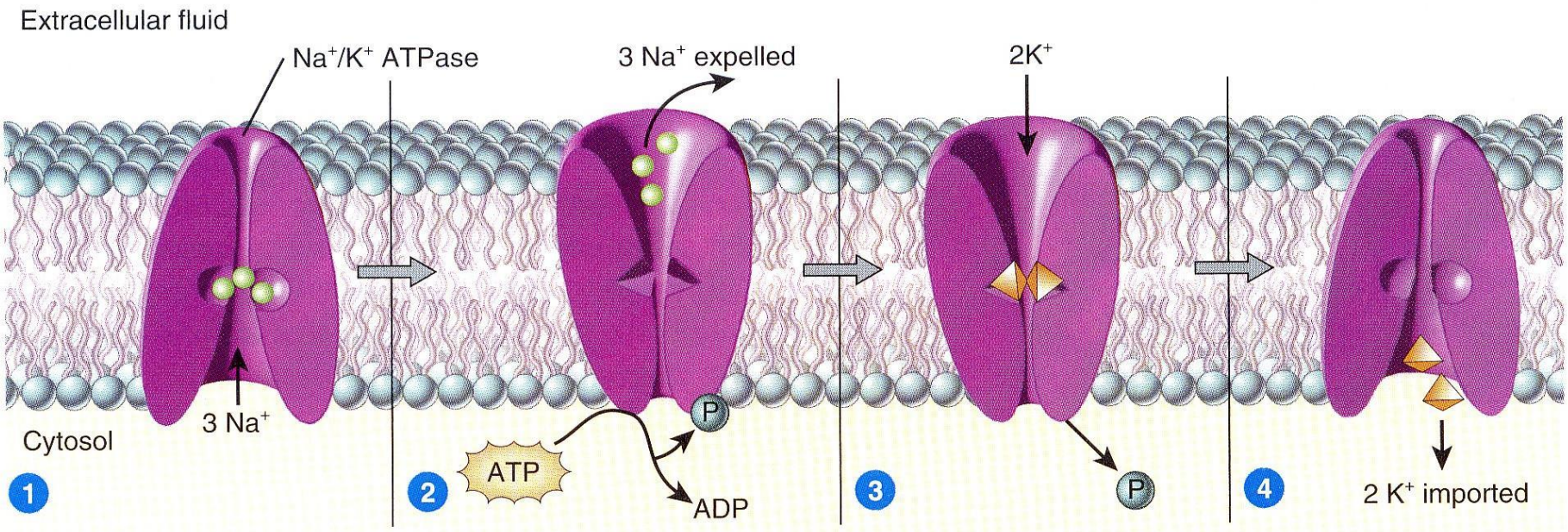


(b) Ligand-gated channel

Tortora & Grabowski – Principles of Anatomy & Physiology; Page 396, Figure 12.8

Mechanically gated channels

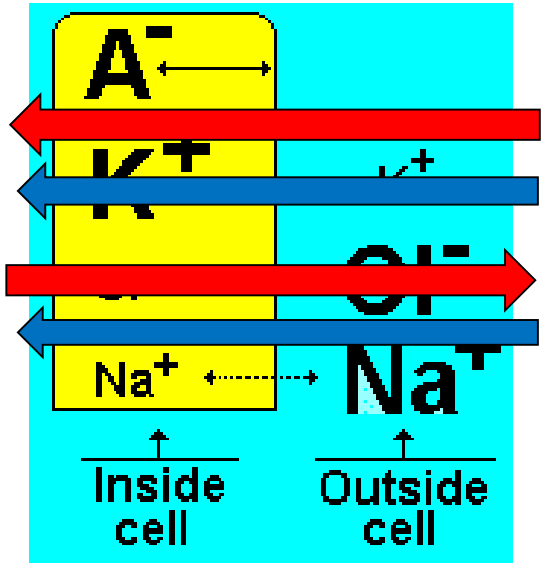
- A mechanically gated channel open or closes in response to mechanical stimulation in the form vibration (such as sound waves), pressure (such a touch), or tissue stretching.
- The force distorts the channel from resting position, opening the gate.


Extracellular fluid
Na+/K+ ATPase
3 Na+ expelled
2K+
3 Na+
Cytosol
ATP
P
ADP
P
2 K+ imported
1
2
3
4

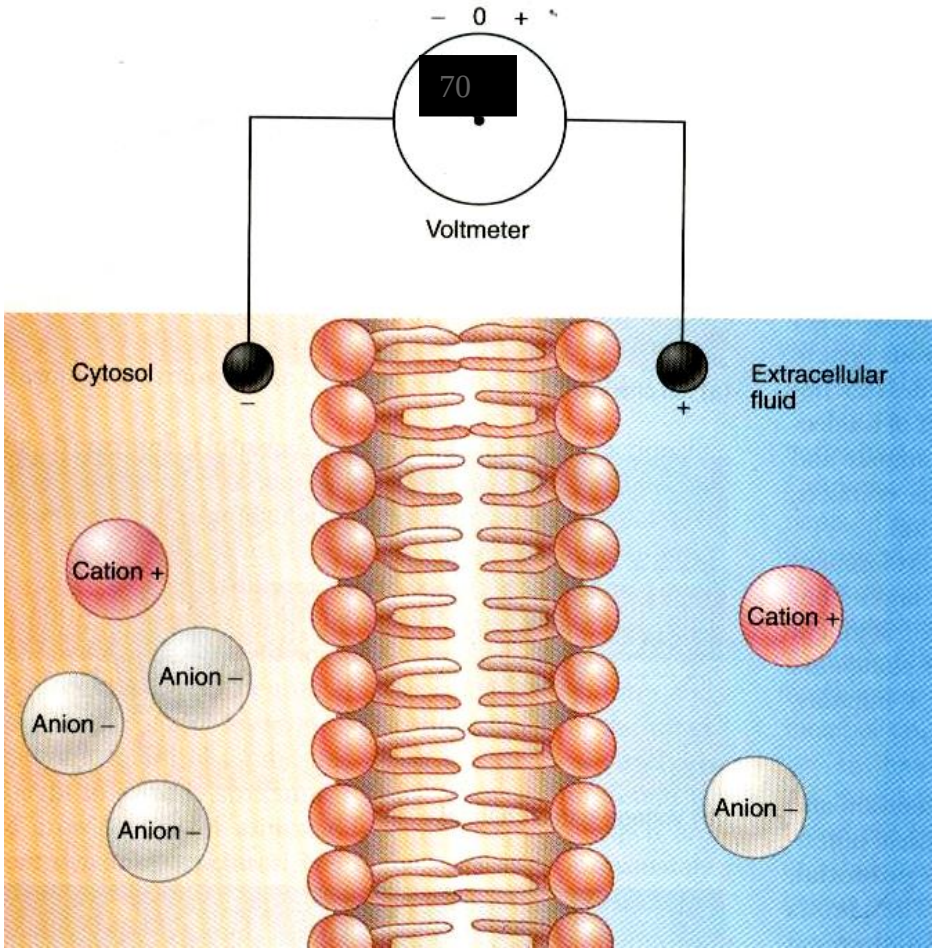
Membrane potential

Membrane permeability, electrical and chemical gradients, Na+/K+ pump, resting and action potential,

Relative concentration of ions inside and outside of cells

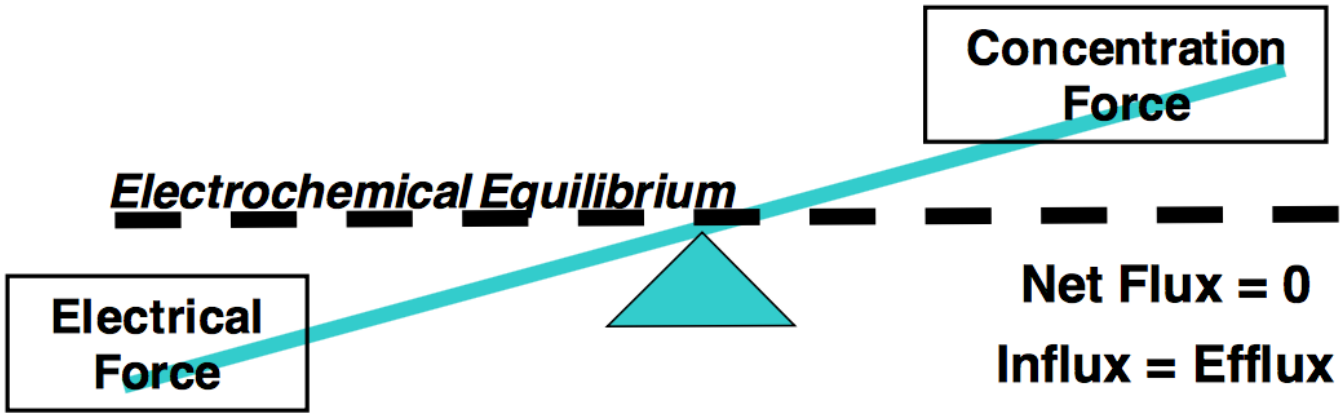
ICF		*ECF*
Na^+ 15		Na^+ 150
K^+ 150		K^+ 5
Cl^- 10		Cl^- 125
Protein anions		

The inside of the cel is negatively charged comparing with the outside

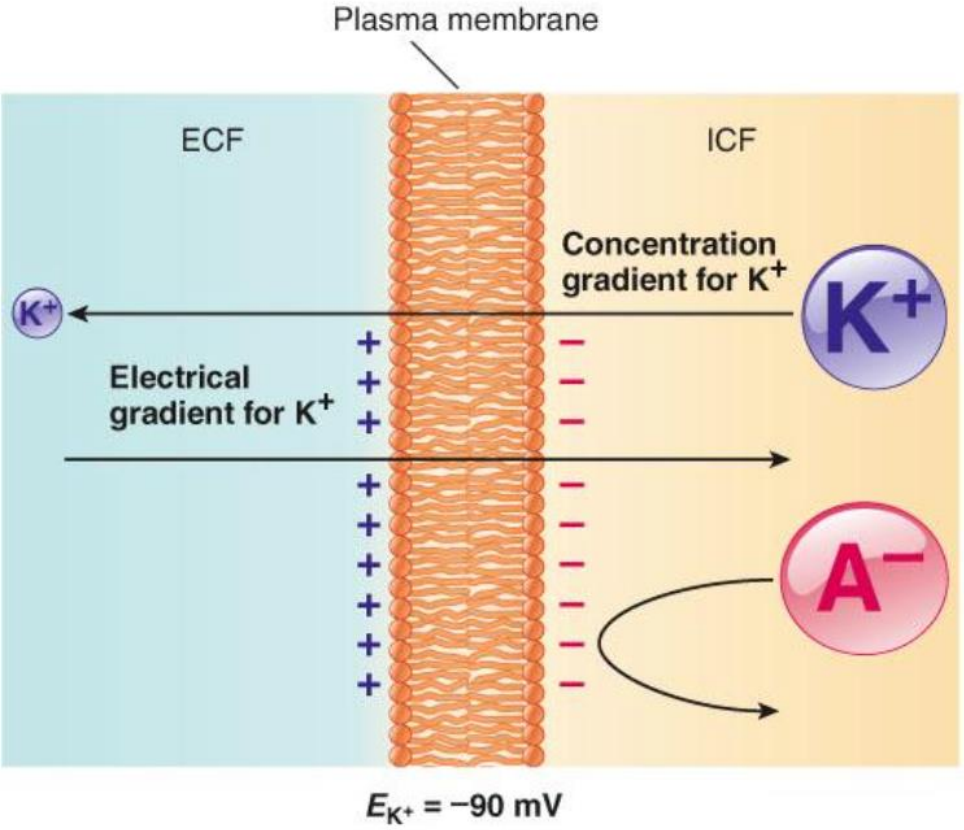


Equilibrium Potential

- Refers to the diffusion potential (electrical force) that exactly balances or opposes the tendency for diffusion down the concentration gradient.
- Net movement STOPS when the ion is in equilibrium (chemical and electrical driving forces are equal and opposite in direction).
- Determine by a given set of ion concentrations.
- Magnitude of potential is directly proportional to magnitude of concentration gradient.



K+ Equilibrium Potential

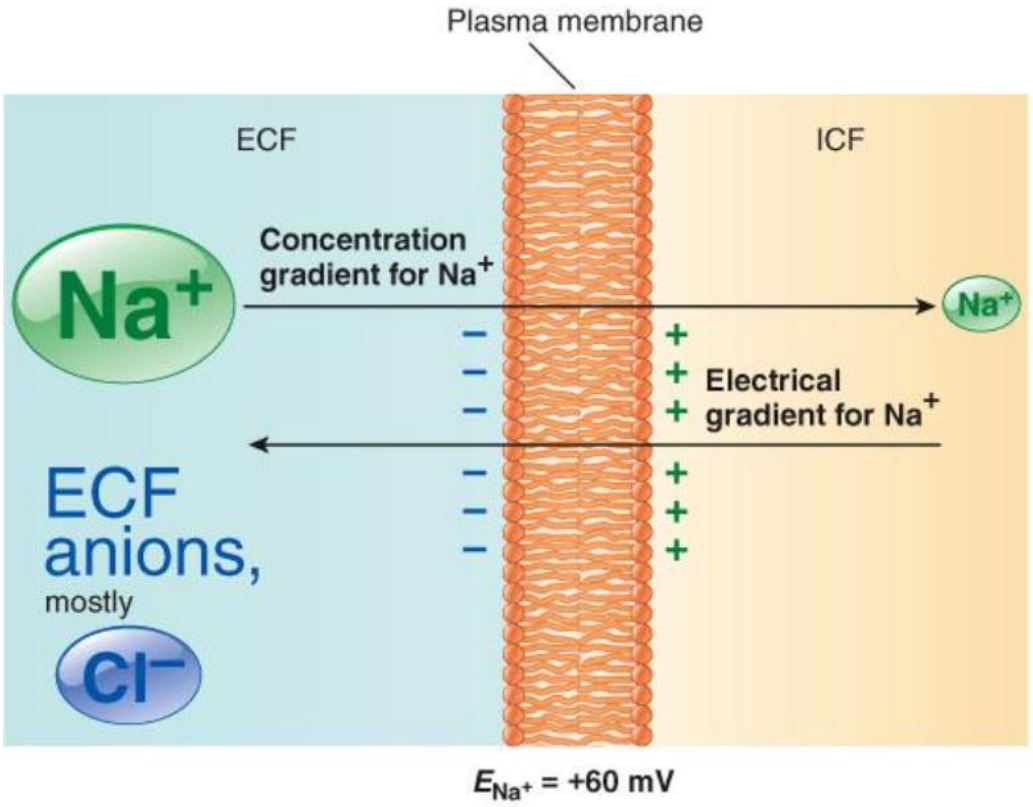


1. The concentration gradient for K^+ tends to move this ion out of the cell.
2. The outside of the cell becomes more positive as K^+ ions move to the outside down their concentration gradient.
3. The membrane is impermeable to the large intracellular protein anion (A^-). The inside of the cell becomes more negative as K^+ ions move out, leaving behind A^-.
4. The resulting electrical gradient tends to move K^+ into the cell.
5. No further net movement of K^+ occurs when the inward electrical gradient exactly counterbalances the outward concentration gradient. The membrane potential at this equilibrium point is the equilibrium potential for K^+ (E_{K^+}) at −90 mV.

E_{K^+} = -90 mV

Sherwood, L., Human Physiology

Na+ Equilibrium Potential

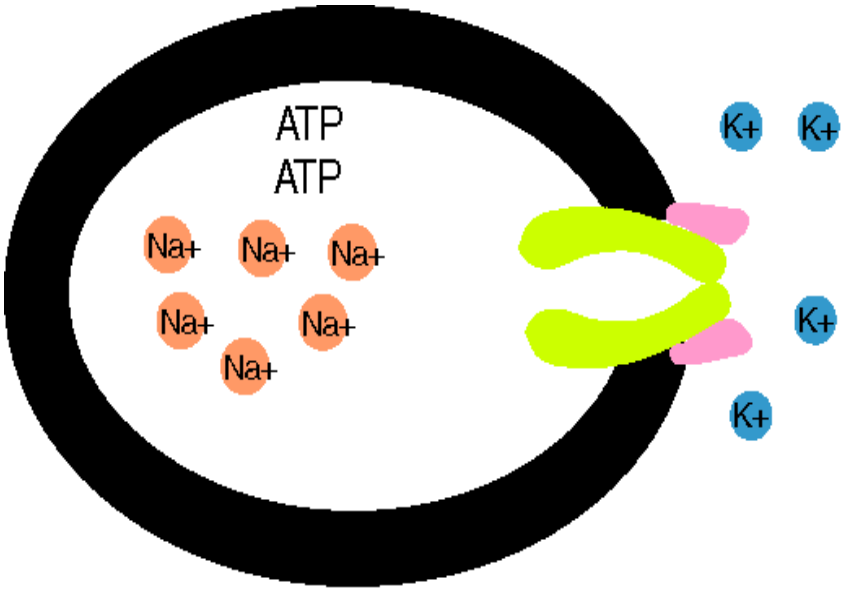


1. The concentration gradient for Na^+ tends to move this ion into the cell.
2. The inside of the cell becomes more positive as Na^+ ions move to the inside down their concentration gradient.
3. The outside becomes more negative as Na^+ ions move in, leaving behind in the ECF unbalanced negatively charged ions, mostly Cl^-.
4. The resulting electrical gradient tends to move Na^+ out of the cell.
5. No further net movement of Na^+ occurs when the outward electrical gradient exactly counterbalances the inward concentration gradient. The membrane potential at this equilibrium point is the equilibrium potential for Na^+ (E_{Na^+}) at +60 mV.

E_{Na^+} = +65 mV

Sherwood, L., Human Physiology

Na+/K+ pump

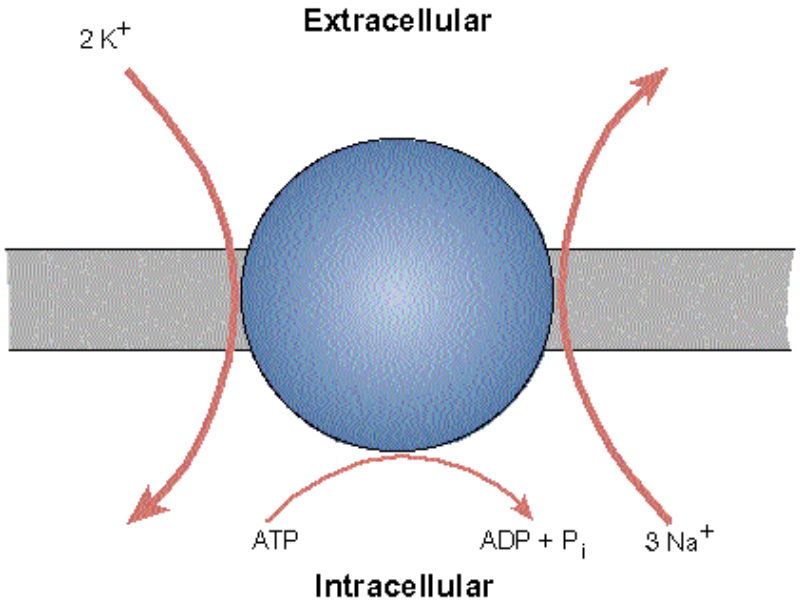


- mechanoenzyme (ATP-ase catalysing dephosphorylation of ATP)
- Helps to transport 3 molecules of Na^+ and 2 molecules of K^+

  for each mol of hydrolysed ATP

Active transport!!!

Na+/K+ pump cont.



- Mg^{2+}
- O_2
- Energy substrates
- 37°C
- Disposal of CO_2
- *Inactivated by digitalis*

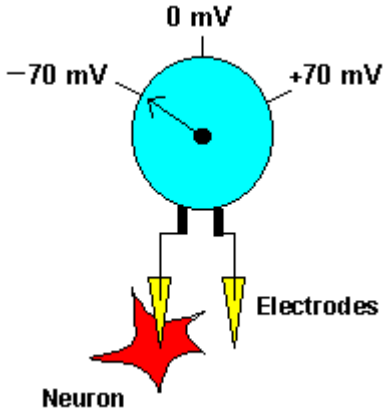
Digitalis purpurea

Electrical signals in neurons

- **Resting membrane potential**
  - resting membrane potential is expressed as the measured potential difference across the cell membrane in millivolts (mV)
  - in neurons a typical value of resting membrane potential is -70mV
  - the minus sign indicates that the inside is negative relative to the outside
  - a cell that exhibits a membrane potential is said to be polarized

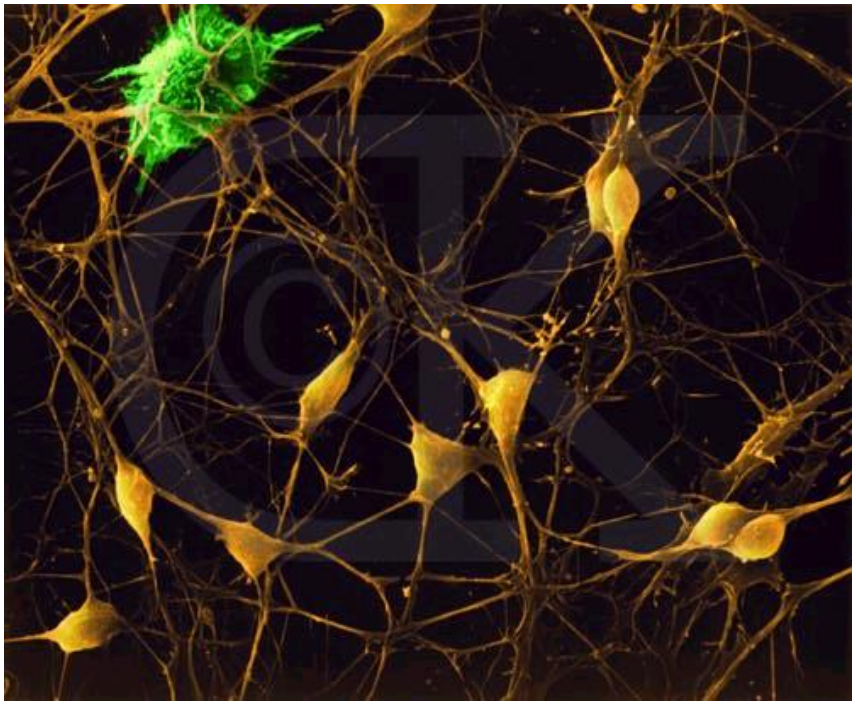
Resting membrane potential between -70 and -80 mV

- It's value approximates equilibrium potential for K+
- Inside: organic anions and K^+
- Activity of Na+/K+ pump
- Presence of ion channels



Resting membrane potential

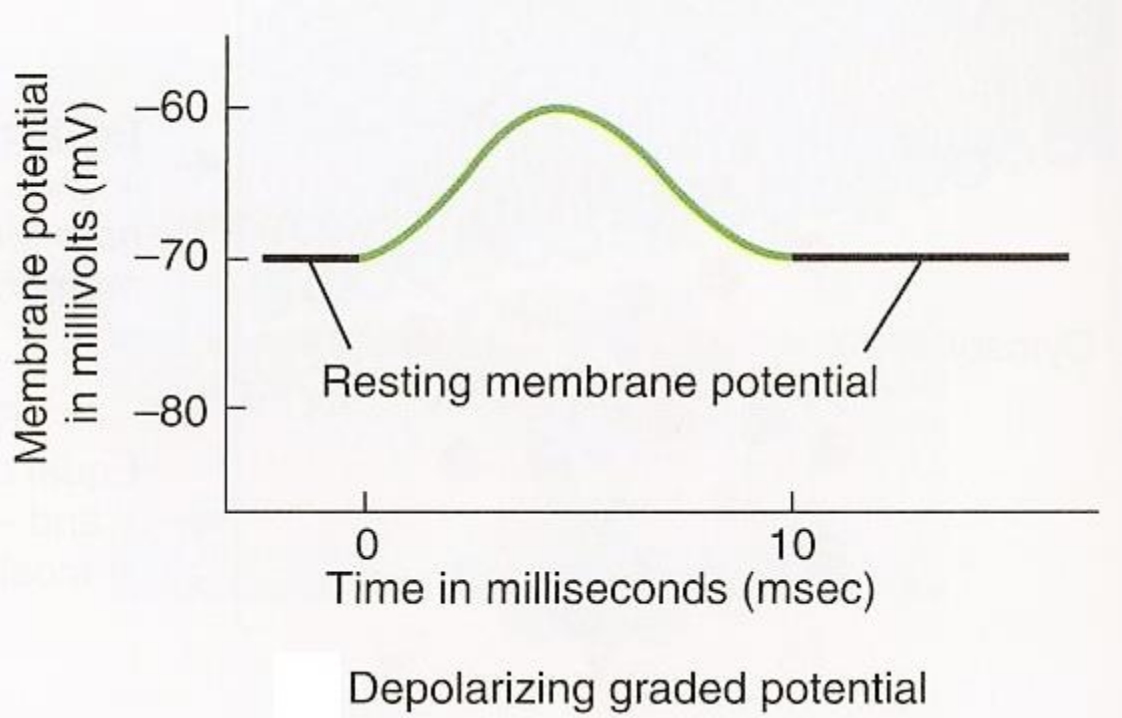
- Resting membrane potential is not unchangeable
- Decreased value – *hyperpolarization*
- Increased value - *hypopolarization*



Graded potential

Depolarizing graded potential (eg. EPSP)

- Graded potential
  - When the response makes the membrane less polarized, it is termed a depolarizing graded potential .

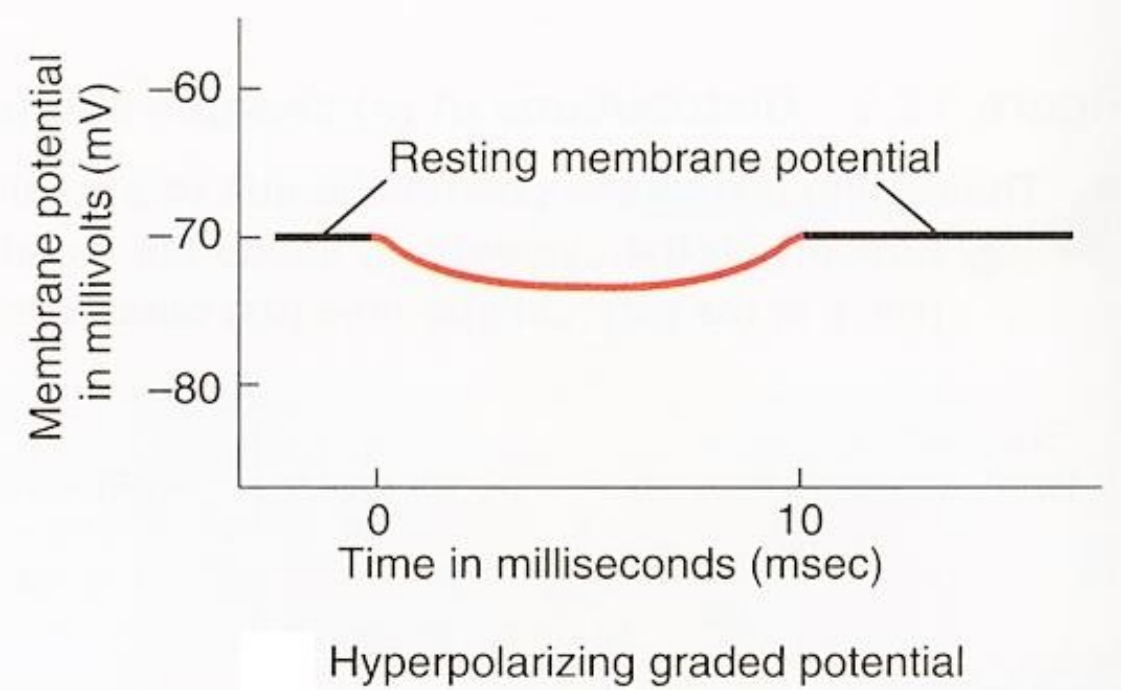


Depolarizing graded potential

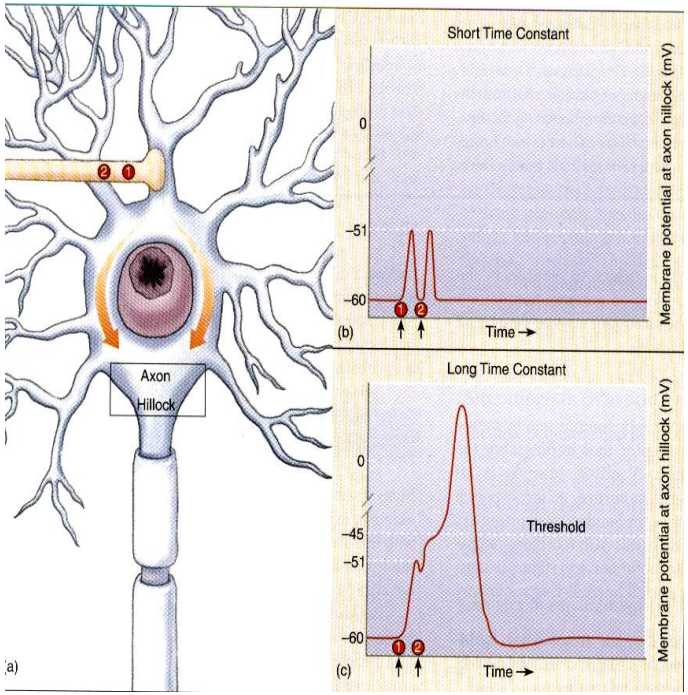
Tortora & Grabowski – Principles of Anatomy & Physiology; Page 398, Figure 12.10

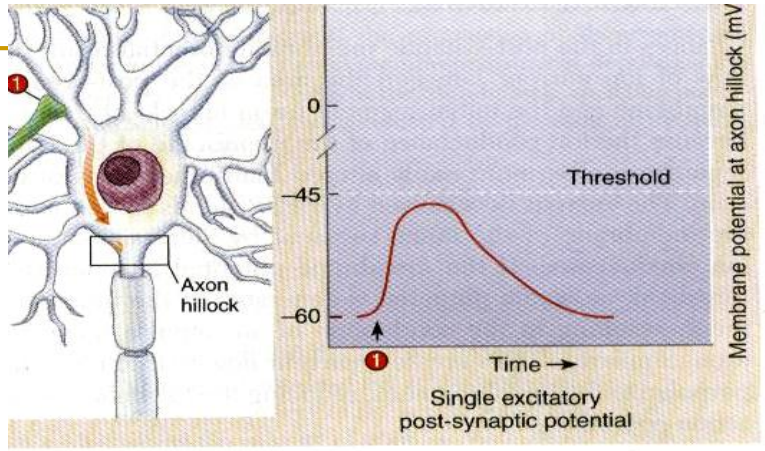
Hyperpolarizing graded potential (eg. IPSP)

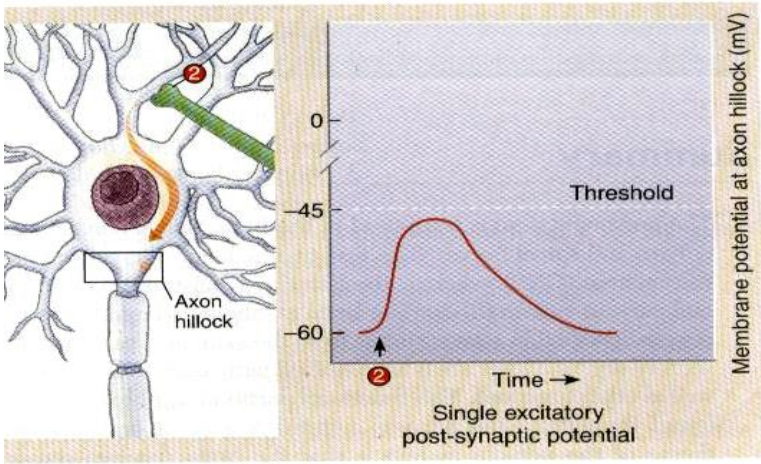
- Graded potential
  - When the response makes the membrane even more polarized (a greater difference in the change between inside and outside) it is termed a hyperpolarizing graded potential.

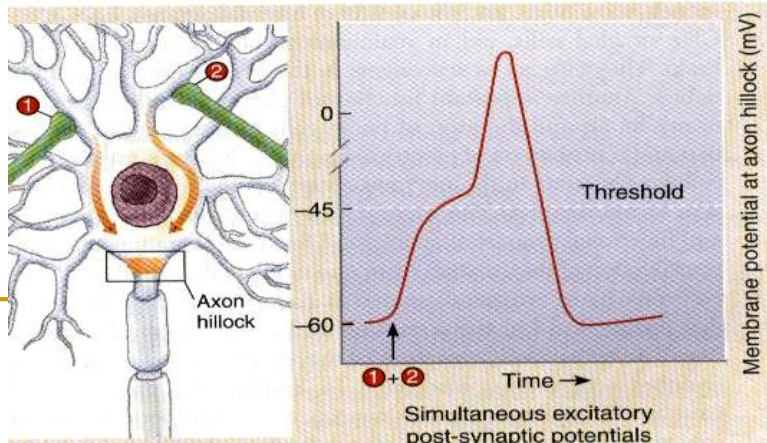


Summation of synaptic potentials







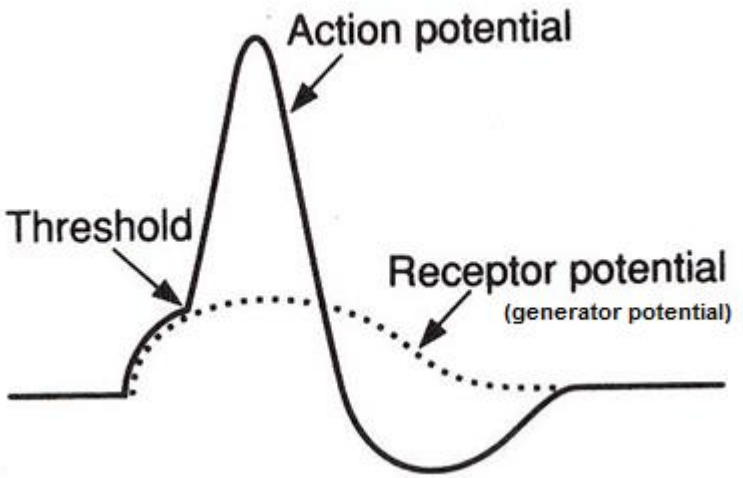


Action potential

Depolarization, repolarization, hyperpolarization, refractory period, propagation and velocity

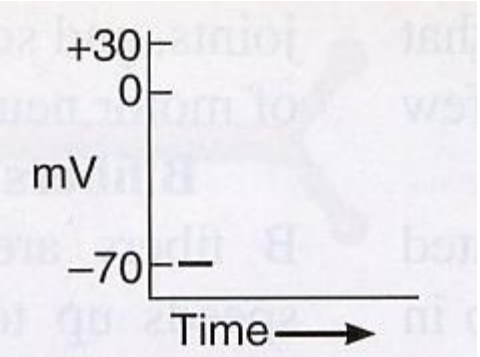
Electrical signals in neurons

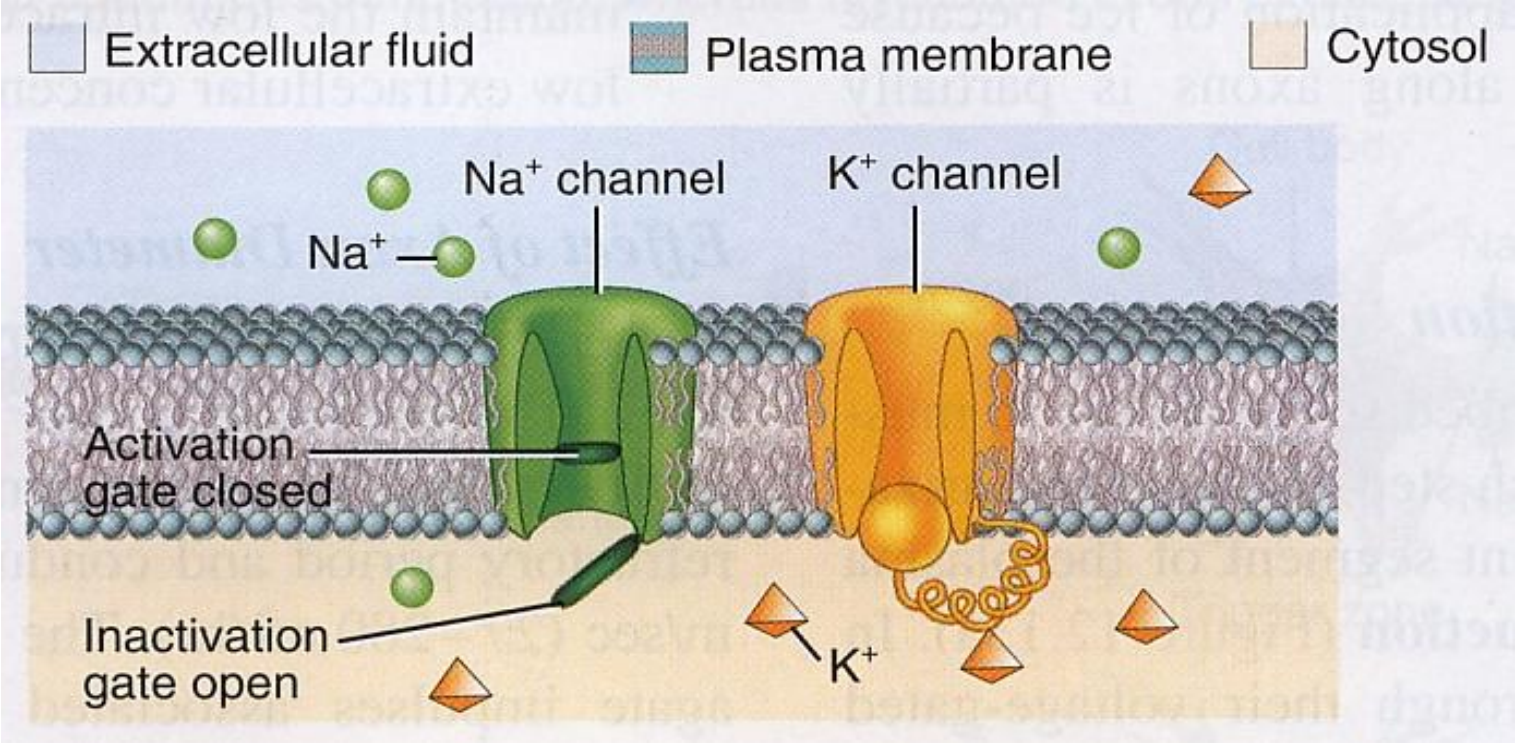
- **Action potentials** (depolarizing phase, threshold, repolarizing phase)
  - is a very rapid change in membrane potential that occurs when a nerve cell membrane is stimulated.
  - specifically, the membrane potential goes from the resting potential (typically -70mV) to some positive value (typically about +30mV) in a very short period of time (just a few milliseconds).
  - action potential have stereotypical size and shape, are propagating and are all-or-none.



1. Resting state:

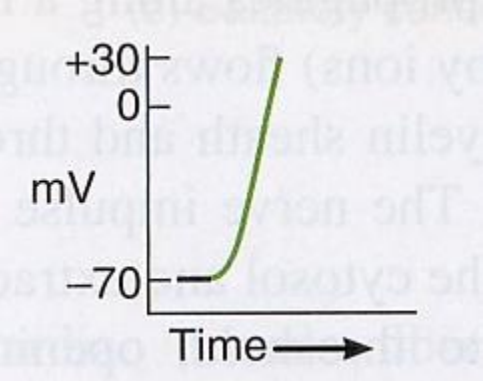
All voltage-gated Na^+ and K^+ channels are closed.

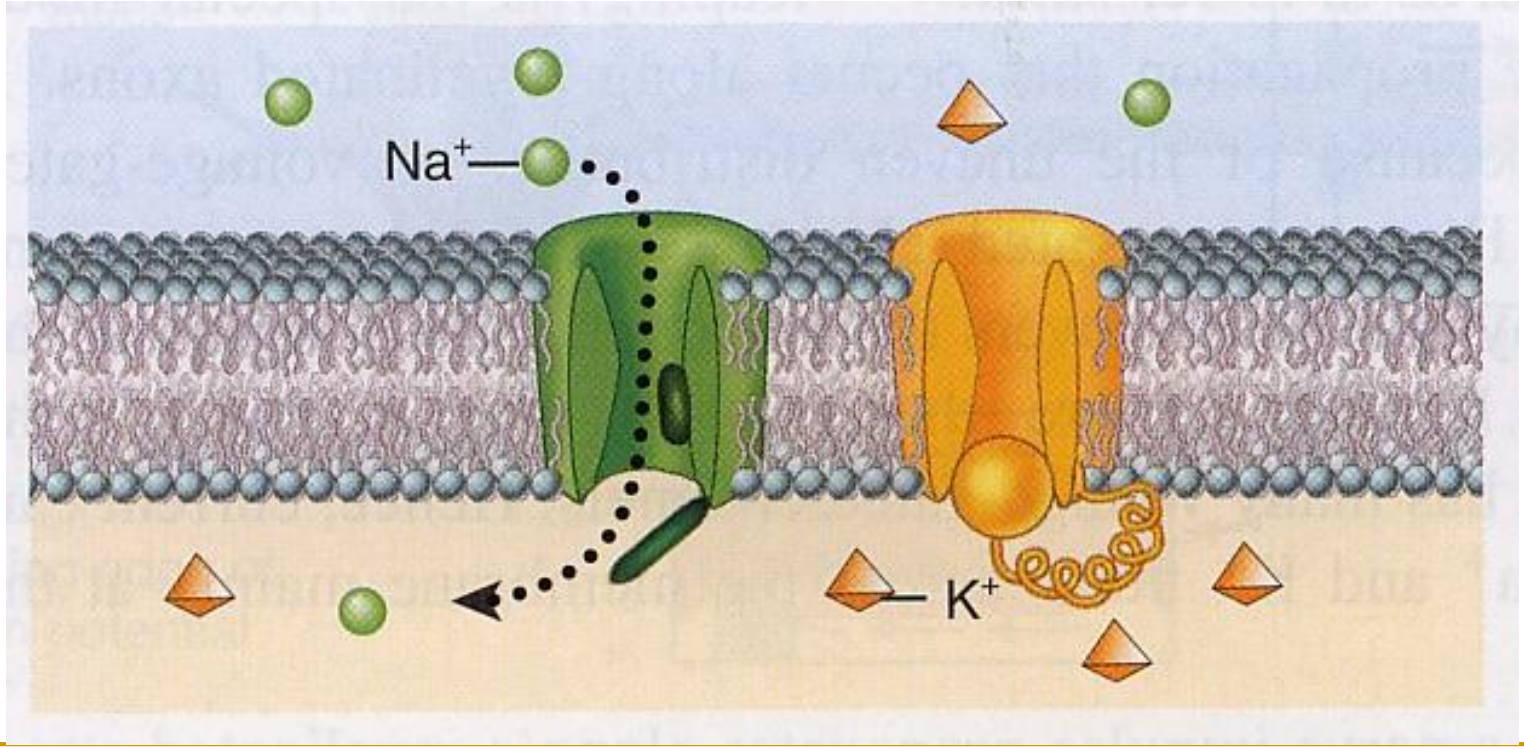




2. Depolarizing phase:

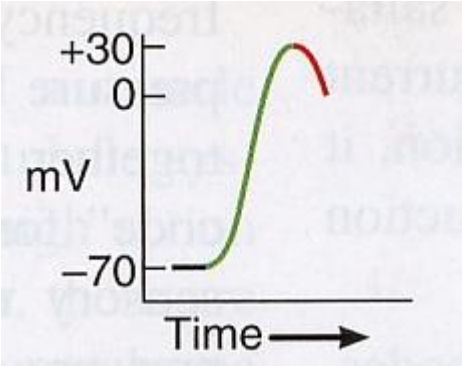
Depolarization to threshold opens Na^+ channel activation gates. Na^+ inflow further depolarizes the membrane, opening more Na^+ channel activation gates.

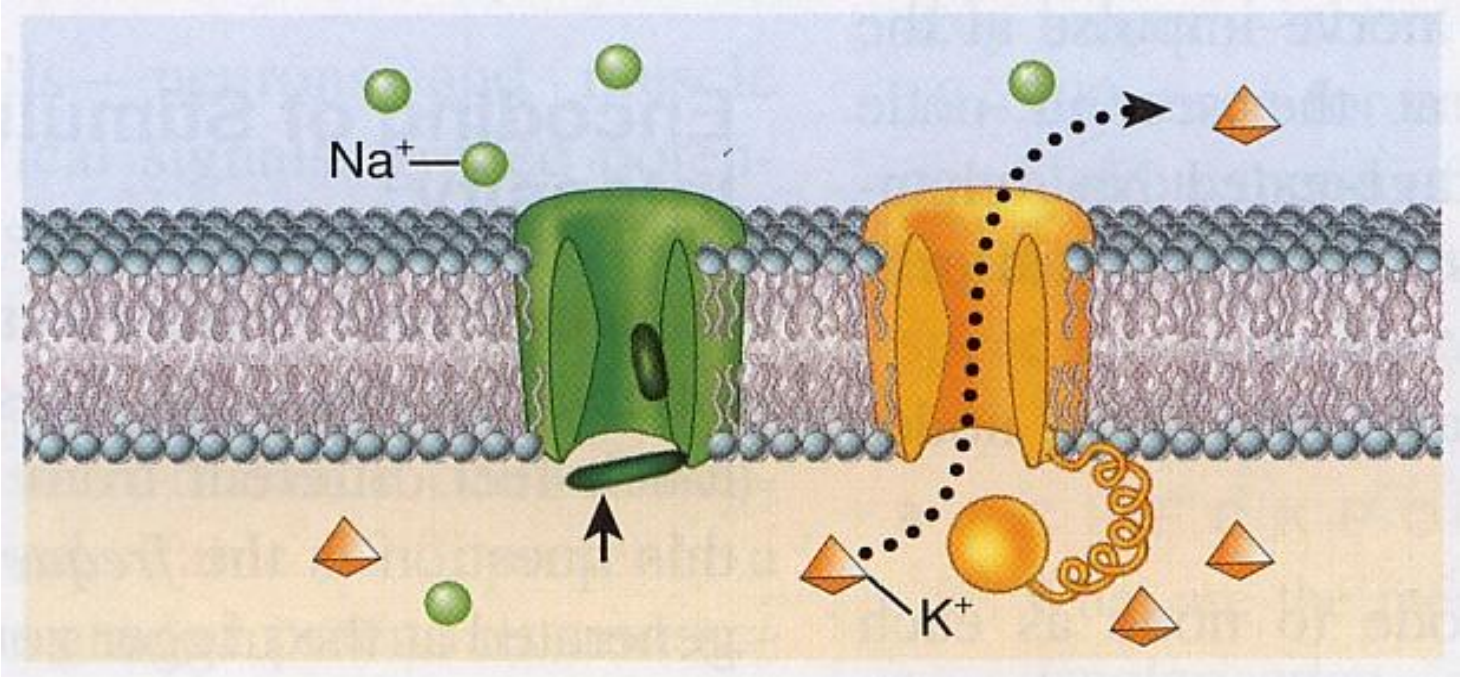




3. Repolarizing phase:

Na^+ channel inactivation gates close and K^+ channels open. Outflow of K^+ causes repolarization.

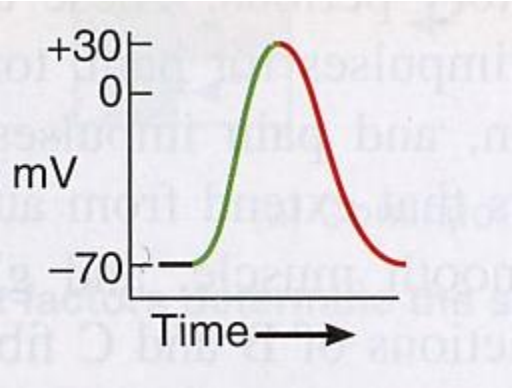


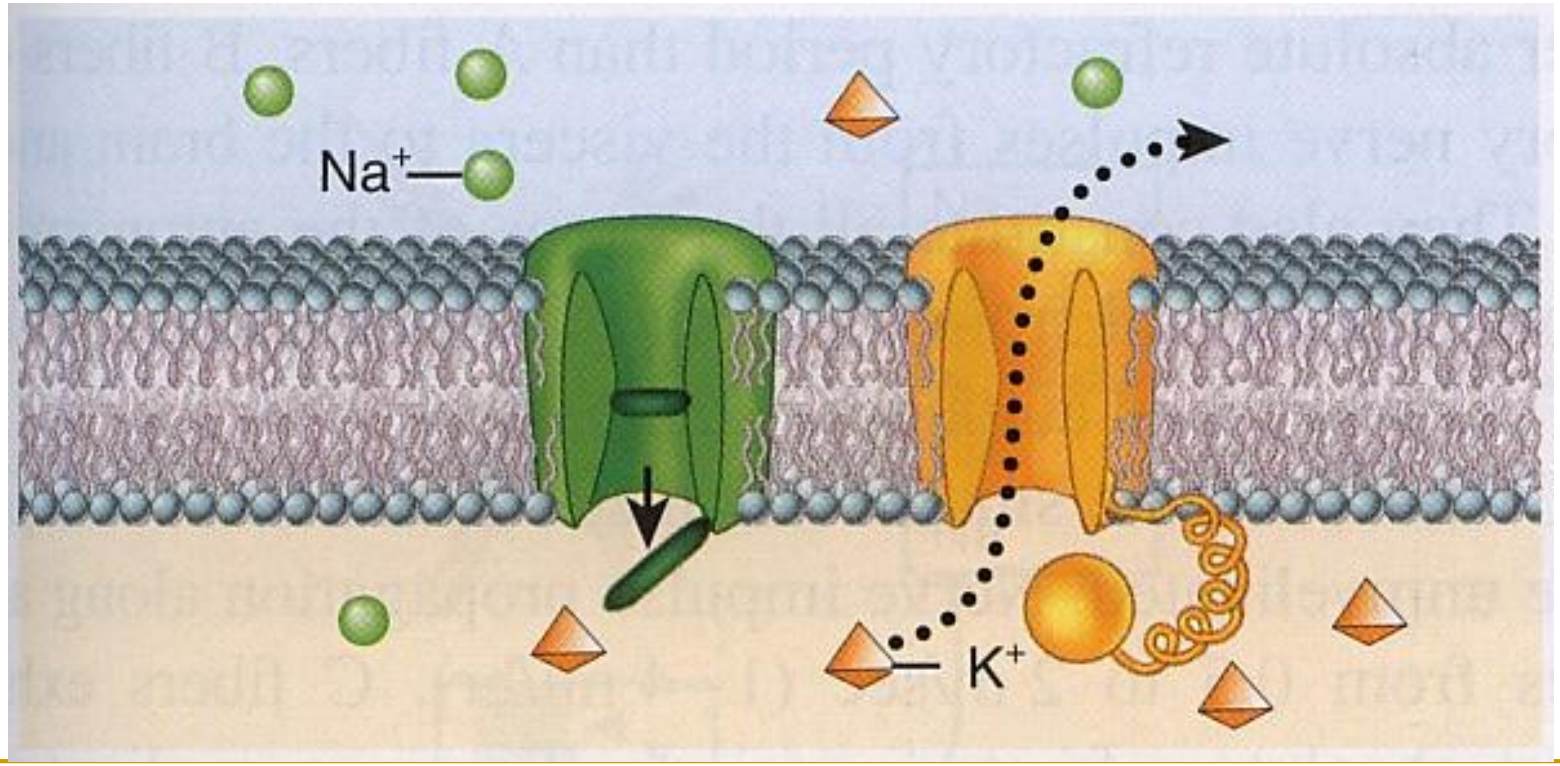


Tortora & Grabowski – Principles of Anatomy & Physiology; Page 401, Figure 12.12

4. Repolarization continues:

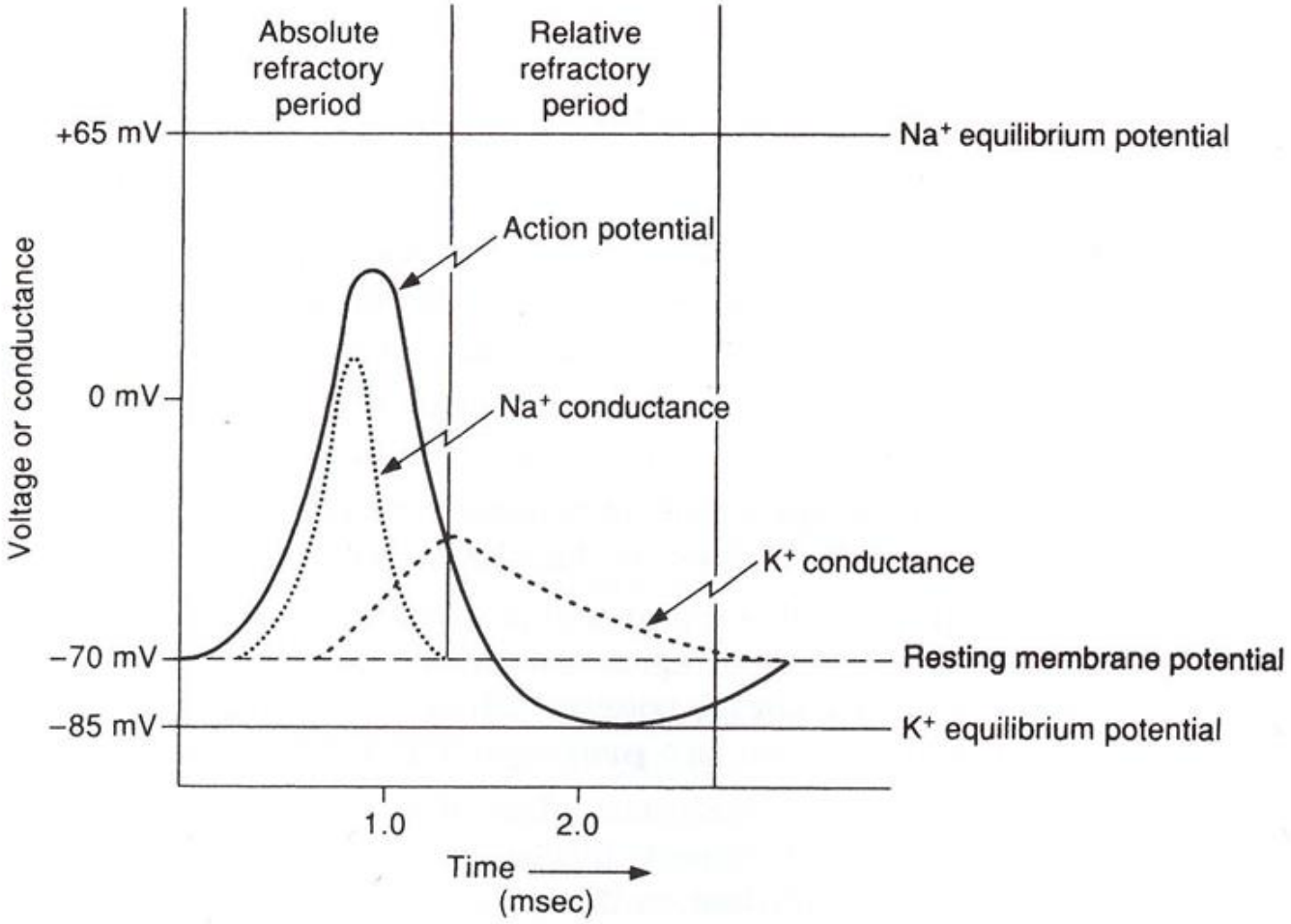
K^+ outflow restores resting membrane potential. Na^+ channel inactivation gates open. Return to resting state when K^+ gates close.





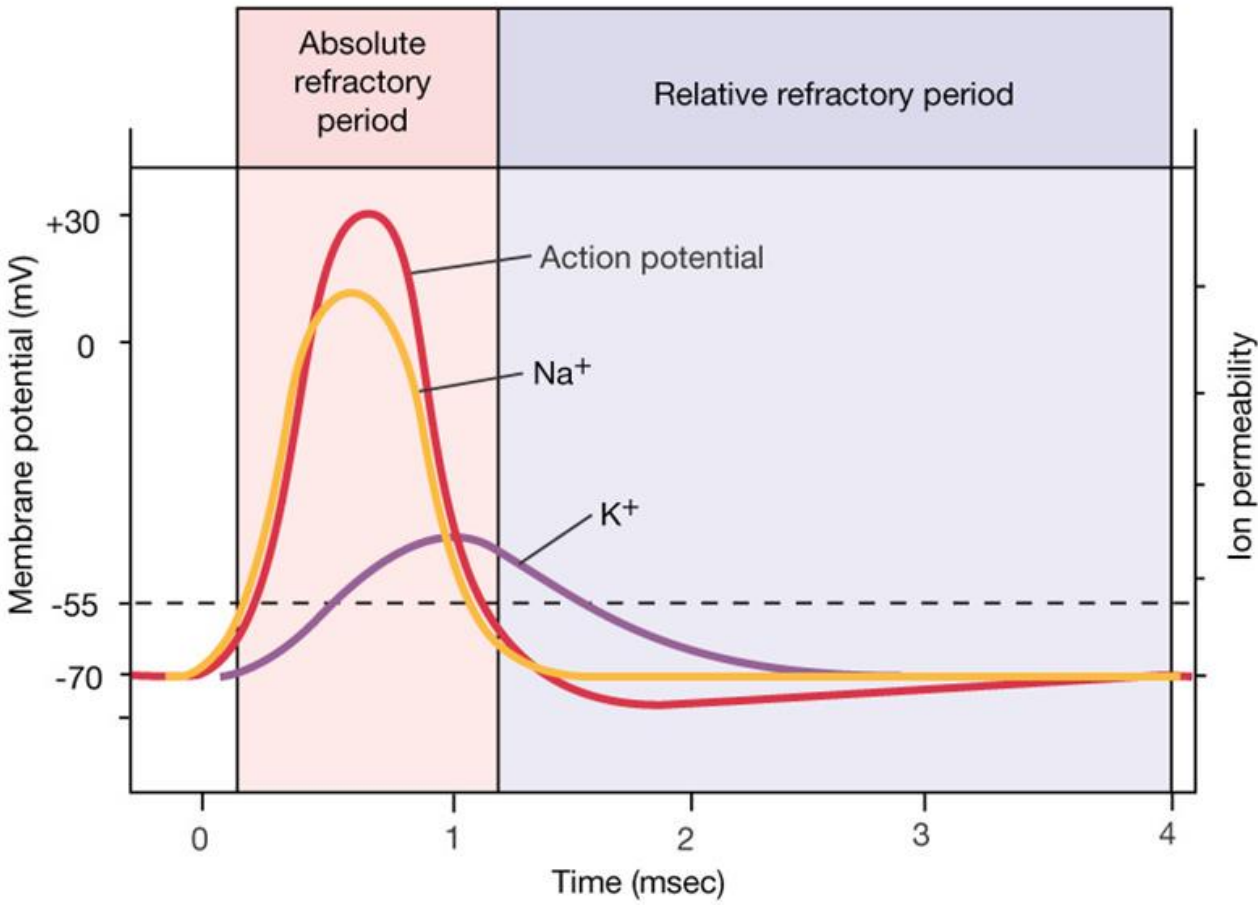
Tortora & Grabowski – Principles of Anatomy & Physiology; Page 401, Figure 12.12

Nerve action potential and associated changes in Na+ and K+ conductance

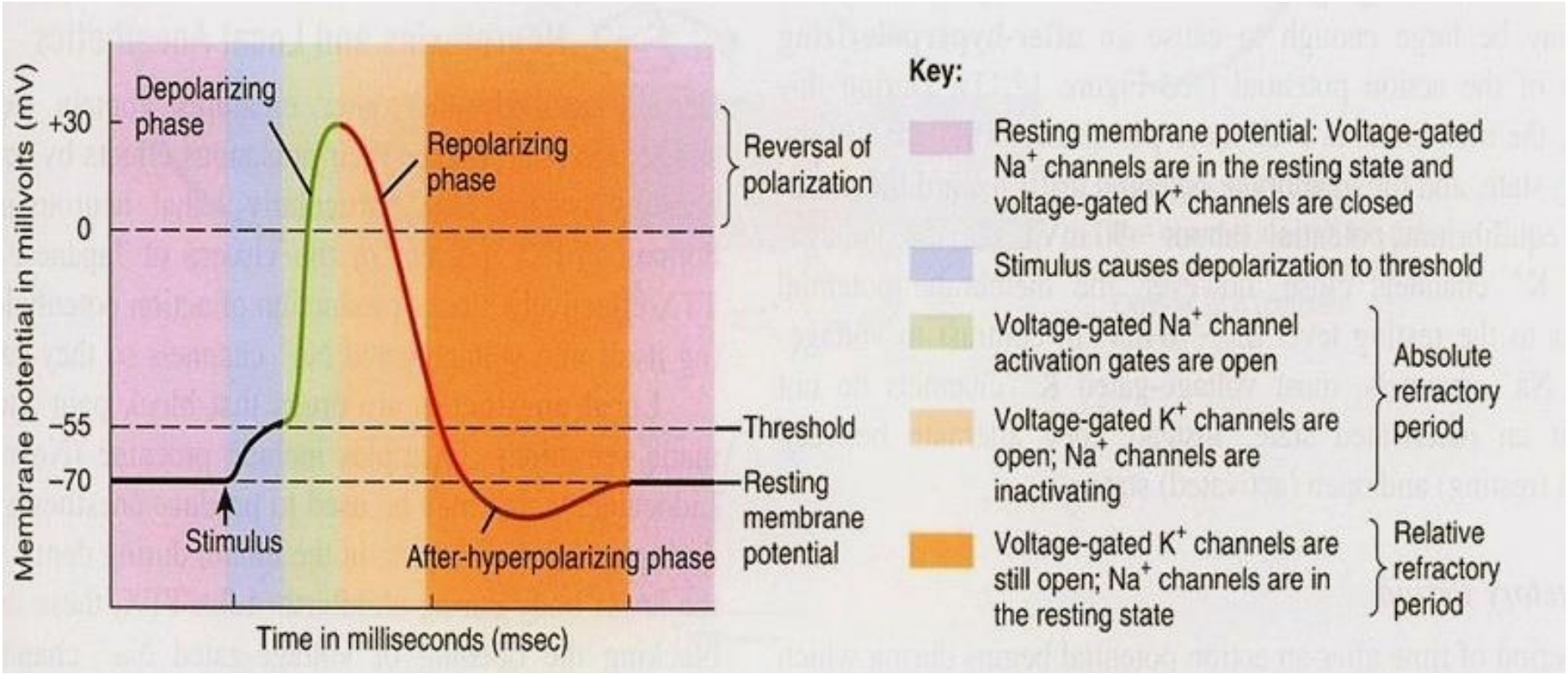


Absolute and relative refractory periods

- **Refractory period**
  - the period of time after an action potential begins during which an excitable cell cannot generate another action potential.

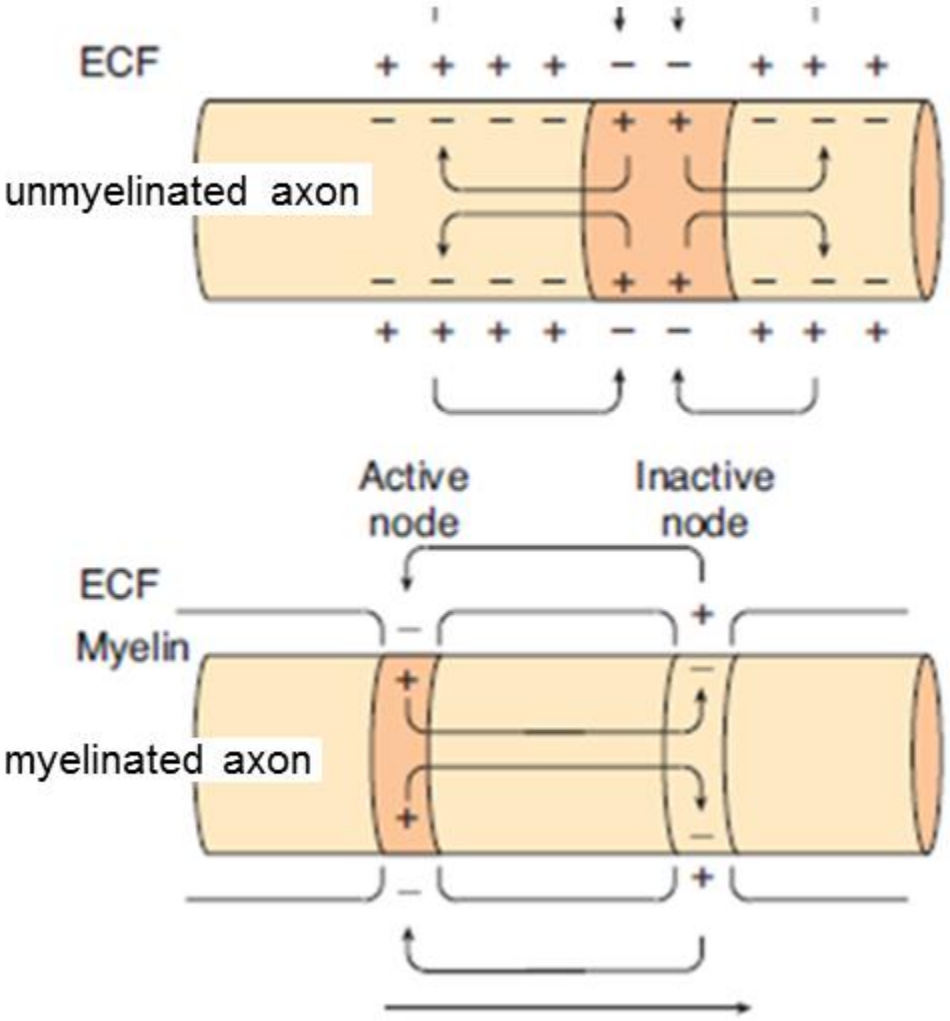


Action potential - overview



Local current flow (movement of positive charges) around an impulse in an axon

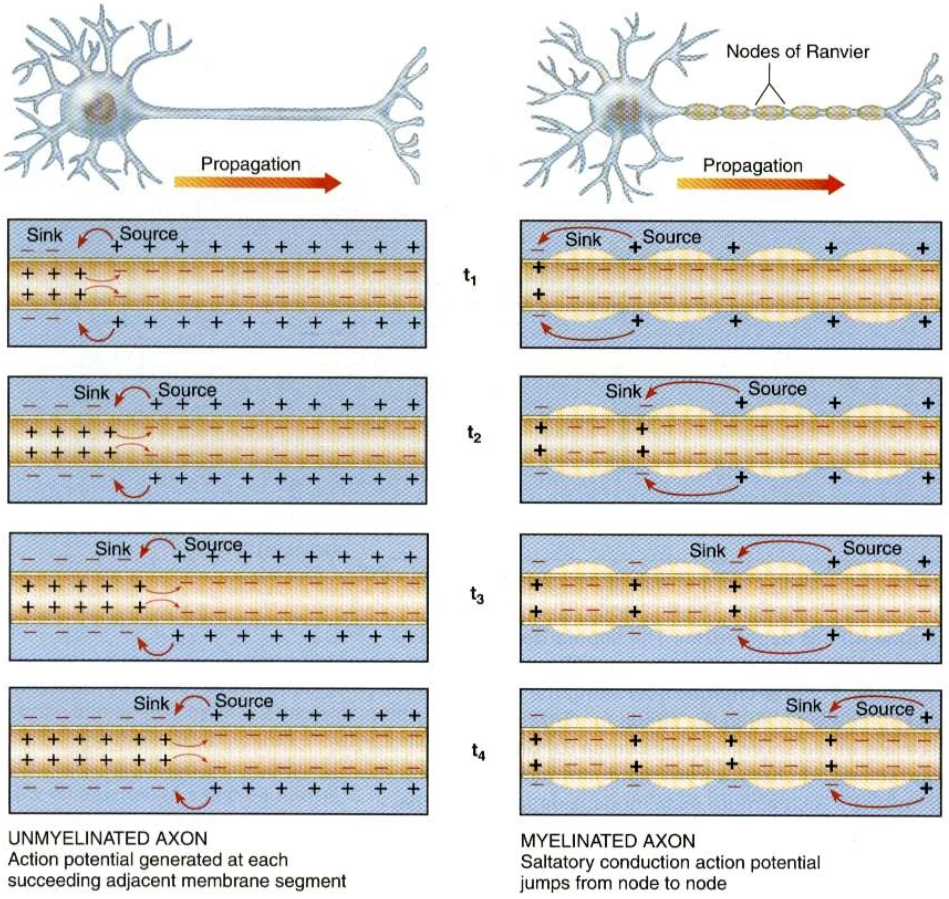
- Positive charges from the membrane ahead of and behind the action potential flow into the area of negatively represented by the action potential („current sink”).
- In myelinated axons, depolarization jumps from one node of Ranvier to the next (salutatory conduction)



Signal propagation

Propagation of nerve impulses

- nerve impulses propagate more rapidly along myelinated axon than along unmyelinated axons
- larger-diameter axon propagate impulses faster than small ones
- temperature
- synapses
- toxin



Nerve fiber types

Fiber Type	Function	Fiber Diameter (μm)	Conduction Velocity (m/s)	Spike Duration (ms)	Absolute Refractory Period (ms)
A					
α	Proprioception; somatic motor	12–20	70–120		
β	Touch, pressure	5–12	30–70	0.4–0.5	0.4–1
γ	Motor to muscle spindles	3–6	15–30		
δ	Pain, cold, touch	2–5	12–30		
B	Preganglionic autonomic	<3	3–15	1.2	1.2
C					
Dorsal root	Pain, temperature, some mechano-reception	0.4–1.2	0.5–2	2	2
Sympathetic	Postganglionic sympathetic	0.3–1.3	0.7–2.3	2	2

[a]A and B fibers are myelinated; C fibers are unmyelinated.

Relative suceptibility of A, B and C nerve fibers to conduction block produced by various agents

Susceptibility to:	Most Susceptible	Intermediate	Least Susceptible
Hypoxia	B	A	C
Pressure	A	B	C
Local anesthetics	C	B	A

Comparison of Graded Potentials and Action Potentials

Characteristic	Graded Potentials	Action Potentials
Origin	Arise mainly in dendrites and cell body (some arise in axons)	Arise at trigger zones and propagate along the axon.
Types of channels	Ligand-gated or mechanically gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Not propagated; localized and thus permit communication over a few micrometers.	Propagate and thus permit communication over long distance.
Amplitude	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All-or-none; typically about 100 mV.
Duration	Typical longer, ranging from several msec to several min.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of an action potential) or depolarizing (excitatory to generation of an action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present, thus spatial and temporal summation can occur.	Present, thus summation cannot occur.

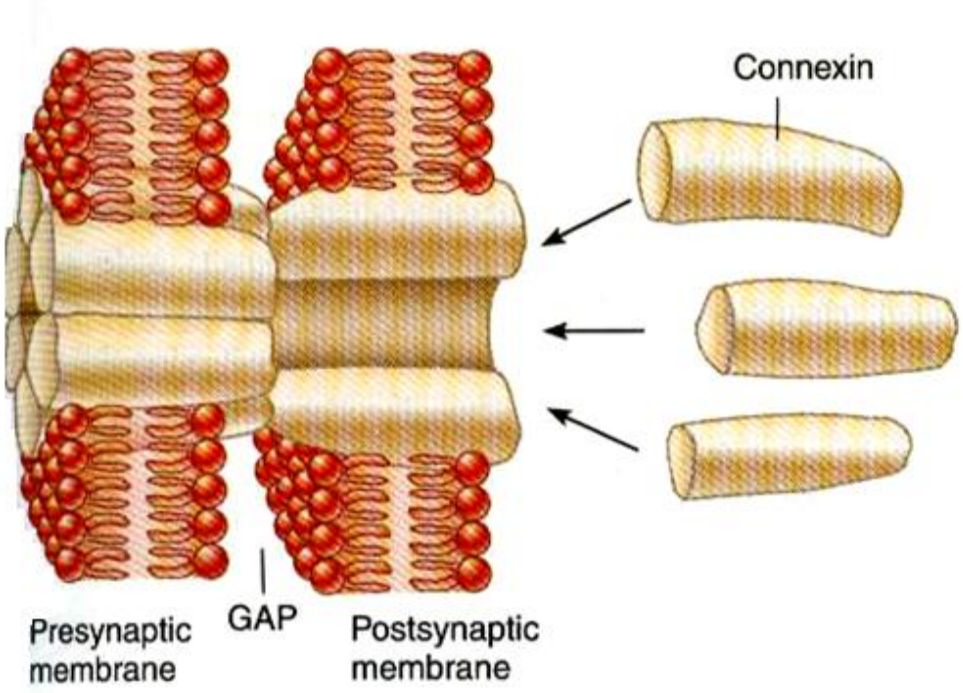
Signal transmission at synapses

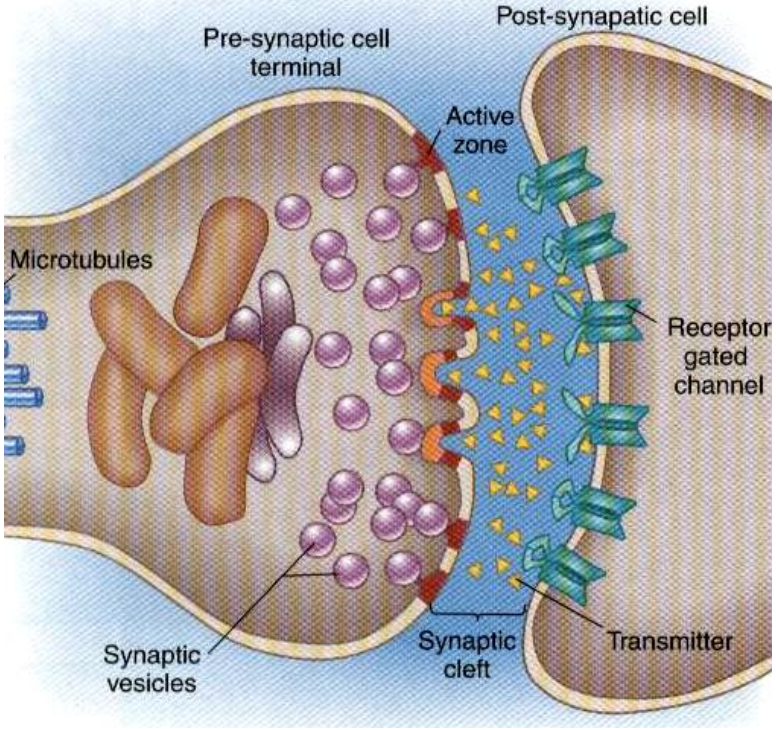
Types of synapses, neurotransmiters acting directly and indirectly, postsynaptic receptors, second messengers

Signal transmission at synapses

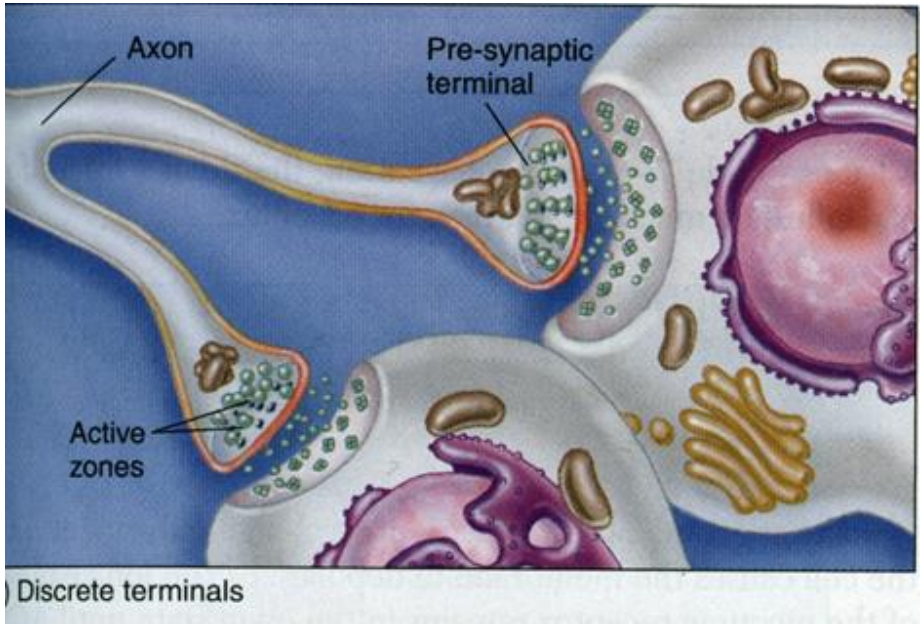
- The role of synapses – synapses determine the directions that the nervous signals will spread in to the nervous system.
- Physiologic anatomy of synapses (presynaptic terminals, synaptic cleft, postsynaptic neuron).
- The major type of synapses
  - **the chemical synapse** (transmitters, “one-way” conduction)
  - **the electrical synapse** (action potentials conduct directly between adjacent cells through gap junctions)

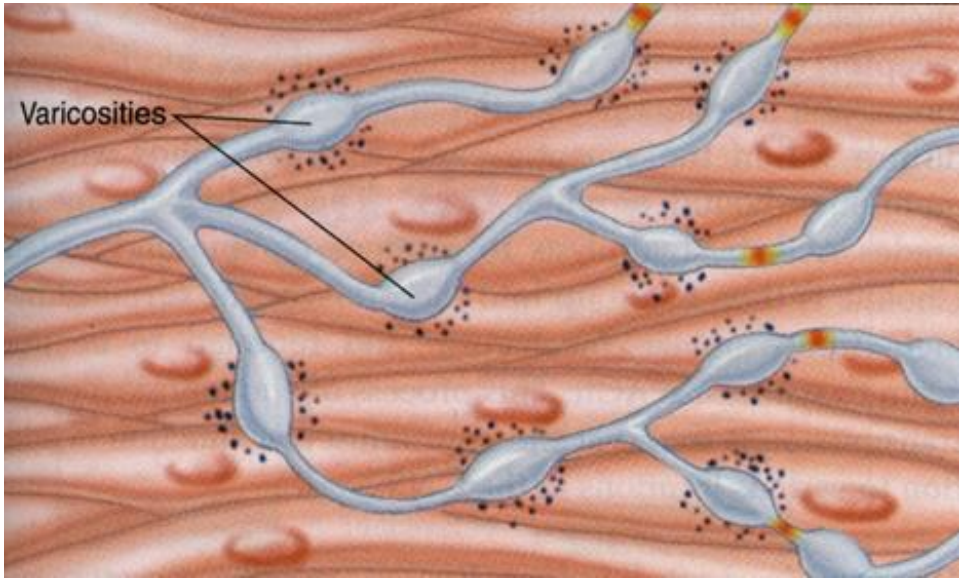
Two types of synapses





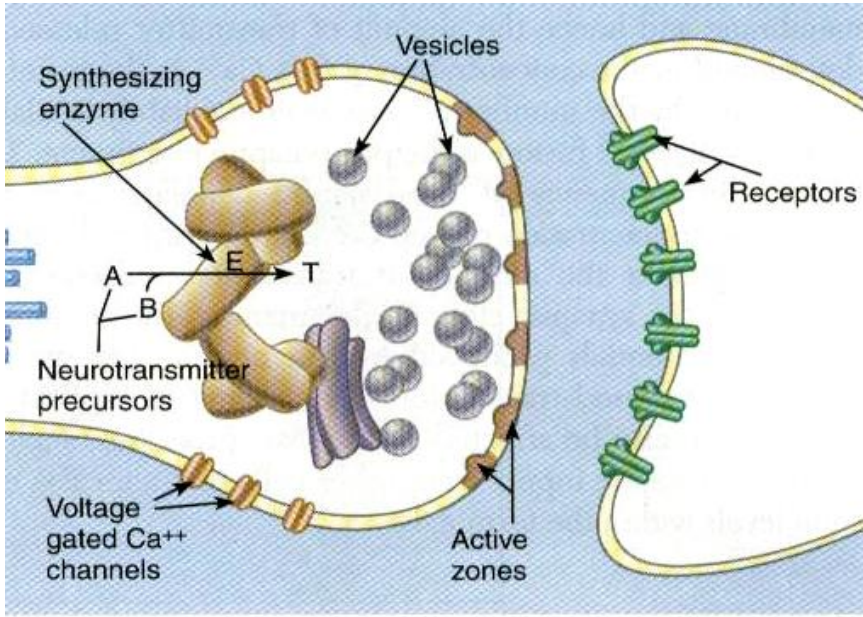
Localised vs. dispersed synpases

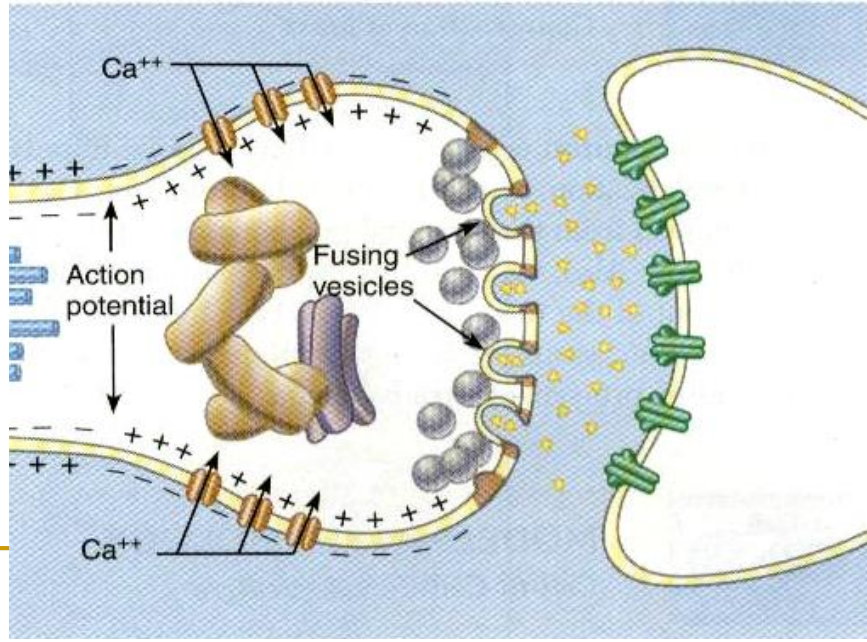




Electro-mechanical coupling

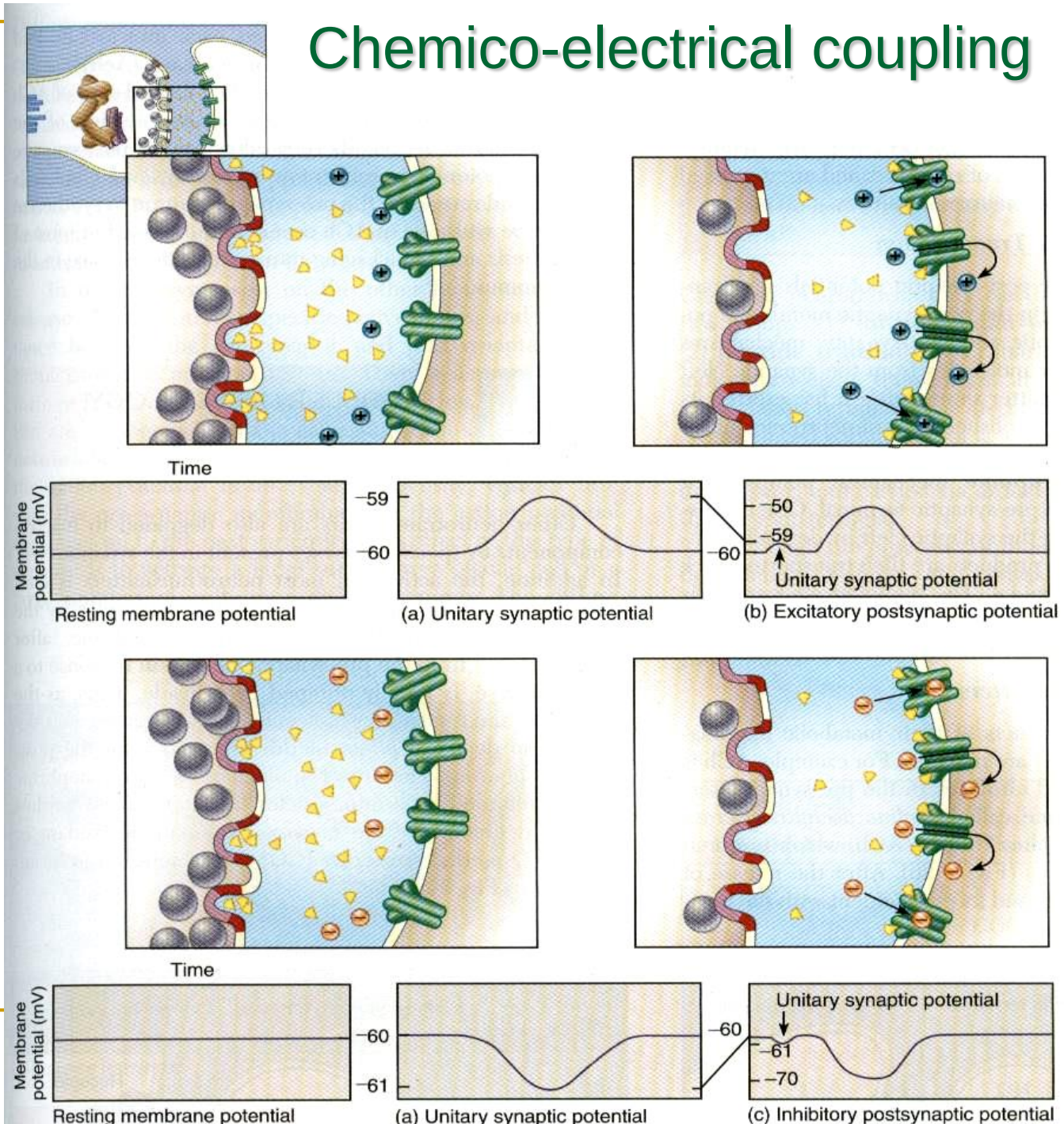
- Depolarization opens Ca^{2+} channels
- Ca^{2+} combine with calmodulin
- calmodulin-Ca^{2+} complex activates synapsin
- exocytosis





Chemico-electrical coupling

- Generation of EPSP or IPSP



Neurotransmitters

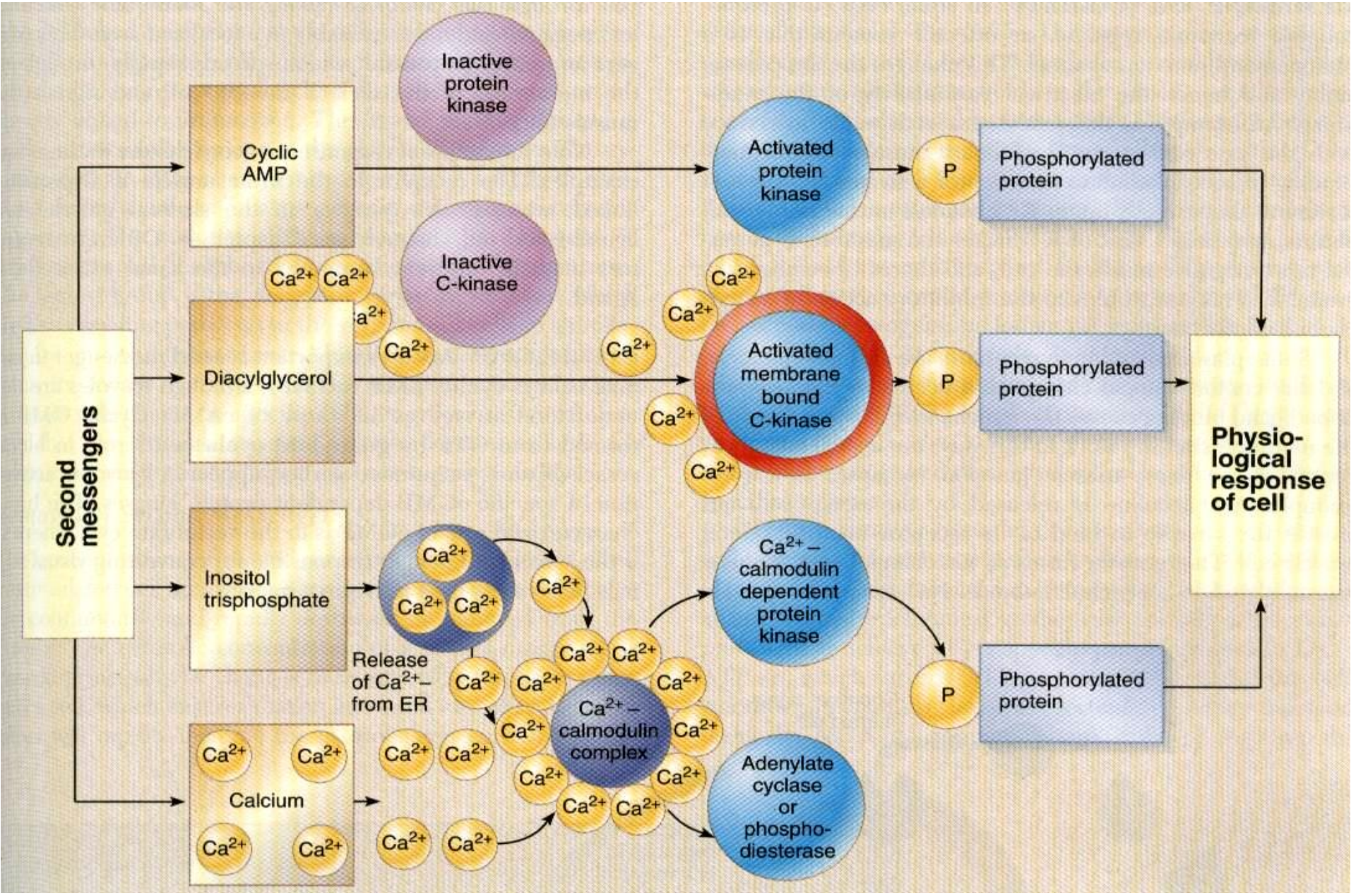
- Neurotransmitters
  - **excitatory** – neurotransmitters that make membrane potential less negative (for example: glutamate, norepinephrine, dopamine, epinephrine, serotonin, histamine)
  - **inhibitory** – neurotransmitters that make membrane more negative (for example Gamma aminobutyric (GABA) and glycine).

Neurotransmitters - meatbolism

- Removal of the neurotransmitter from the synaptic cleft is essential for normal synaptic function. Neurotransmitter is removed in three ways:
  - **Diffusion**. Some of the released neurotransmitter molecules diffuse away from the synaptic cleft.
  - **Enzymatic degradation**. Certain neurotransmitters are inactivated through enzymatic degradation. For example, the enzyme acetylocholinesterase breaks down acetylocholine in the synaptic cleft.
  - **Uptake by cells**. Many neurotransmitters are actively transported back into the neuron that released them (reuptake).

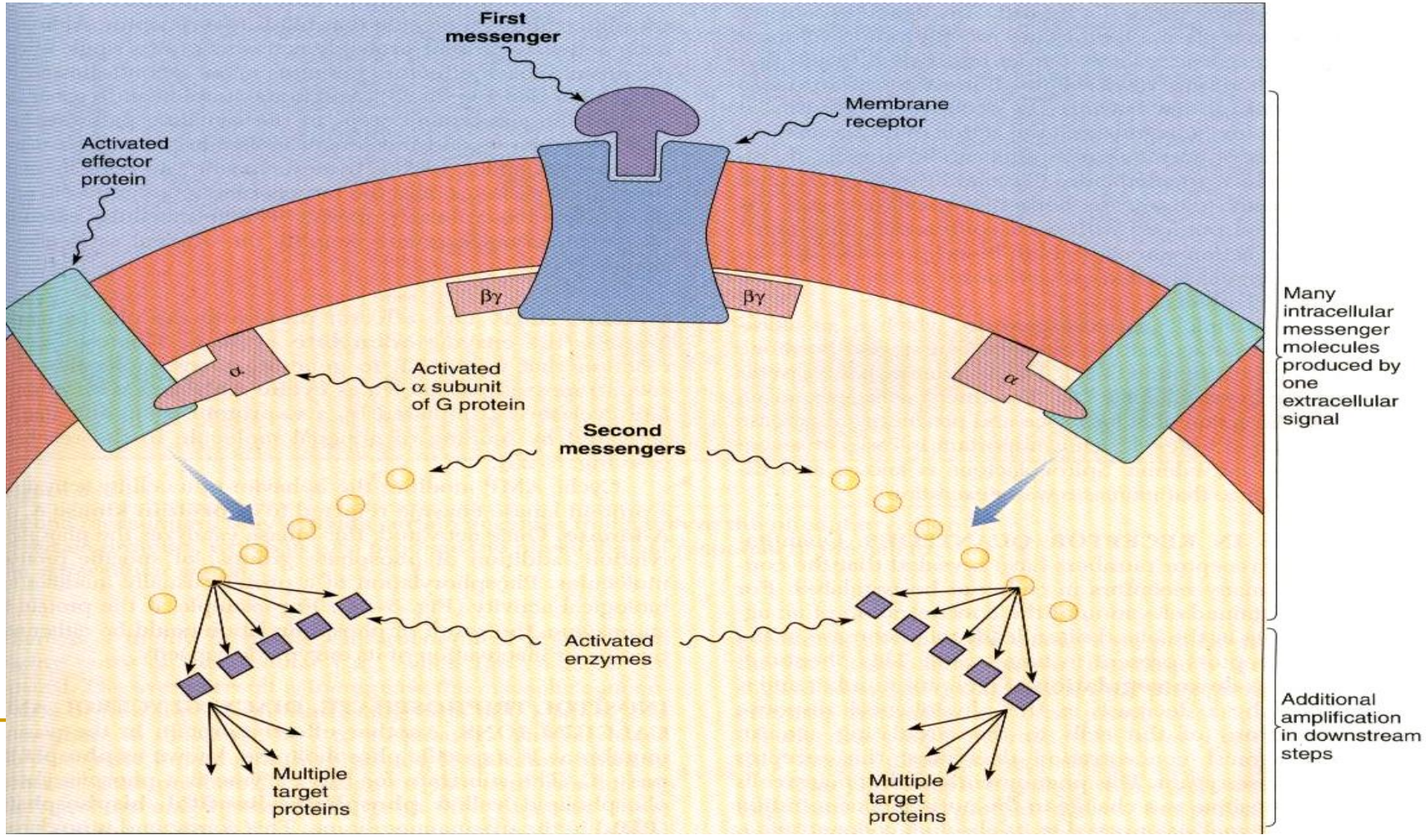
Signal transmission at synapses

- **Binding of a signal molecule – into an intracellular response that modifies the behavior of target cell**
  - Phase I – binding of first messenger (transmitter) to the receptor (T+R)
  - Phase II – transduction of a signal into the intracellular compartment. T+R complex interacts with a specific G-protein; T+R+G complex binds GTP, which activates alpha subunit of G protein
  - Phase III – activated alpha subunit of G protein activates (or inhibits) a specific enzyme (eg. adenylate cyclase or phospholipase C), which causes synthesis of **second messenger**


Second messengers
Cyclic AMP
Inactive protein kinase
Activated protein kinase
P
Phosphorylated protein
Diacylglycerol
Inactive C-kinase
Activated membrane bound C-kinase
P
Phosphorylated protein
Physio-logical response of cell
Inositol trisphosphate
Release of Ca2+– from ER
Ca2+ – calmodulin dependent protein kinase
P
Phosphorylated protein
Calcium
Ca2+ – calmodulin complex
Adenylate cyclase or phospho-diesterase
Ca2+

Second messengers

- **Second-messengers** may activate certain enzymes that catalyze the phosphorylation of certain proteins, which in turn produce the physiological response of the cell to the extracellular signal (first messenger)

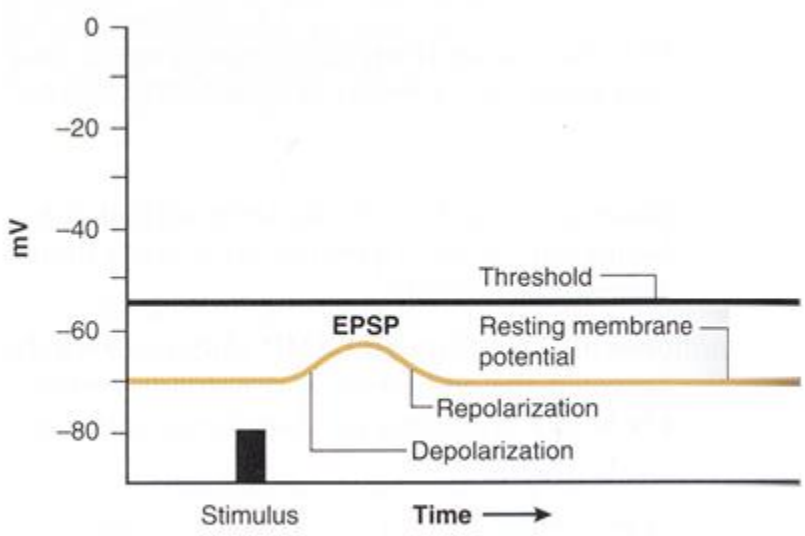


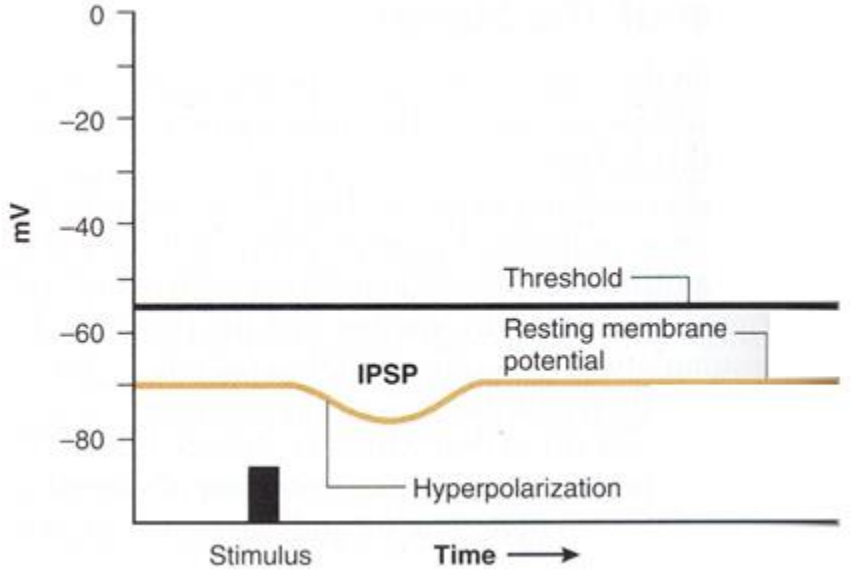
Amplification

- When a first messenger binds to a G-protein coupled receptor, the receptor changes its conformation and activates several G-protein alpha subunits.
- Each alpha subunit breaks away from this complex, and activates a single effector protein, which, in turn, generates many intracellular second-messenger molecules.
- One second messenger activates many enzymes, and each activated enzyme can regulate many target proteins (amplification).

Signal transmission at synapses in nerve cells

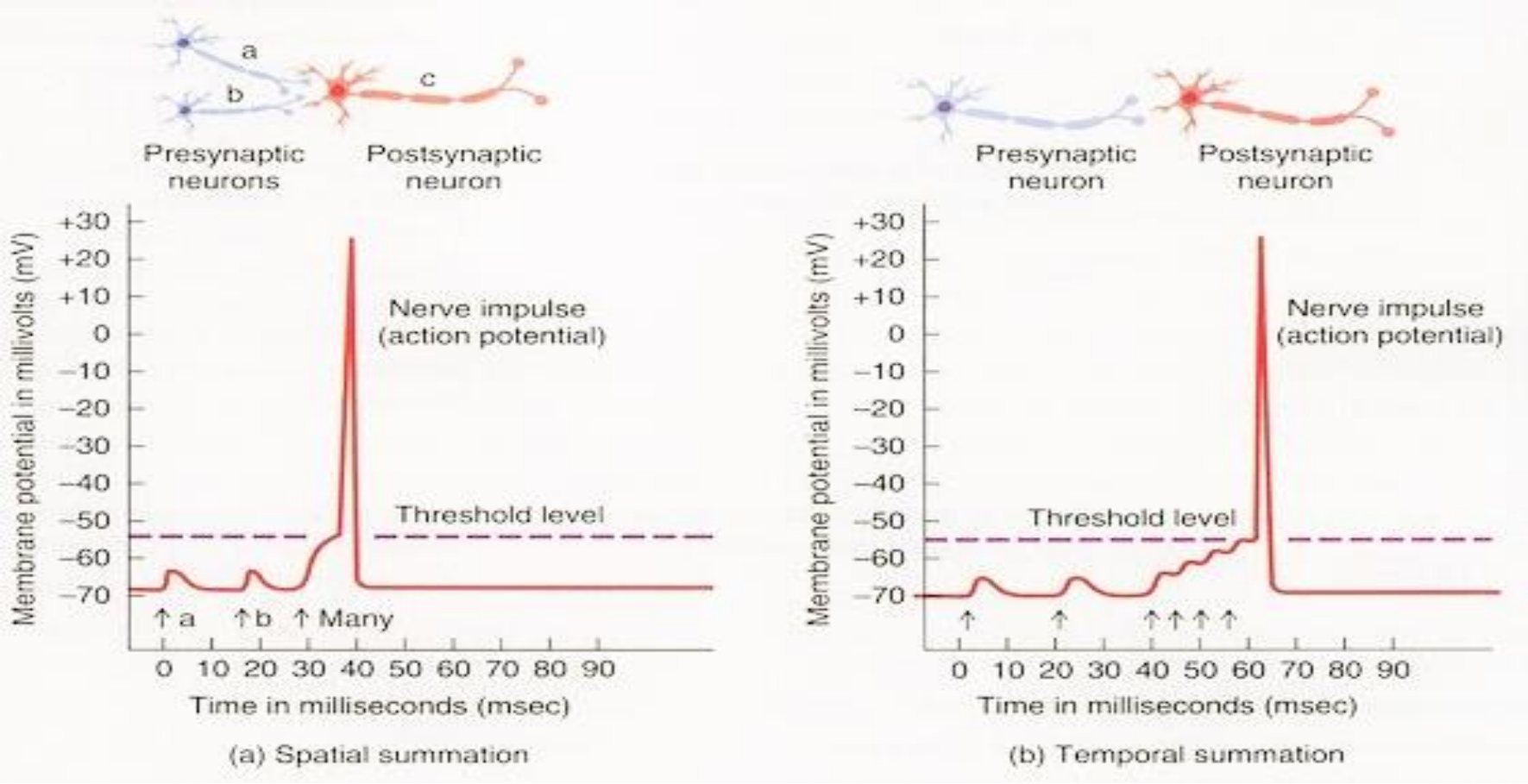
- Excitatory and inhibitory synaptic potential
  - EPSP – a depolarizing postsynaptic potential is called an **excitatory postsynaptic potential**
  - IPSP – a hyperpolarizing postsynaptic potential is termed an **inhibitory postsynaptic potential**



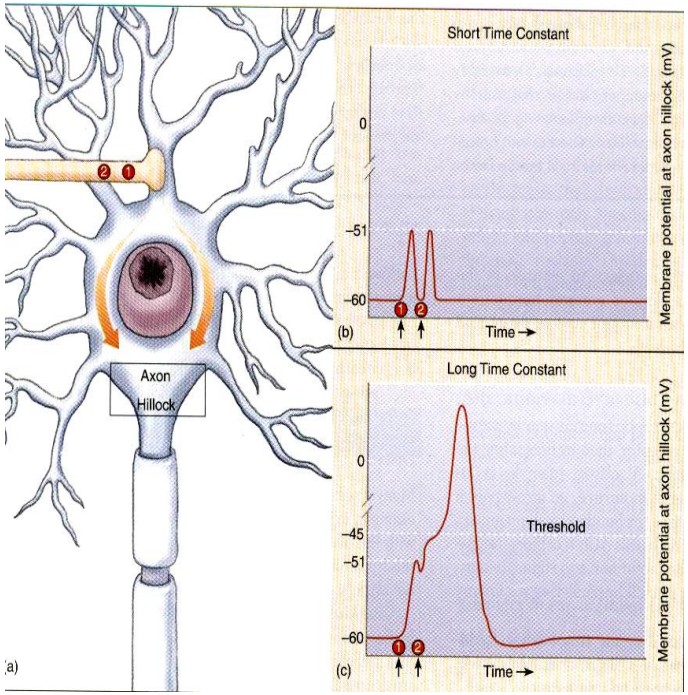


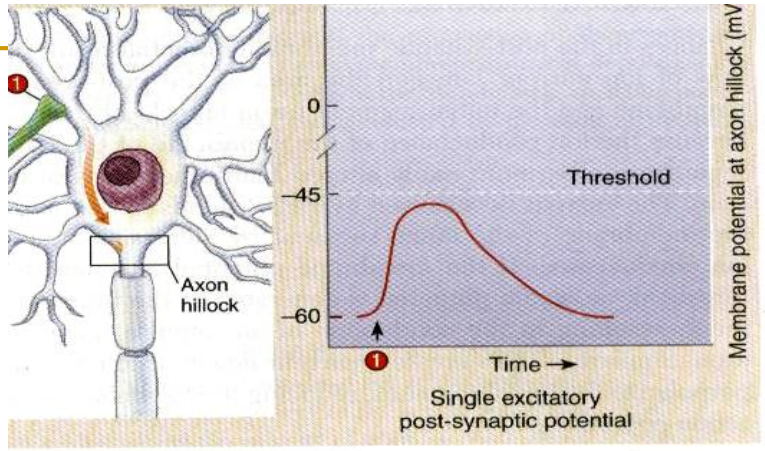
Summation at synapses

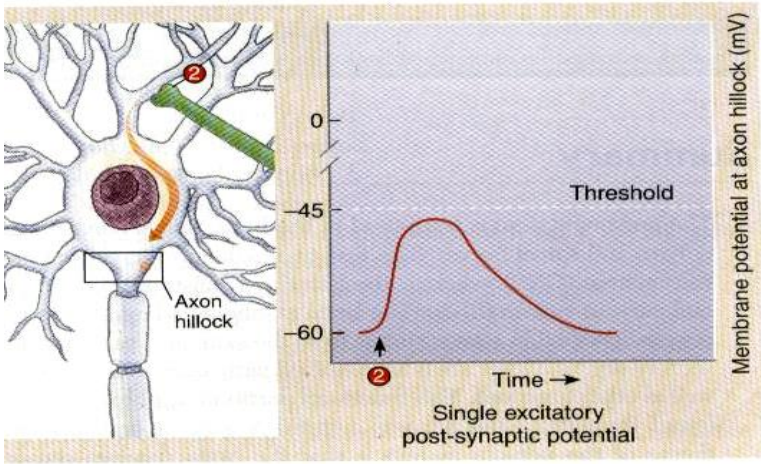
- **temporal summation** - occurs when two or more excitatory inputs arrive at a postsynaptic neurons in rapid succession.
- **spatial summation** – occurs when two or more excitatory inputs arrive at a postsynaptic neuron simultaneously.

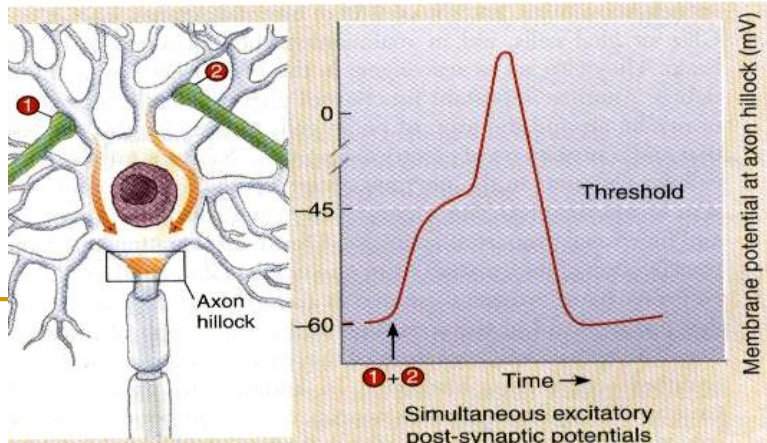


Summation of synaptic potentials







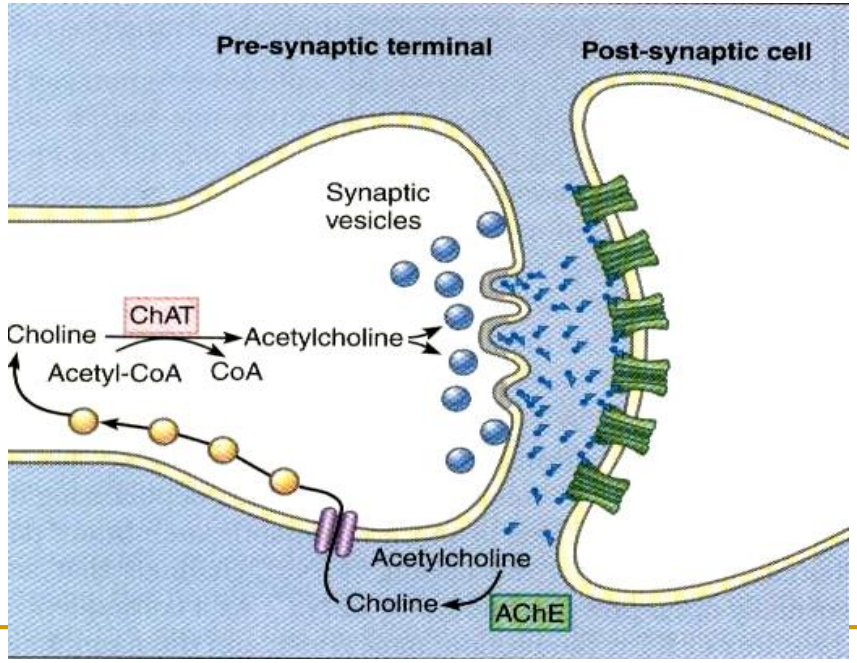


Acetylcholine metabolism

Acetylcholine

Choline acetyltransferase (ChAT)

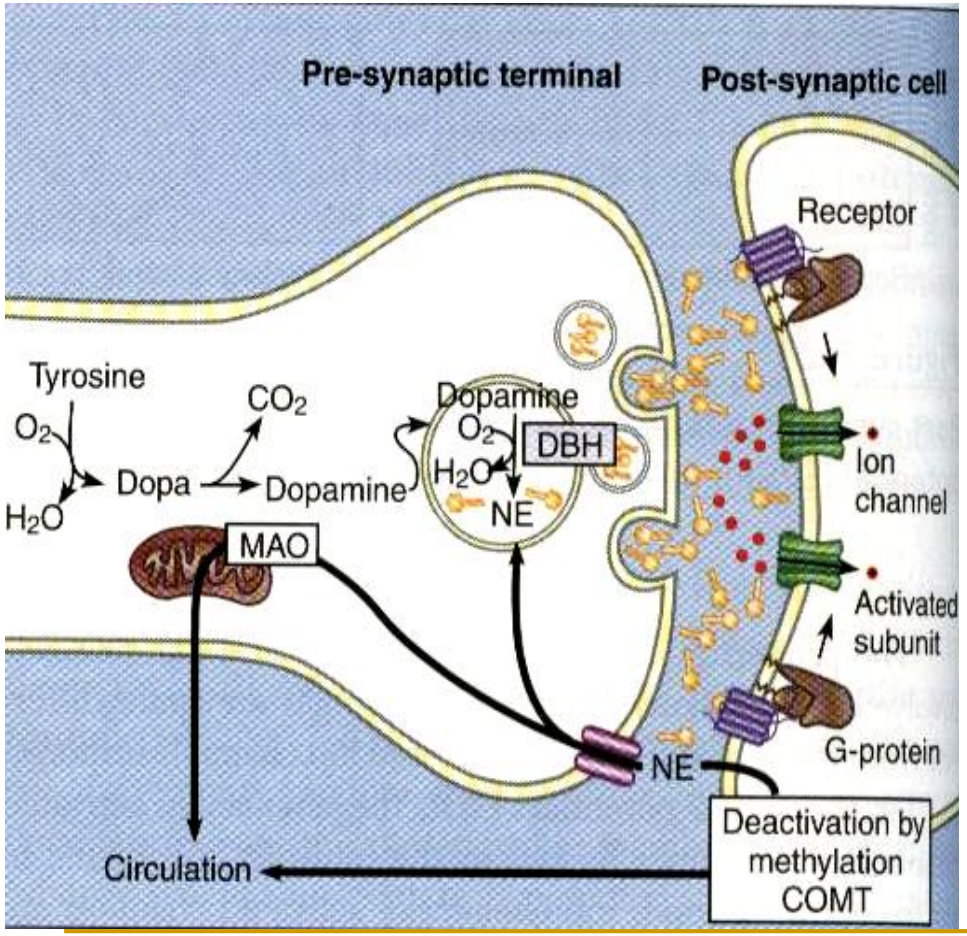
Acetyl-CoA
+
Choline



Acetylcholinesterase (AchE)

Acetate
+
Choline

Norepinephrine metabolism



- may be recycled back into vesicles for later release (80%)
- may be degraded by the enzymes:
  - *monoamine oxidase (MAO)*
  - *catechol-O-methyltransferase (COMT)*
- may difuse to blood

Table 1-2. Agents Affecting Neuromuscular Transmission

Example	Action	Effect on Neuromuscular Transmission
Botulinus toxin	Blocks release of ACh from presynaptic terminals	Total blockade
Curare	Competes with ACh for receptors on motor end plate	Decreases size of EPP; maximal doses produce paralysis of respiratory muscles and death
Neostigmine	Anticholinesterase	Prolongs and enhances action of ACh at muscle end plate
Hemicholinium	Blocks reuptake of choline into presynaptic terminal	Depletes ACh stores from presynaptic terminal

ACh = acetylcholine; EPP = end plate potential.

Thank you! ☺