MSS

Physiology

|Modified slides

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Skeletal muscle physiology for medical students 2022

Action potential and NMJ

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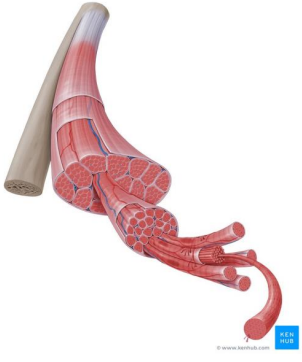
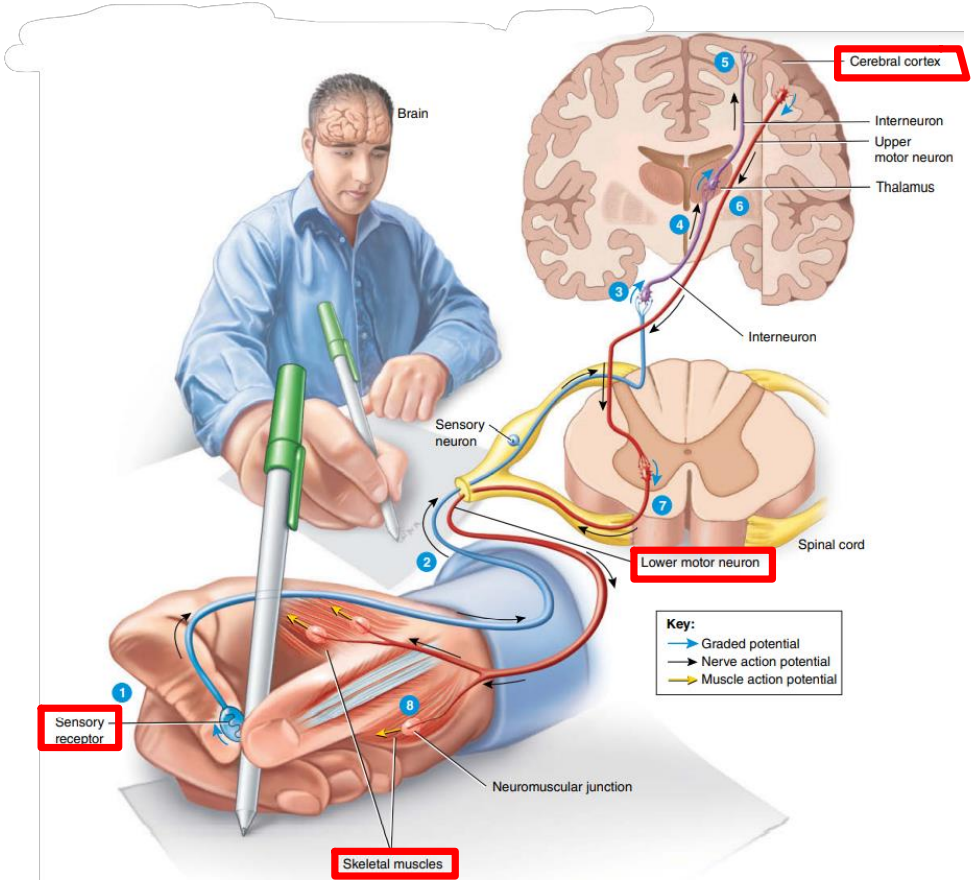


Outline of muscle physiology lectures

- Action potential and NMJ.
- Excitation-contraction coupling of skeletal muscles.
- Skeletal muscle contraction-1
- Skeletal muscle contraction-2


Cerebral cortex
Brain
Interneuron
Upper motor neuron
Thalamus
Interneuron
Sensory neuron
Spinal cord
Lower motor neuron
Key:
Graded potential
Nerve action potential
Muscle action potential
Sensory receptor
Neuromuscular junction
Skeletal muscles

Have you thought of the physiology behind holding the pen? how did you walk to the room? What do you need to move? You need skeletal muscles to contract and pull the bones at the joints through the tendons. But it is not as simple as this; the skeletal muscles need an order first from the CNS (brain+spinal cord) to contract. The process starts from the sensory receptors, for example touch receptors here, the information will be travelled via sensory neurons to the CNS, that analyzes these information and integrate it with other information then decide the action in a complex process, then motor areas in the cerebral cortex decides the specific muscle fibers that will contract with the exact duration and order. And that will be sent down to the muscles through motor pathway. (by the way, cerebral cortex is the area where perception takes place, i.e. you are aware of this sensation and this movement). The motor pathway transmit the order via sequence of neurons. The last one, that will supply the skeletal muscle is called lower motor neuron or final common pathway. Neurons are composed of cell body, dendrites and axons, the signals transmit from another neuron at the synapses to the body and dendrites then to the axons. The way to transmit a precise signal very fast is electrical signal through action potential.

(these information are not for the sake of the exam; you will take them in detail in CNS.)

Outline of this lecture

- Membrane potential
- Excitable cells
- Neuronal action potential
- Neuromuscular junction
- Acetylcholine and its receptor

Gradient across the membrane

- The selective permeability of the plasma membrane allows a living cell to maintain different concentrations of certain substances on either side of the plasma membrane.

- The plasma membrane also creates a difference in the distribution of positively and negatively charged ions between the two sides of the plasma membrane.

Major cation inside the cell: K+
Major cation outside the cell: Na+
Major anion inside the cell: phosphate+amino acid in the proteins
Major anion outside the cell: Cl-

Gradient across the membrane

- Typically, the inner surface of the plasma membrane is more negatively charged and the outer surface is more positively charged.

- This charge difference is termed the **membrane potential**.

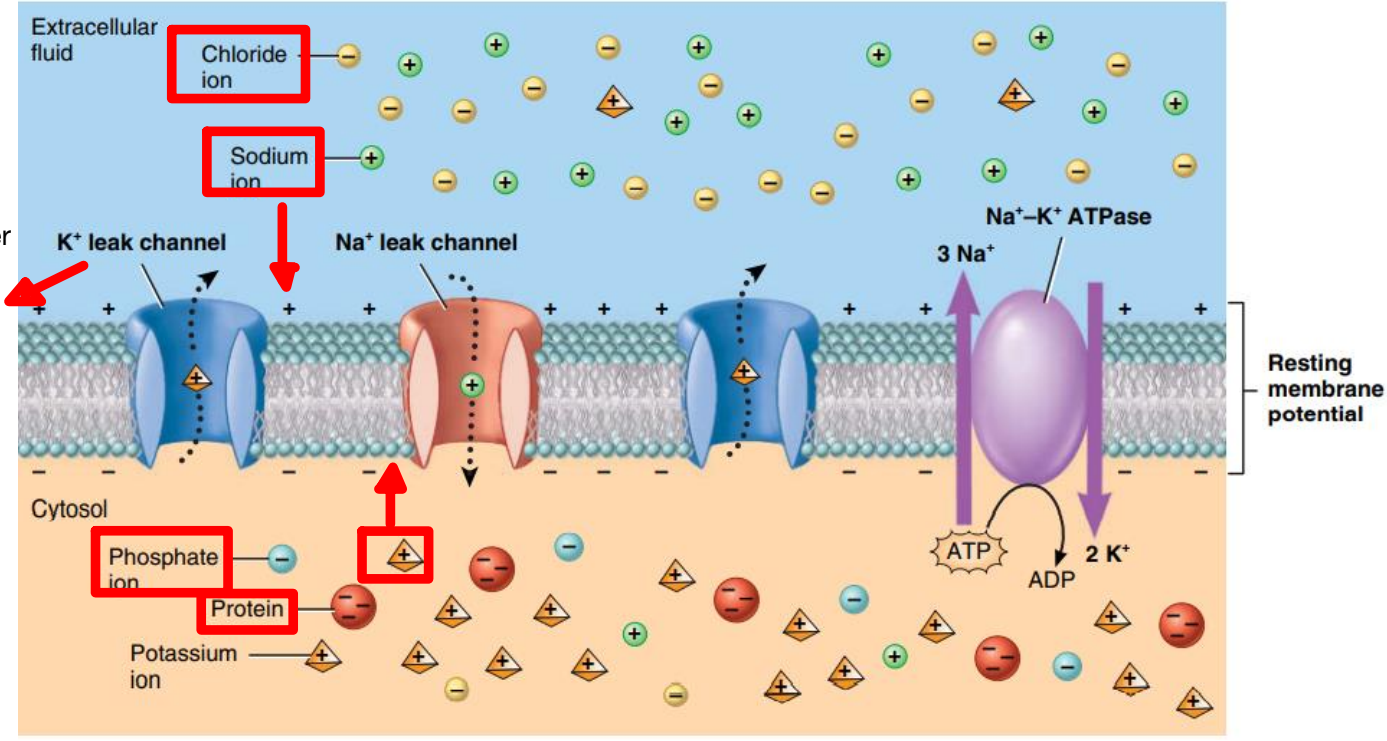
Resting membrane potential

- A separation of positive and negative electrical charges is a form of potential energy, which is measured in volts or millivolts. The greater the difference in charge across the membrane, the larger the membrane potential (voltage).

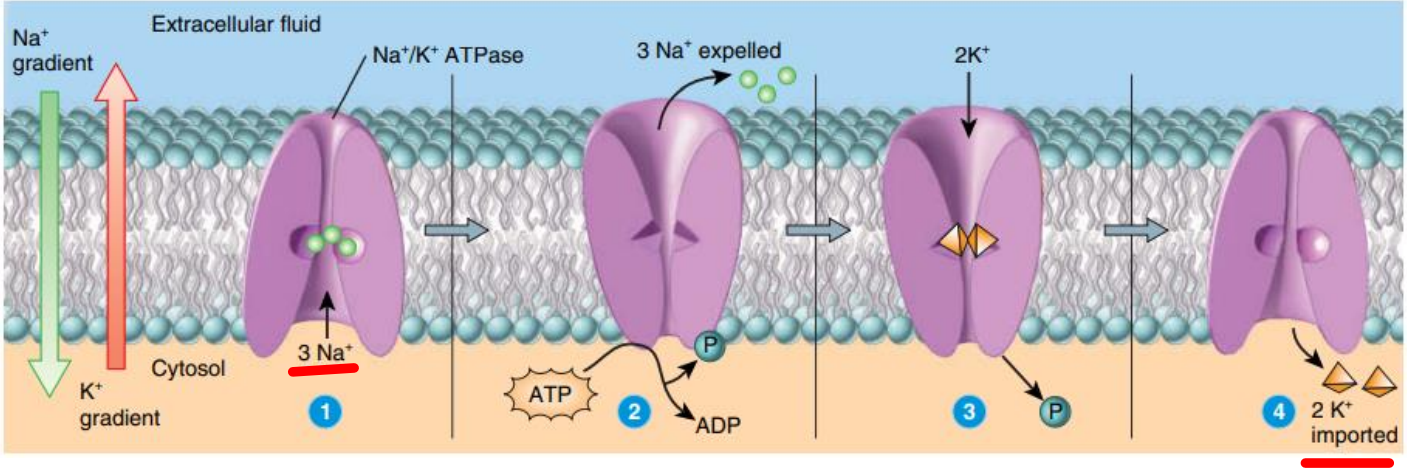
- The buildup of charge occurs only very close to the membrane. The cytosol or extracellular fluid elsewhere in the cell contains equal numbers of positive and negative charges and is electrically neutral.

Resting membrane potential

Its number is greater than Na+ leak channel.



Na+/ K+ pump


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

Resting membrane potential

The resting membrane potential arises from three major factors:

- 1- **Unequal distribution of ions in the ECF and cytosol**. Extracellular fluid is rich in Na+ and Cl−. In cytosol, however, the main cation is K+, and the two dominant anions are phosphates attached to molecules, such as ATP, and amino acids in proteins.

Resting membrane potential

Why is the membrane potential negative?

- Because the plasma membrane typically has more K+ channels than Na+ channels, the number of K+ that diffuse down their concentration gradient out of the cell into the ECF is greater than the number of Na+ that diffuse down their concentration gradient from the ECF into the cell.

- As more and more positive K+ exit, the inside of the membrane becomes increasingly negative, and the outside of the membrane becomes increasingly positive.

Resting membrane potential

2- **Inability of most anions to leave the cell**.

Most anions inside the cell are not free to leave. They cannot follow the K+ out of the cell because they are attached to non-diffusible molecules such as ATP and large proteins.

Phosphate is part of large molecule (ATP) and Amino acids (protein) so it will be difficult for them to leave the cell, and stay kind of entrapped within the cell.

Resting membrane potential

3- **Electrogenic nature of the Na+–K+ ATPases.** (Active transport,against concentration gradients)

Na+–K+ ATPases (sodium–potassium pumps) help maintain the resting membrane potential by pumping out Na+ as fast as it leaks in. At the same time, the Na+–K+ ATPases bring in K+. However, K+ eventually leak back out of the cell as they move down their concentration gradient.

Resting membrane potential

The Na+–K+ ATPases expel three Na+ for each two K+ imported. Since these pumps remove more positive charges from the cell than they bring into the cell, they are electrogenic, which means they contribute to the negativity of the resting membrane potential.

Excitable cells

(muscle fiber=muscle cell=Myocyte)

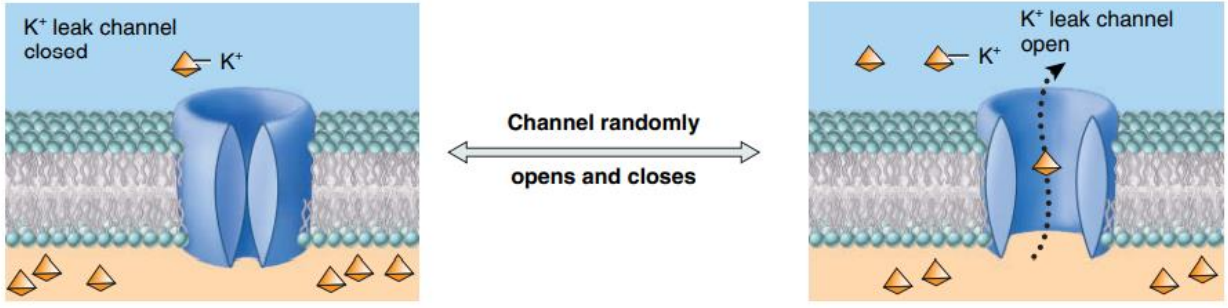
- **Neurons and muscle fibers** are considered excitable cells because they exhibit electrical excitability, the ability to respond to certain stimuli by producing electrical signals (action potential).

- These cells generate rapidly changing electrochemical impulses at their membranes, and these impulses are used to transmit signals along their membranes.

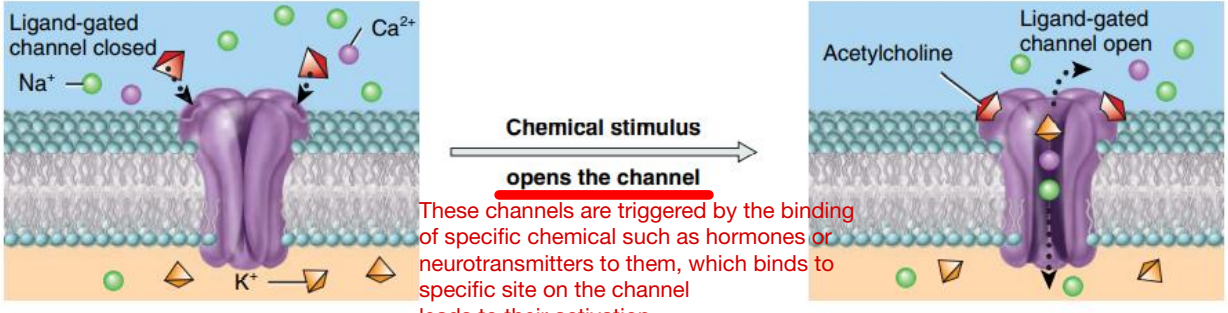
Ion channels in excitable cells

- The electrical signals produced by neurons and muscle fibers rely on four types of ion channels: leak channels, ligand-gated channels, mechanically-gated channels, and voltage-gated channels:

Ion channels in excitable cells



(a) Leak channel

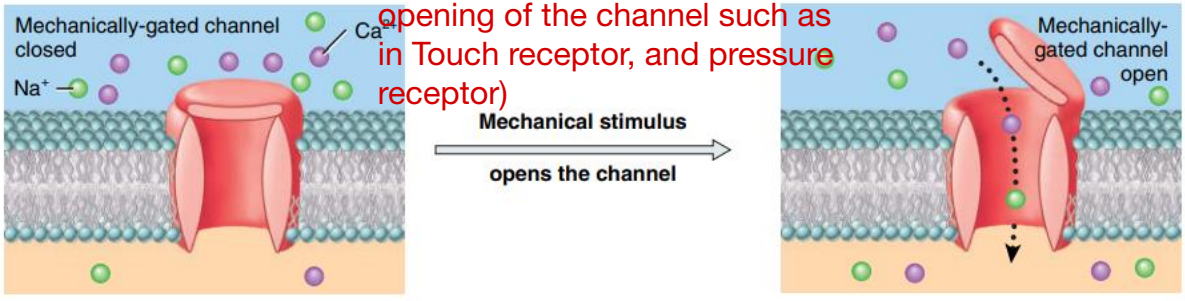


These channels are triggered by the binding of specific chemical such as hormones or neurotransmitters to them, which binds to specific site on the channel leads to their activation

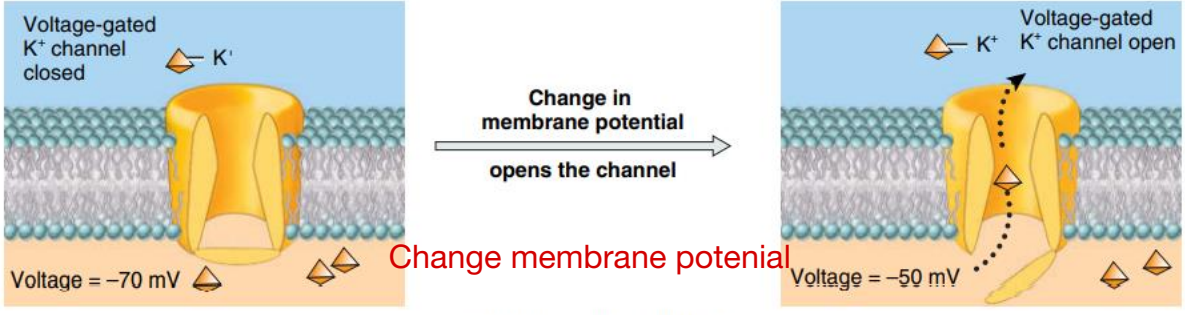
(b) Ligand-gated channel

Ion channels in excitable cells

mechanical deformation leads to opening of the channel such as in Touch receptor, and pressure receptor)



(c) Mechanically-gated channel



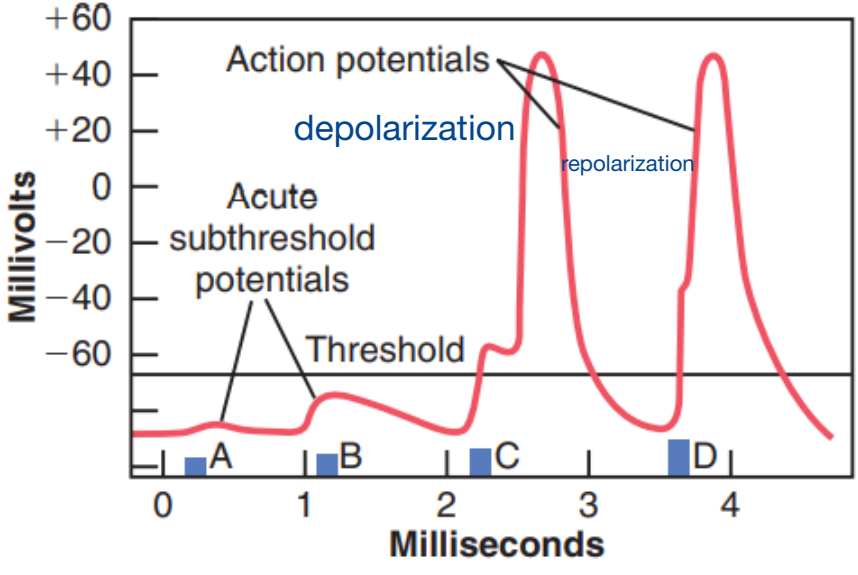
Change membrane potenial

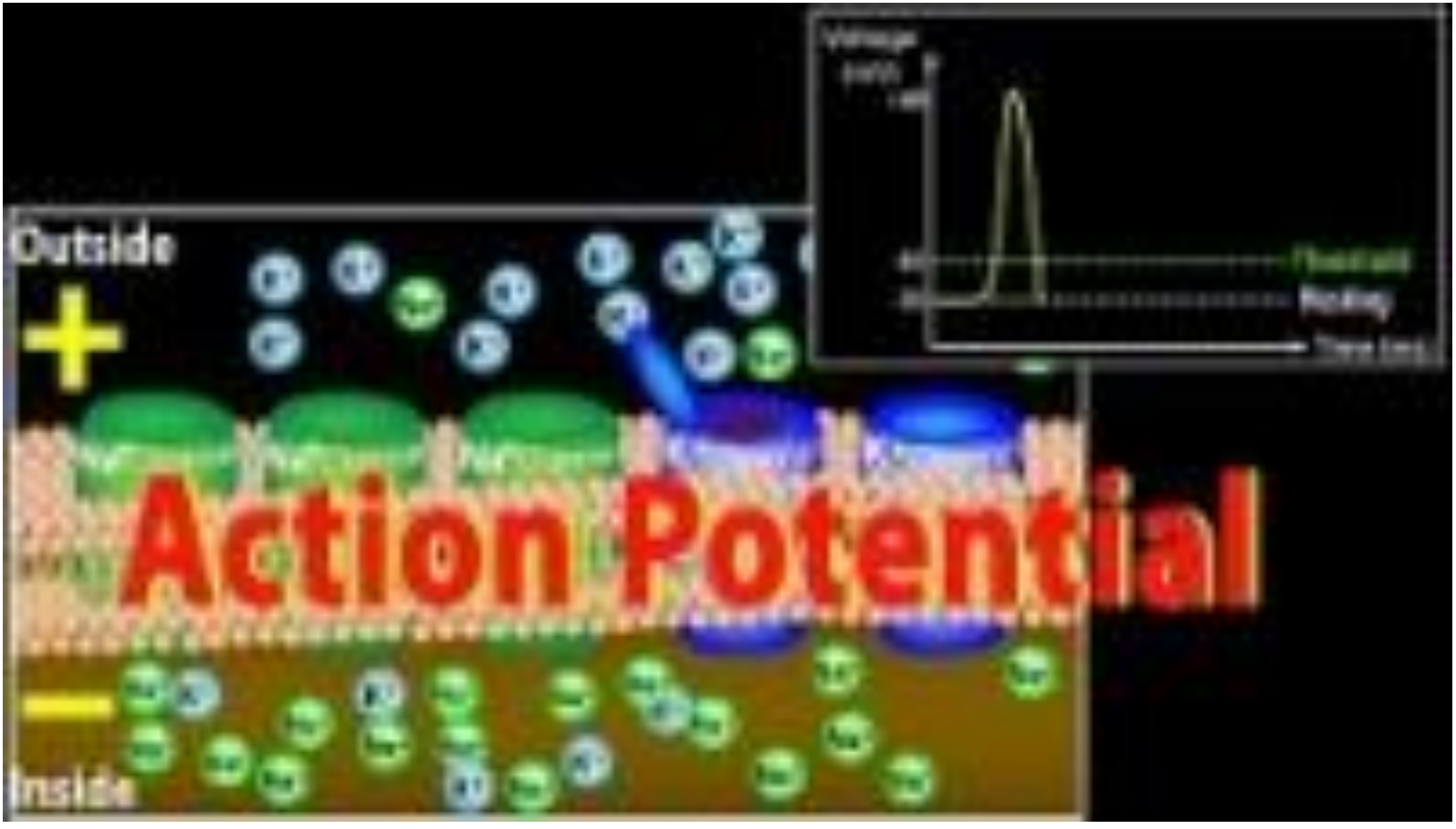
(d) Voltage-gated channel Causes activation of these channels

Graded potential vs Action potential

CHARACTERISTIC	GRADED POTENTIALS	ACTION POTENTIALS
Origin	Arise mainly in dendrites and cell body.	Arise at trigger zones and propagate along axon.
Types of channels	Ligand-gated or mechanically-gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Decremental (not propagated); permit communication over short distances.	Propagate and thus permit communication over longer distances.
Amplitude (size)	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All or none; typically about 100 mV. Faster
Duration	Typically longer, ranging from several milliseconds to several minutes.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of action potential) or depolarizing (excitatory to generation of action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present; summation can occur.	Present; summation cannot occur.

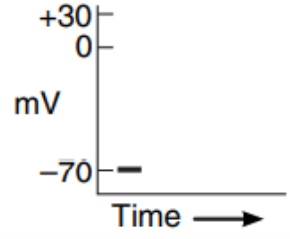
Graded potential vs action potential



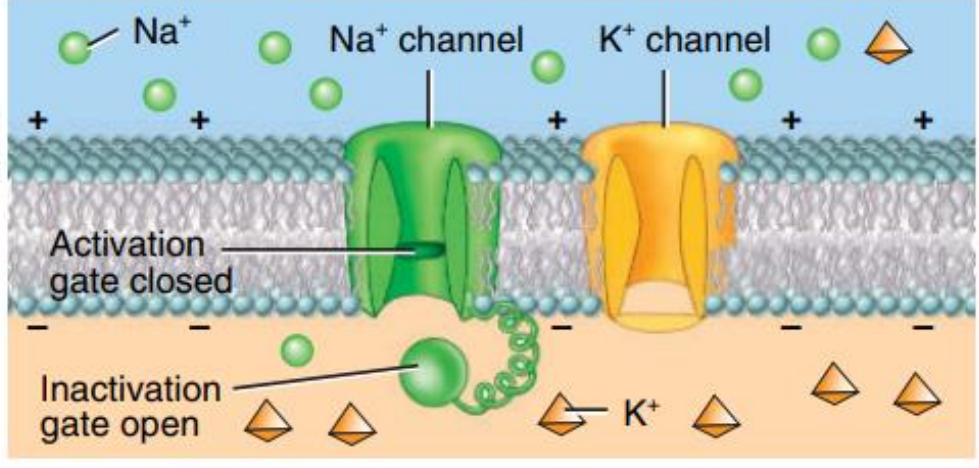

Outside
Inside
Action Potential

Action potential

Th stimulus is not present

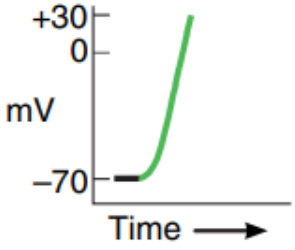


1. **Resting state:**
   All voltage-gated Na^+ and K^+ channels are closed. The axon plasma membrane is at resting membrane potential: small buildup of negative charges along inside surface of membrane and an equal buildup of positive charges along outside surface of membrane.

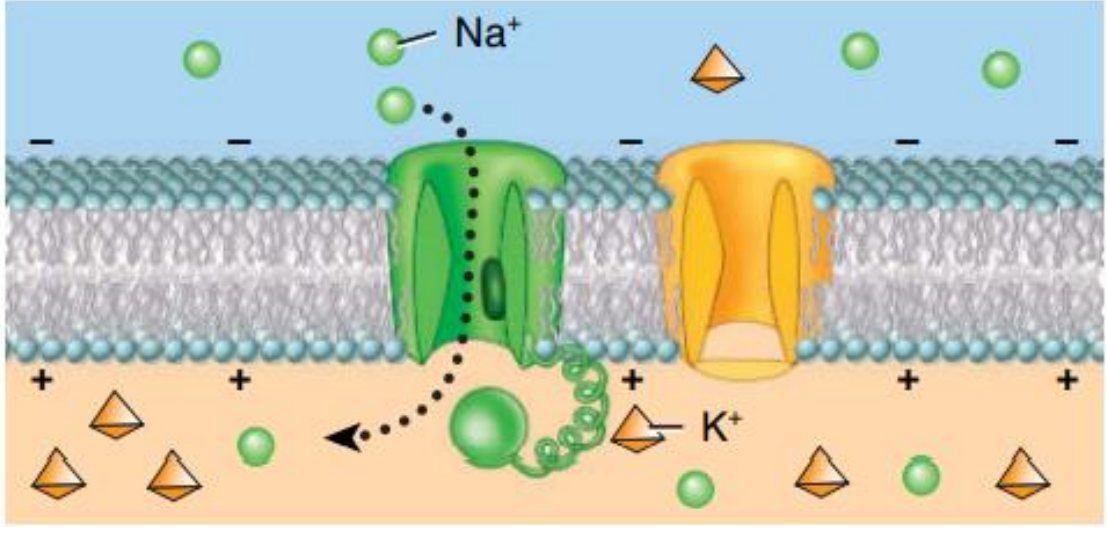


Action potential

Sodium is introduced at high speed and in large quantities

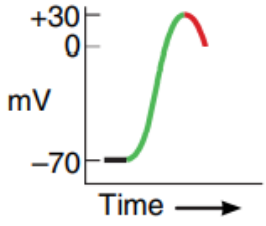


2. **Depolarizing phase:** When membrane potential of axon reaches threshold, the Na^+ channel activation gates open. As Na^+ ions move through these channels into the neuron, a buildup of positive charges forms along inside surface of membrane and the membrane becomes depolarized.

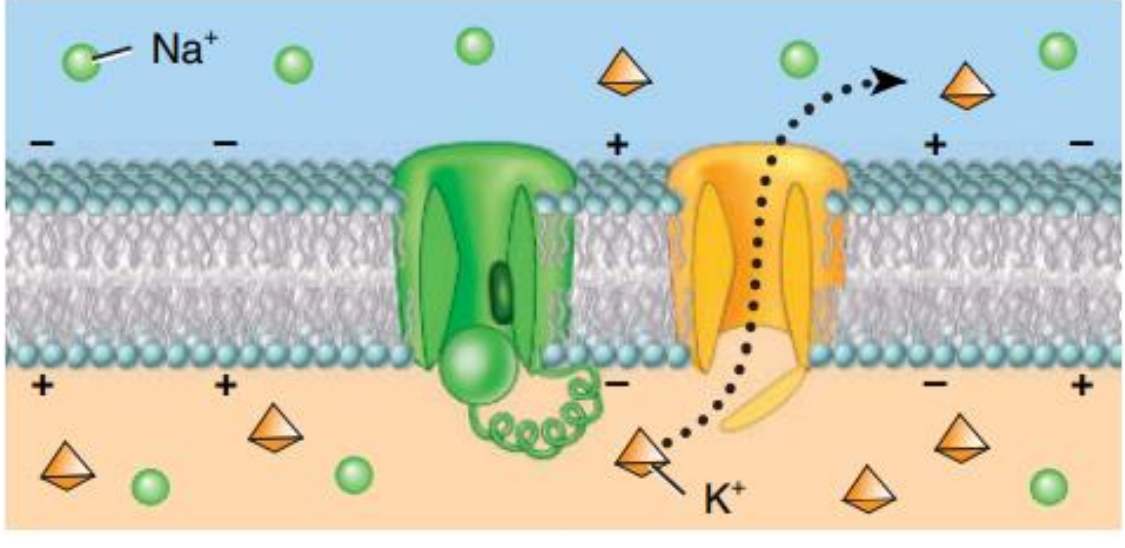


Action potential

First part of the Repolarization: channel inactivation gates close thats mean , even if the stimulus is present and very strong there will be no response.

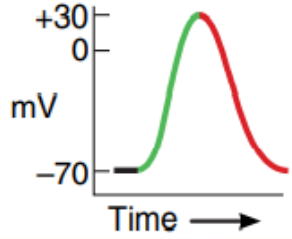


Repolarizing phase begins:
Na+
channel inactivation gates close and K+ channels open. The membrane starts to become repolarized as some K+ ions leave the neuron and a few negative charges begin to build up along the inside surface of the membrane.

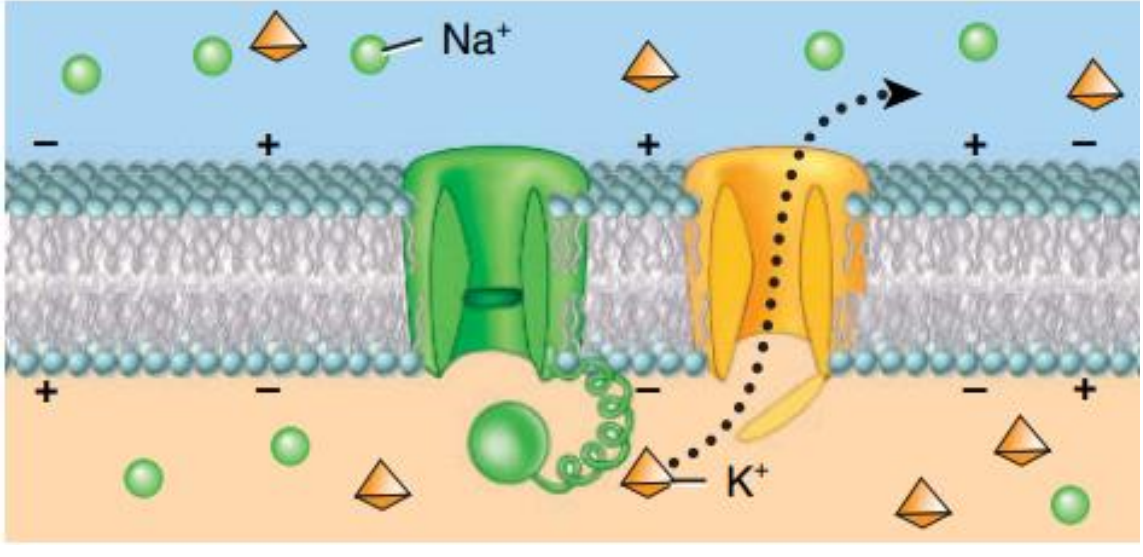


Action potential

Last part of repolarization: in this stage it is possible to recreate the action potential because the channel inactivation gates are open



Repolarization phase continues: K+ outflow continues. As more K+ ions leave the neuron, more negative charges build up along inside surface of membrane. K+ outflow eventually restores resting membrane potential. Na+ channel activation gates close and inactivation gates open. Return to resting state when K+ gates close.



Refractory period

- Shortly after the action potential is initiated, the sodium channels become inactivated and no amount of excitatory signal applied to these channels at this point will open the inactivation gates.

- The period during which a second action potential cannot be elicited, even with a strong stimulus, is called the absolute refractory period.

Refractory period

- The only condition that will allow them to reopen is for the membrane potential to return to or near the original resting membrane potential level. Then, within another small fraction of a second, the inactivation gates of the channels open and a new action potential can be initiated.

Re-establishing membrane potential

- Because **Na+ -K+ ATPase pump** requires energy for operation, this “recharging” of the nerve fiber is an active metabolic process.

- A special feature of this pump is that its degree of activity is strongly stimulated when excess sodium ions accumulate inside the cell membrane.

Clinical connection

- **Local anesthetics** are drugs that block pain and other somatic sensations. Examples include procaine and lidocaine.

- These drugs act by blocking the opening of voltage-gated Na+channels. Action potentials cannot propagate past the obstructed region, so pain signals do not reach the CNS.

Test your self

Depolarization:

a. Is associated with increase in membrane permeability to Na+.
b. Is terminated with closure of voltage activated K+ channels.
c. Is followed by muscle relaxation.
d. Is caused by K+ efflux.

ANSWER: A

Action potential:

a. Is a graded potential.
b. Is produced by sub threshold stimulus.
c. Starts with repolarization caused by outward movement of Cl-.
d. Is conducted slower in thin nerve fibers.

ANSWER: D

The resting membrane potential is caused by:

a. Diffusion of K+ ions outside the nerve fibers.
b. Diffusion of Na+ ions inside the nerve fibers.
c. Opening of the voltage activated ion channels.
d. Opening of the voltage activated ion channels.

ANSWER: A

Repolarization:

a. Occurs at first gradual then becomes fast.
b. Results from closure of sodium gates and opening of potassium gates.
c. Is represented by the ascending limb of the spike.
d. Is followed by appearance of response.

ANSWER: B

TO BE CONTINUED