Skeletal muscle physiology for medical students 2022

Action potential and NMJ

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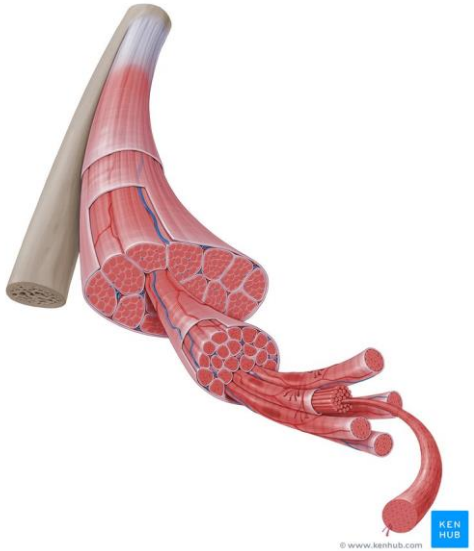


Overview

- Muscle physiology will be covered in 4 lectures and 1 lab within the first 2 weeks and before the mid exam.

- Lectures will be downloaded as PowerPoint presentation on E-learning and will be recorded.

Study material

- During the lectures, will try my best to implement active learning process.

- Students are encouraged to ask. In order to minimize the interruption of the lecture flow and confusion for other students, I will assign the last 5 minutes of each lecture for Q & A.

Office hours

- You are welcome to reach out to me during the assigned office hours:
- 9-10 am, and 12-1 pm: Sunday- Wednesday.
- Office location: School of Medicine, 3rd floor, 1st office to the left.
- You are also welcome to reach out to me using MS teams chat function.

References

- **Guyton and Hall Textbook of Medical Physiology, 13th edition.**
- Principles of Anatomy and Physiology Tortora and Derrickson 15th edition.
- Other references will be cited on individual slides.

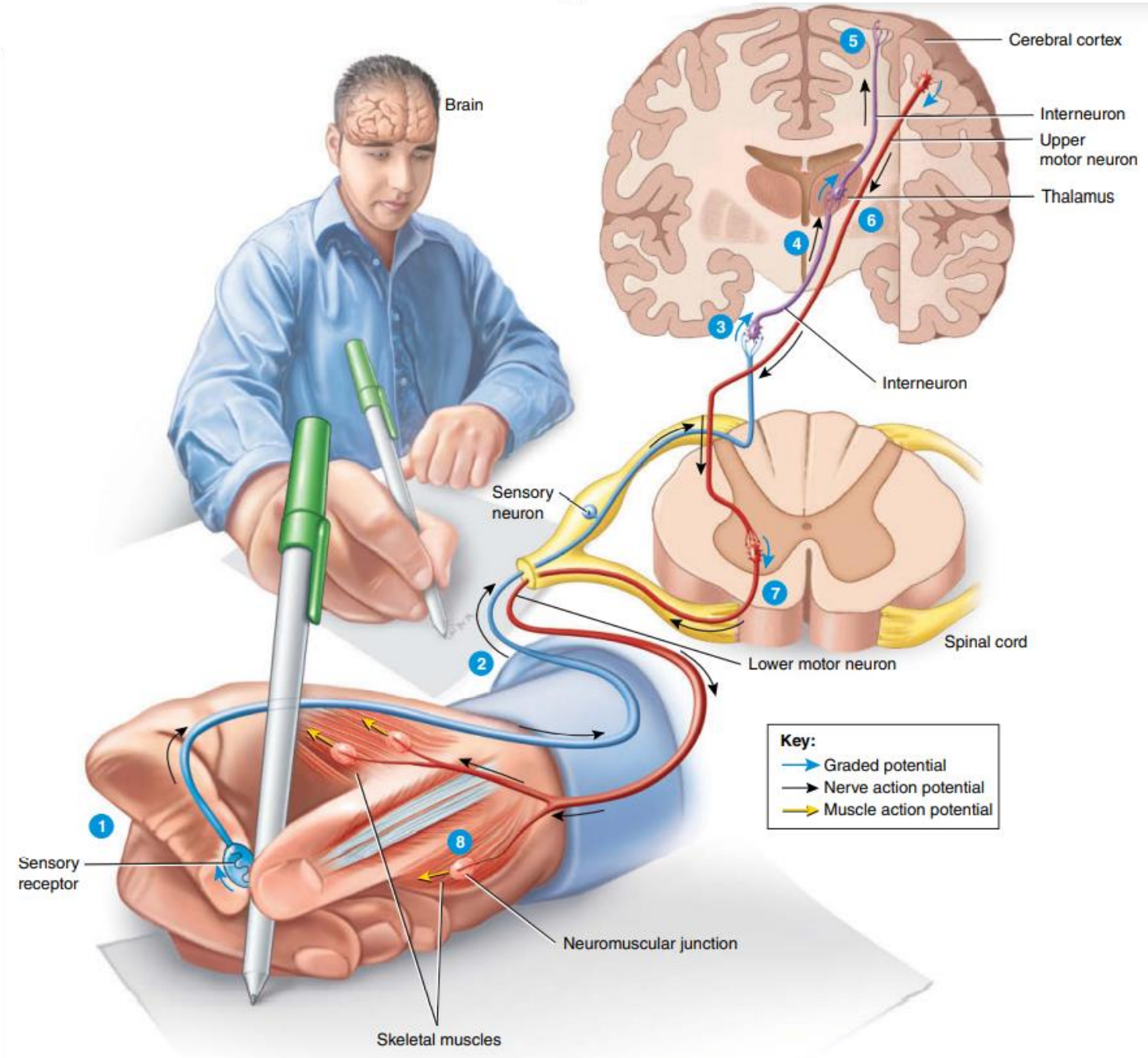
COVID precautions

- Please, You need to stay masked all the time during the lectures and keep distance from each other.

- Please, notify me and Dr. Heba Kalbouneh if you tested positive or a close contact with someone who is COVID positive.

Outline of muscle physiology lectures

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


Brain
Cerebral cortex
Interneuron
Upper motor neuron
Thalamus
Interneuron
Sensory neuron
Spinal cord
Lower motor neuron
Sensory receptor
Neuromuscular junction
Skeletal muscles
Key:
Graded potential
Nerve action potential
Muscle action potential
1
2
3
4
5
6
7
8

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.

Gradient across the membrane

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

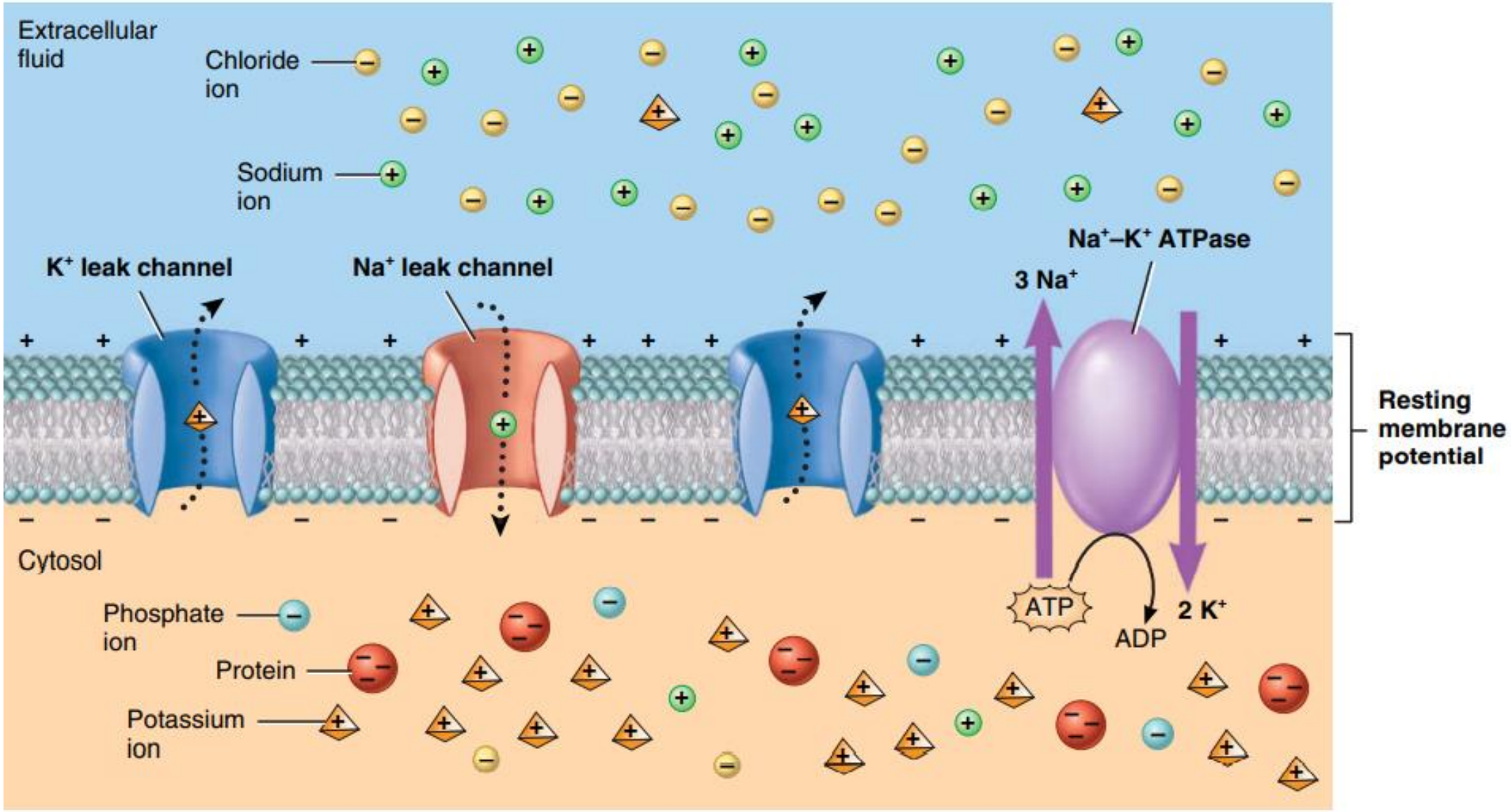
- This charge difference is termed the **membrane potential**.

Resting membrane potential

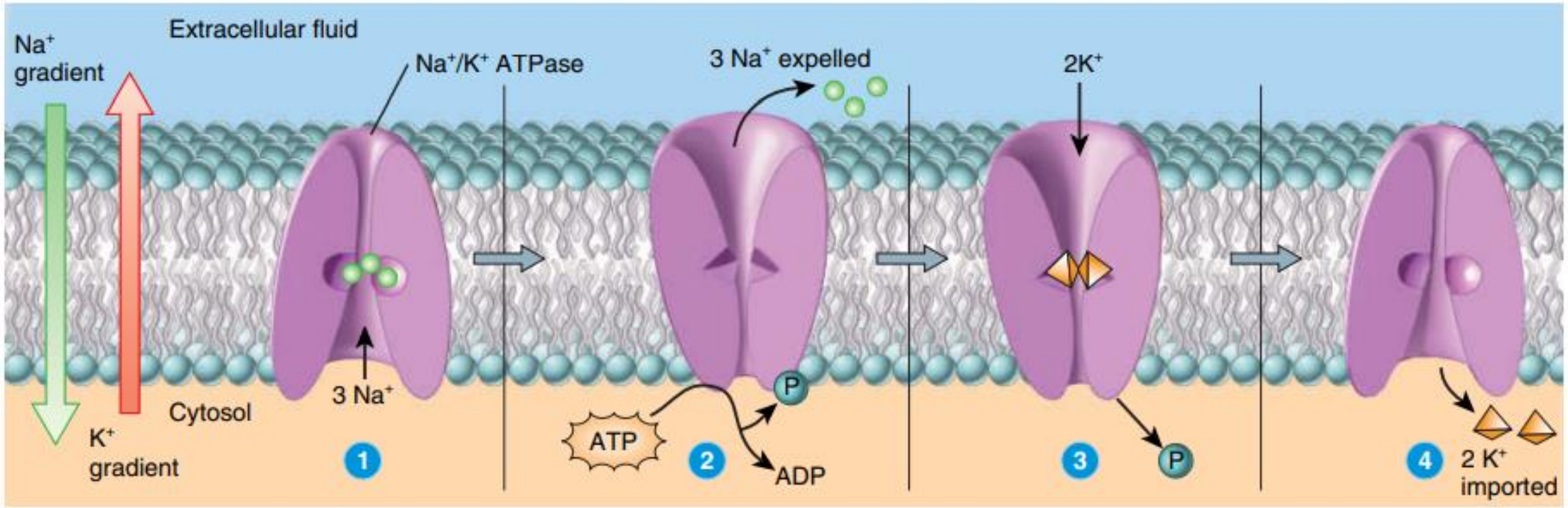
- A separation of positive and negative electrical charges is a form of potential energy, which is measured in volts or millivolts. The greater the difference in charge across the membrane, the larger the membrane potential (voltage).

- 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



Na+/ K+ pump


Extracellular fluid
Na+ gradient
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

- 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.

Resting membrane potential

3- **Electrogenic nature of the Na+–K+ ATPases**.

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

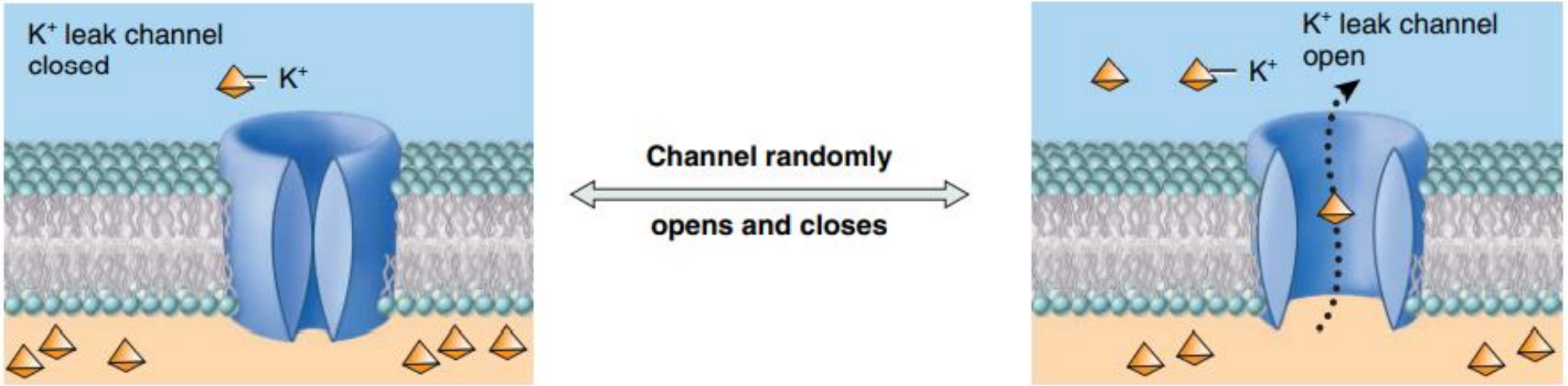
- **Neurons and muscle fibers** are considered excitable cells because they exhibit electrical excitability, the ability to respond to certain stimuli by producing electrical signals (action potential).

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

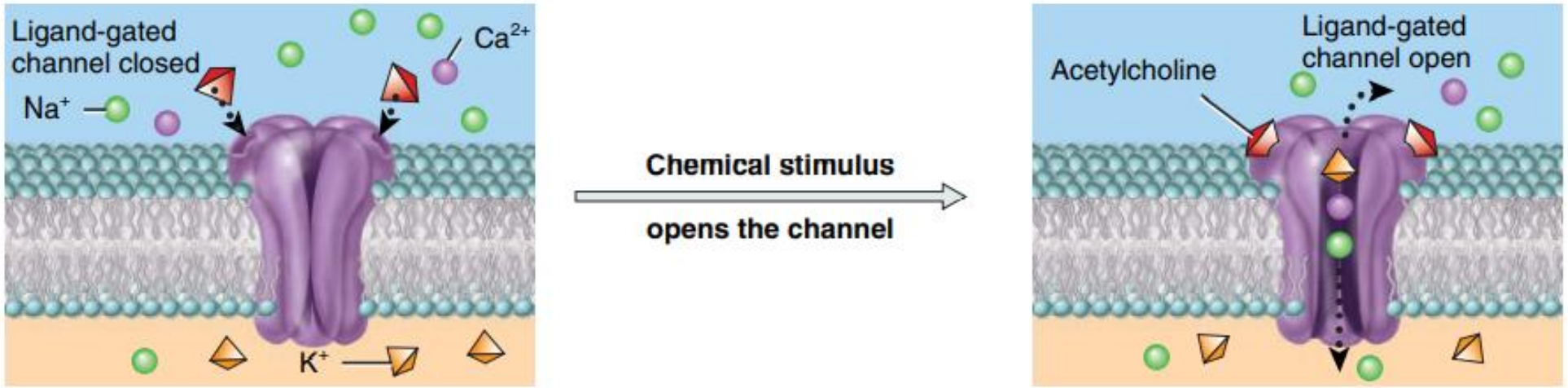
Ion channels in excitable cells

- 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

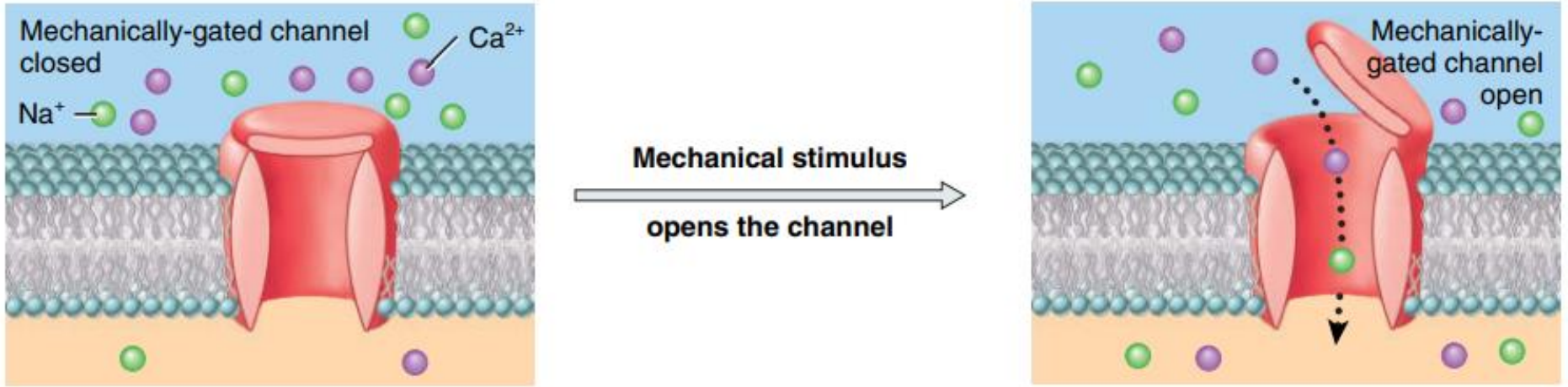


(a) Leak channel

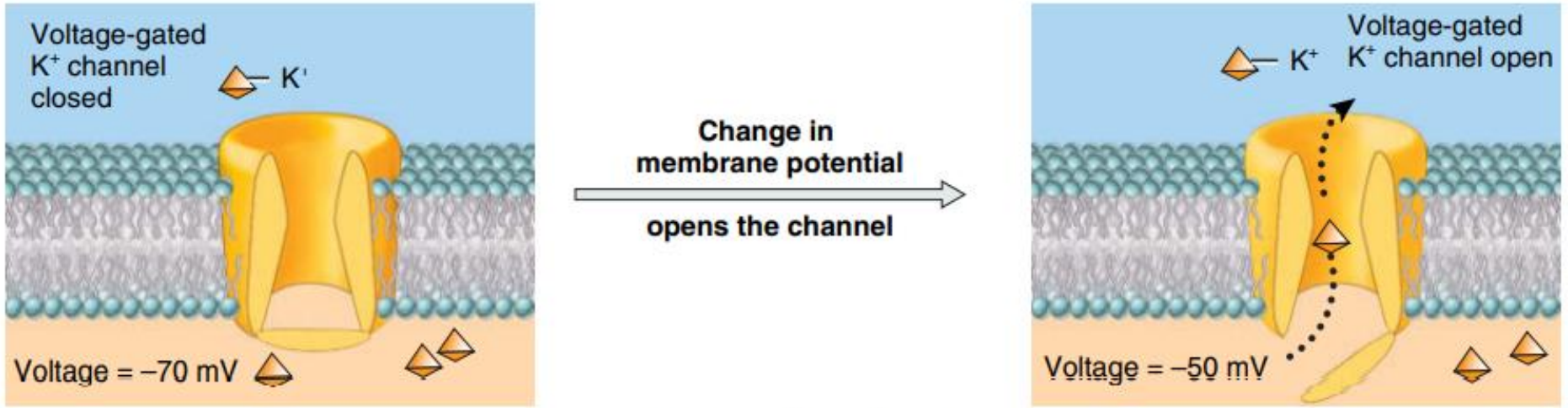


(b) Ligand-gated channel

Ion channels in excitable cells



(c) Mechanically-gated channel

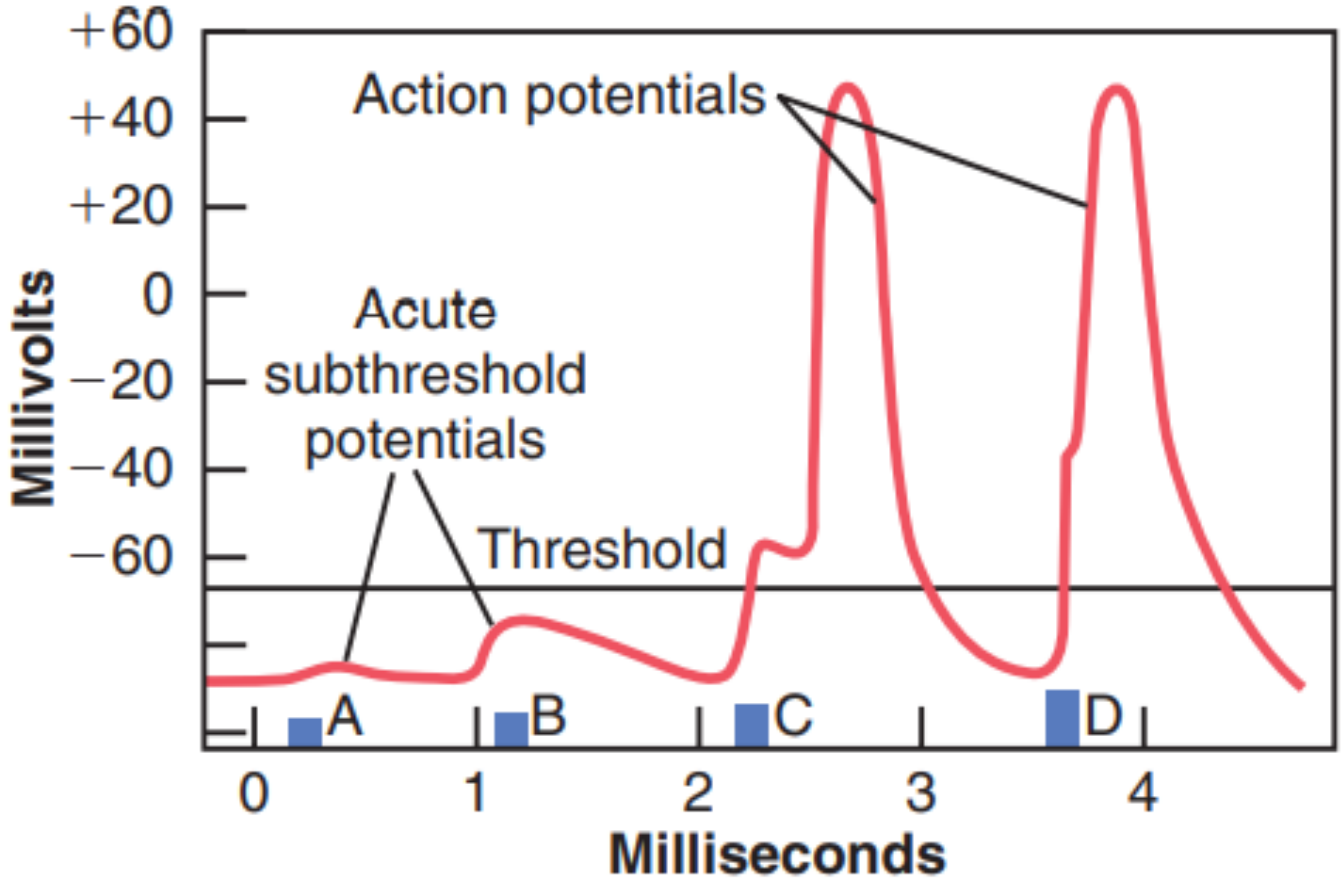


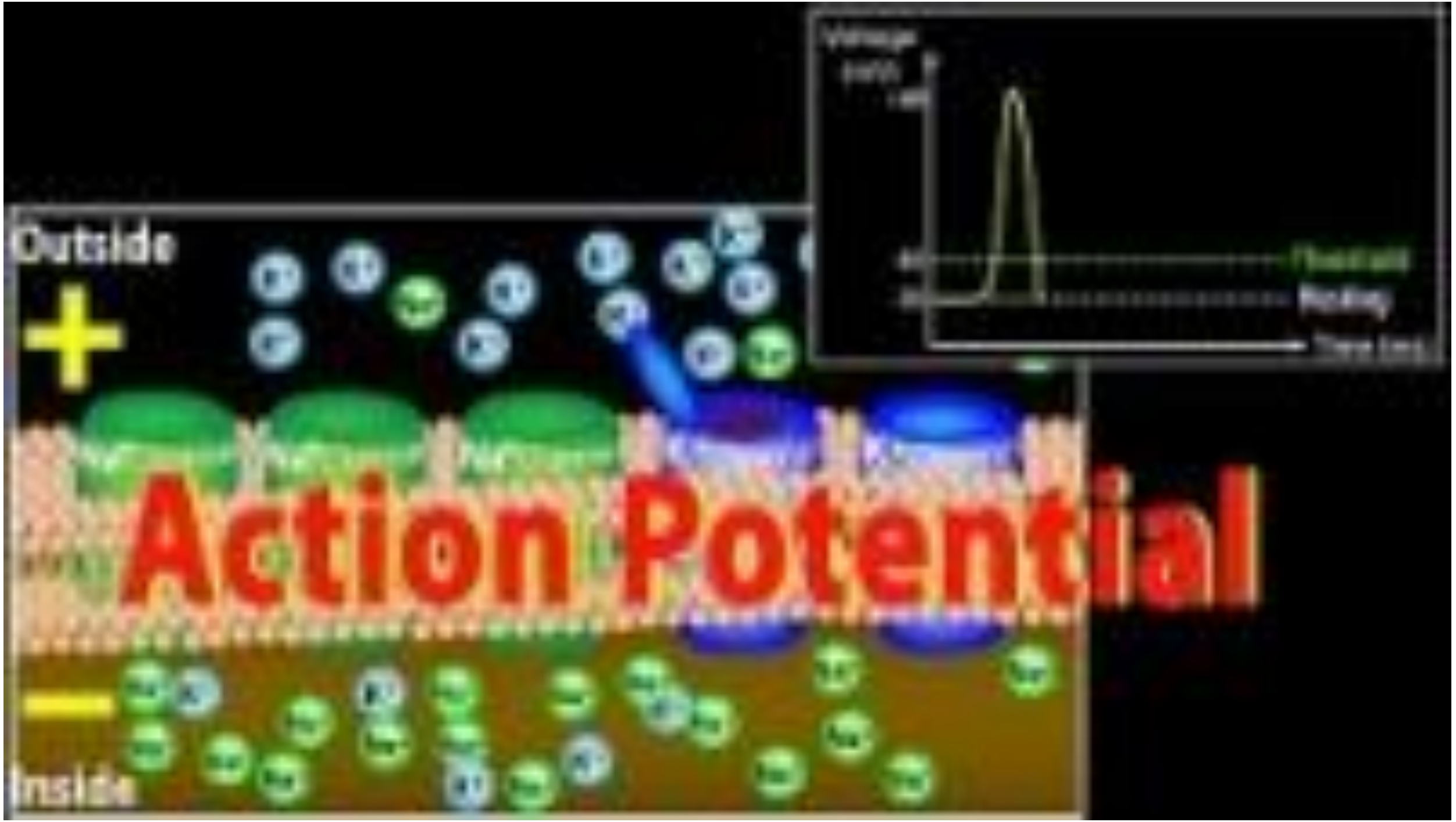
(d) Voltage-gated channel

Graded potential vs Action potential

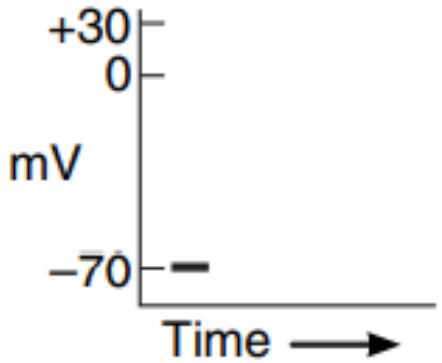
CHARACTERISTIC	GRADED POTENTIALS	ACTION POTENTIALS
Origin	Arise mainly in dendrites and cell body.	Arise at trigger zones and propagate along axon.
Types of channels	Ligand-gated or mechanically-gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Decremental (not propagated); permit 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.
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

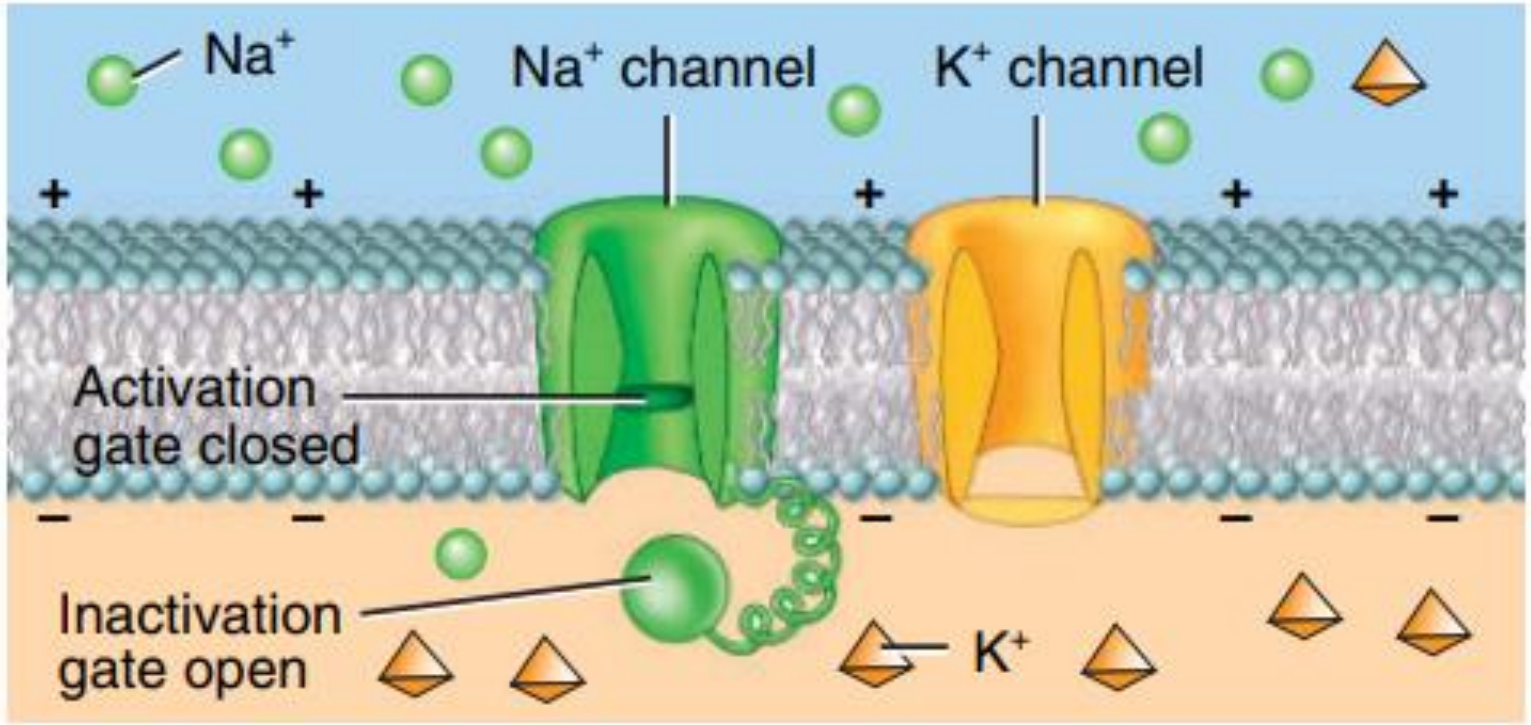



Outside
Inside
Action Potential

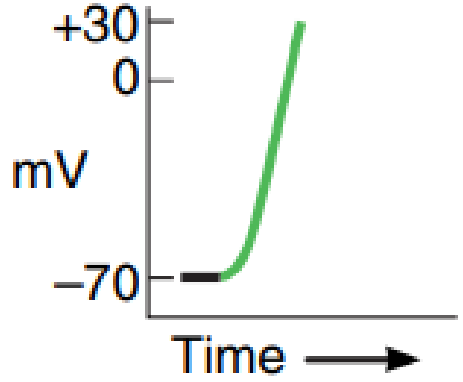
Action potential



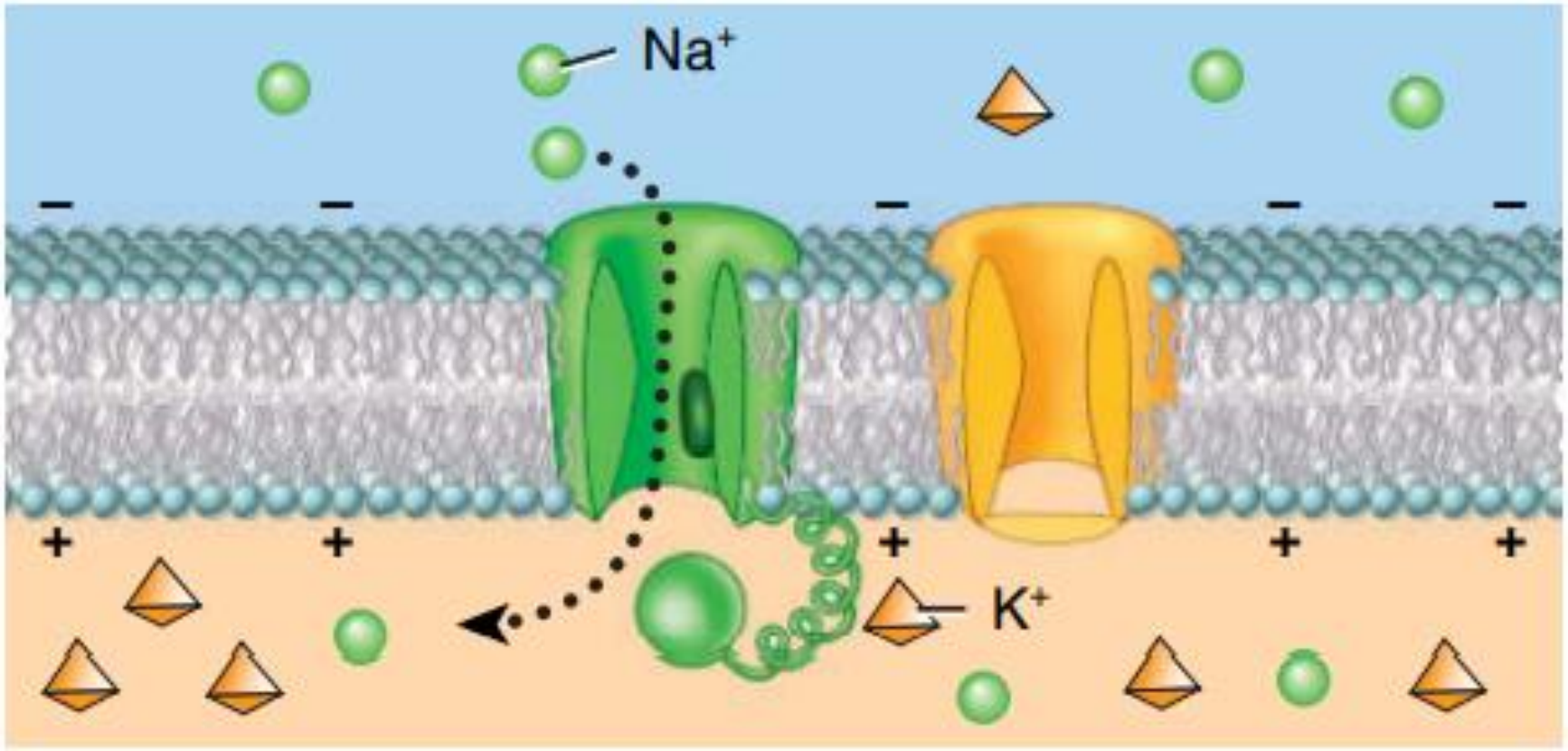
1. **Resting state:**
   All voltage-gated Na^+ and K^+ channels are closed. The axon plasma membrane is at resting membrane potential: small buildup of negative charges along inside surface of membrane and an equal buildup of positive charges along outside surface of membrane.



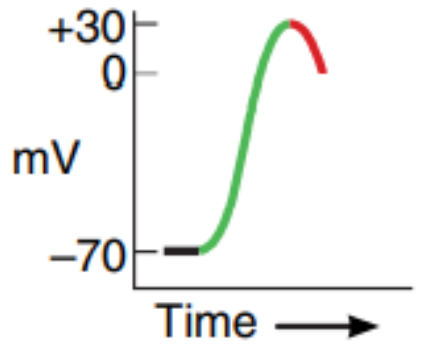
Action potential



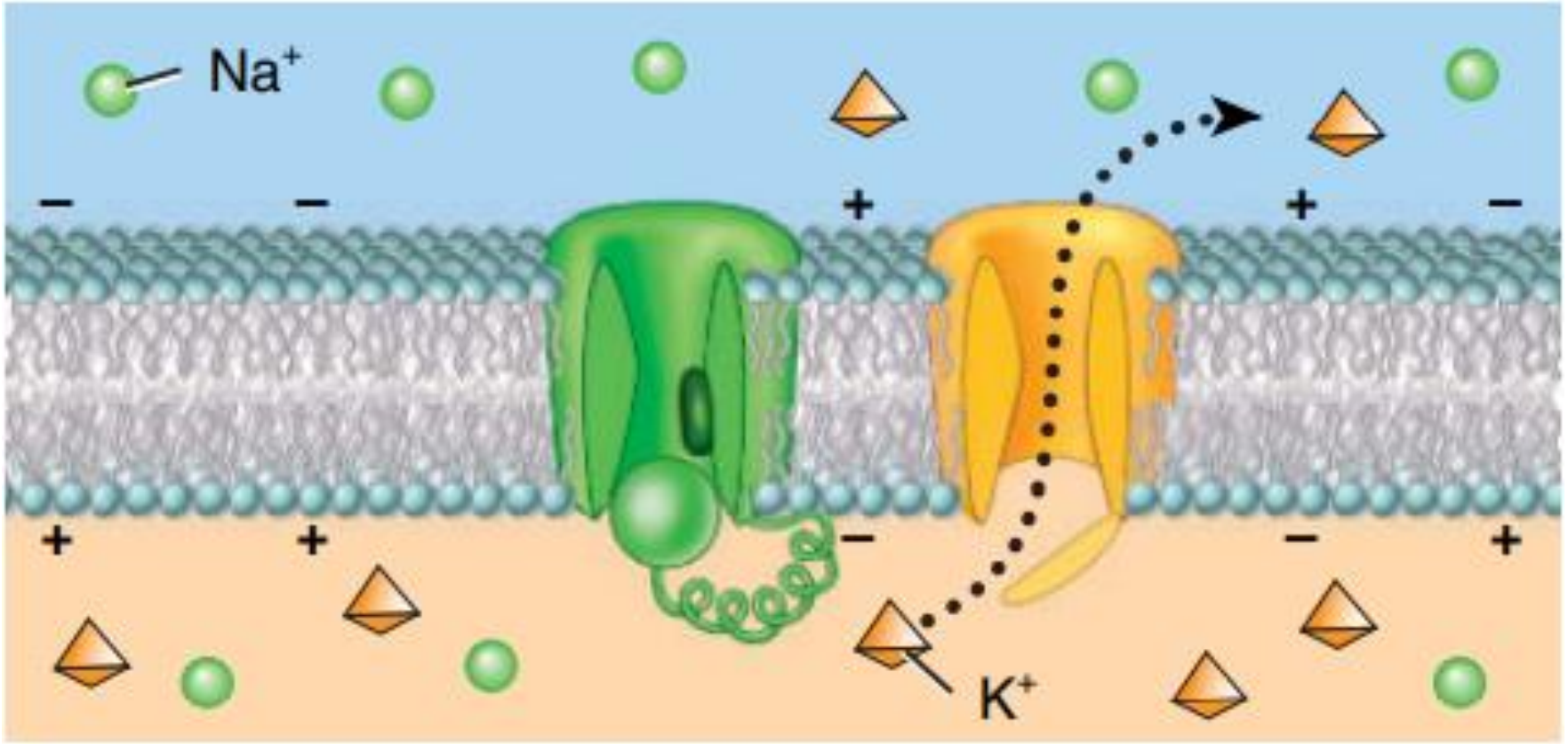
2. **Depolarizing phase:** When membrane potential of axon reaches threshold, the Na^+ channel activation gates open. As Na^+ ions move through these channels into the neuron, a buildup of positive charges forms along inside surface of membrane and the membrane becomes depolarized.



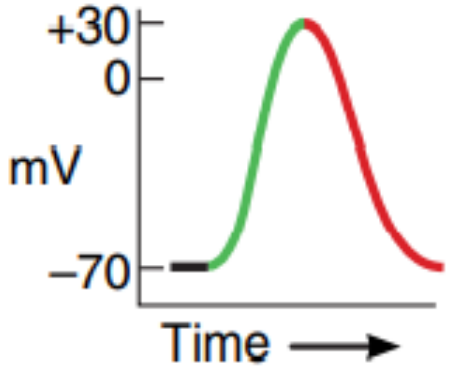
Action potential



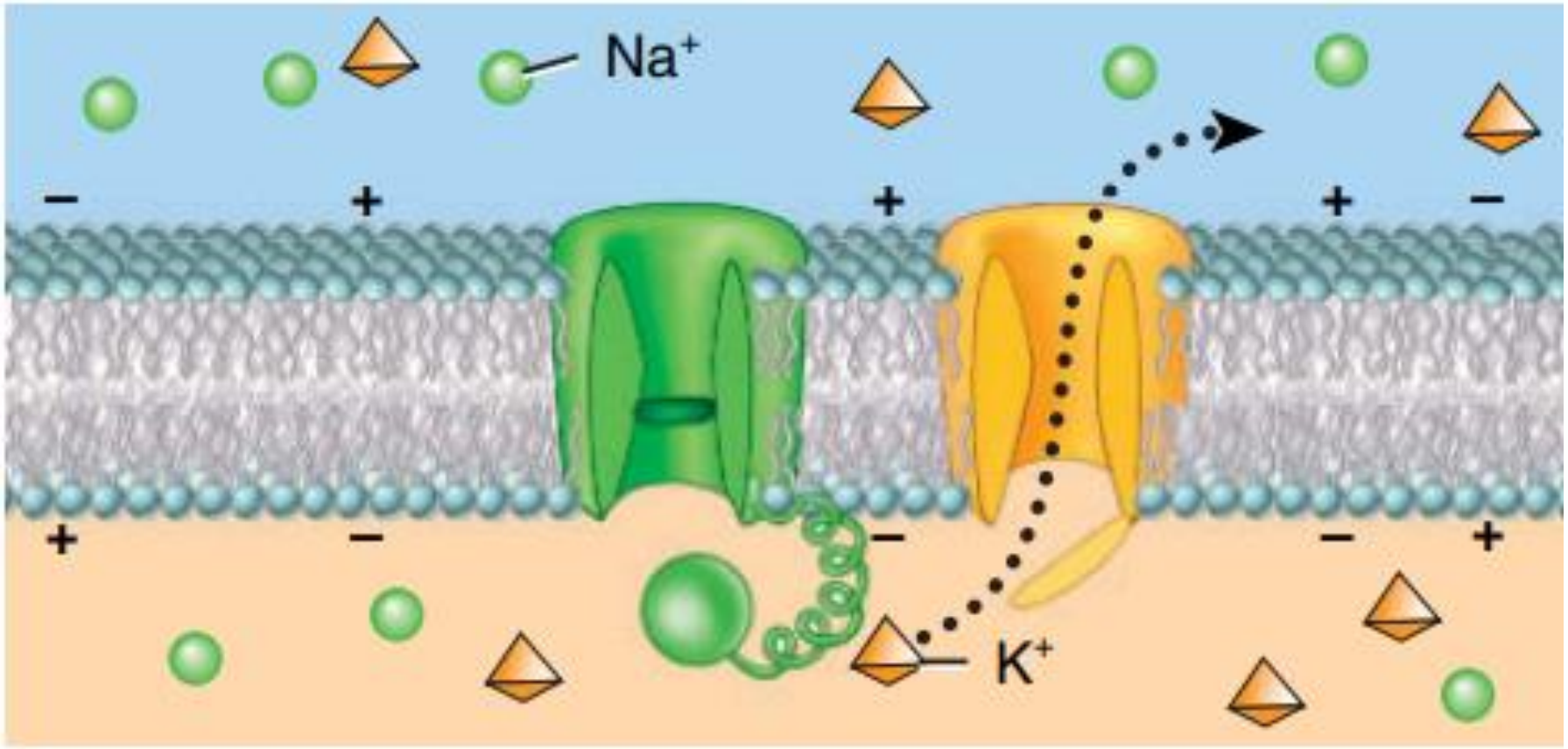
Repolarizing phase begins:
Na+
channel inactivation gates close and K+ channels open. The membrane starts to become repolarized as some K+ ions leave the neuron and a few negative charges begin to build up along the inside surface of the membrane.



Action potential



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.

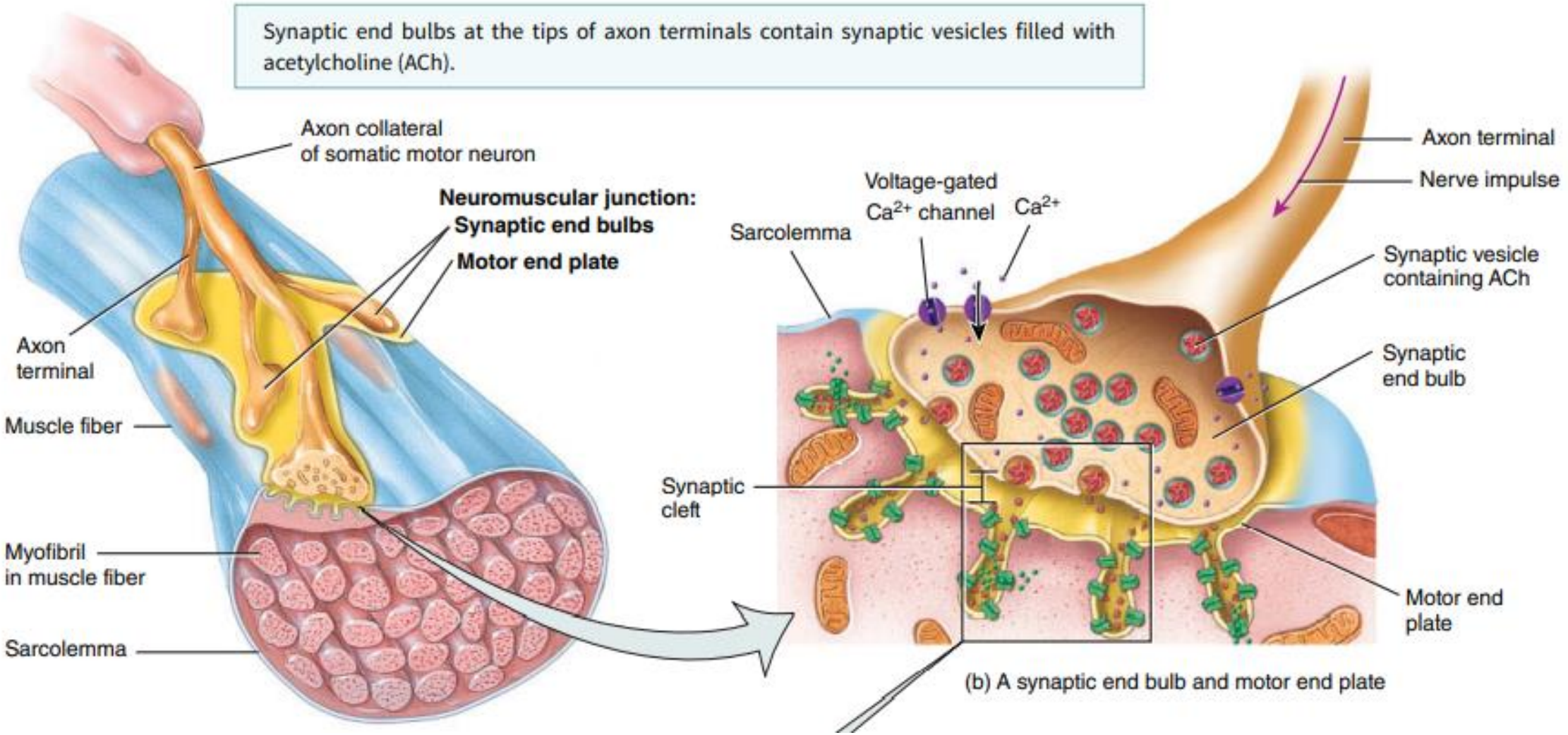
- A special feature of this pump is that its degree of activity is strongly stimulated when excess sodium ions accumulate inside the cell membrane.

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.

Neuromuscular junction (NMJ)



NMJ

- Skeletal muscle fibers are innervated by large, myelinated nerve fibers that originate from large motoneurons in the anterior horns of the spinal cord.

- Each nerve fiber, after entering the muscle belly, normally branches and stimulates from three to several hundred skeletal muscle fibers.

NMJ

- Each nerve ending makes a junction, called the neuromuscular junction, with the muscle fiber near its midpoint.

- The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends.

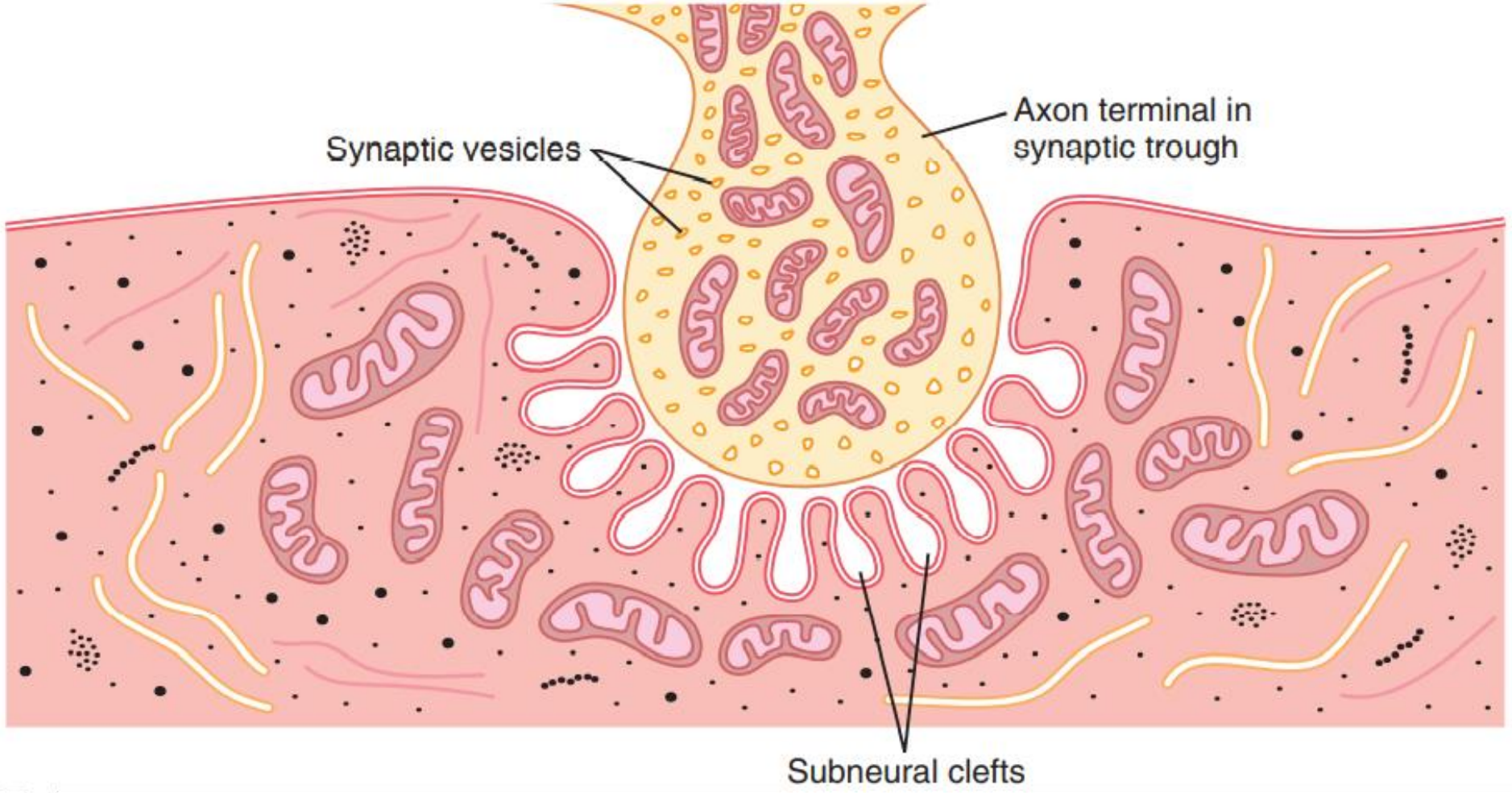
Acetylcholine

- In the axon terminal are many mitochondria that supply ATP, the energy source that is used for synthesis of an excitatory transmitter, acetylcholine.

- The acetylcholine in turn excites the muscle fiber membrane.

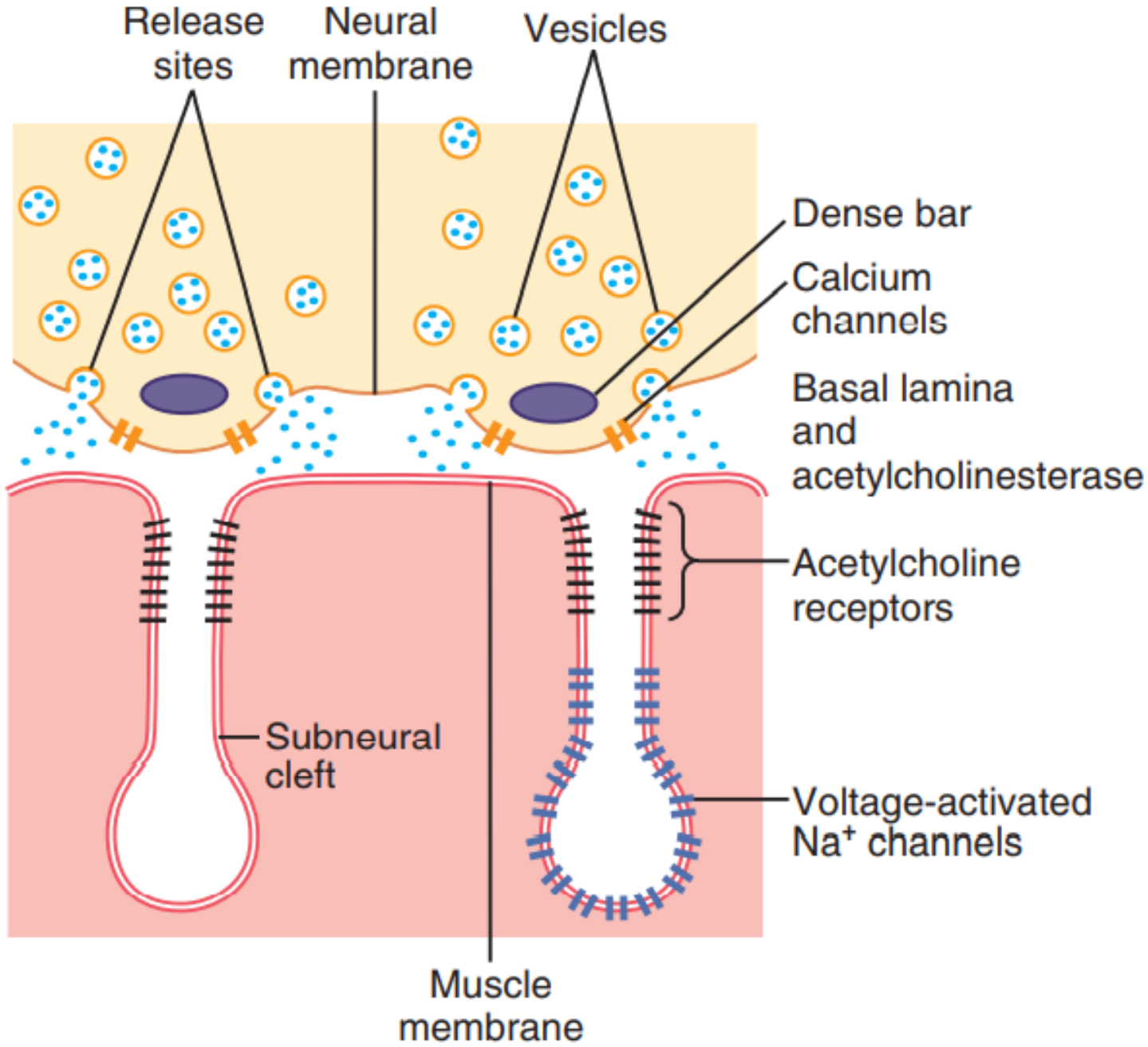
- Acetylcholine is synthesized in the cytoplasm of the terminal, but it is absorbed rapidly into many small synaptic vesicles which are normally in the terminals of a single end plate.

Excitation of skeletal muscles



Voltage-gated Calcium channels

- On the inside surface of the neural membrane are linear dense bars.
- To each side of each dense bar are protein particles that penetrate the neural membrane; these are voltage-gated calcium channels.
- When an action potential spreads over the terminal, these channels open and allow calcium ions to diffuse from the synaptic space to the interior of the nerve terminal.


Release sites
Neural membrane
Vesicles
Dense bar
Calcium channels
Basal lamina and acetylcholinesterase
Acetylcholine receptors
Subneural cleft
Voltage-activated Na+ channels
Muscle membrane

Release of Acetylcholine

- The calcium ions are believed to activate Ca2+-calmodulin dependent protein kinase, which, in turn, phosphorylates synapsin proteins that anchor the acetylcholine vesicles to the cytoskeleton of the presynaptic terminal.

Release of Acetylcholine

- This process frees the acetylcholine vesicles from the cytoskeleton and allows them to move to the active zone of the presynaptic neural membrane adjacent to the dense bars.

- The vesicles then dock at the release sites, fuse with the neural membrane, and empty their acetylcholine into the synaptic space by the process of exocytosis.

Acetylcholine-gated channels

- Acetylcholine receptors in the muscle fiber membrane are acetylcholine-gated ion channels.

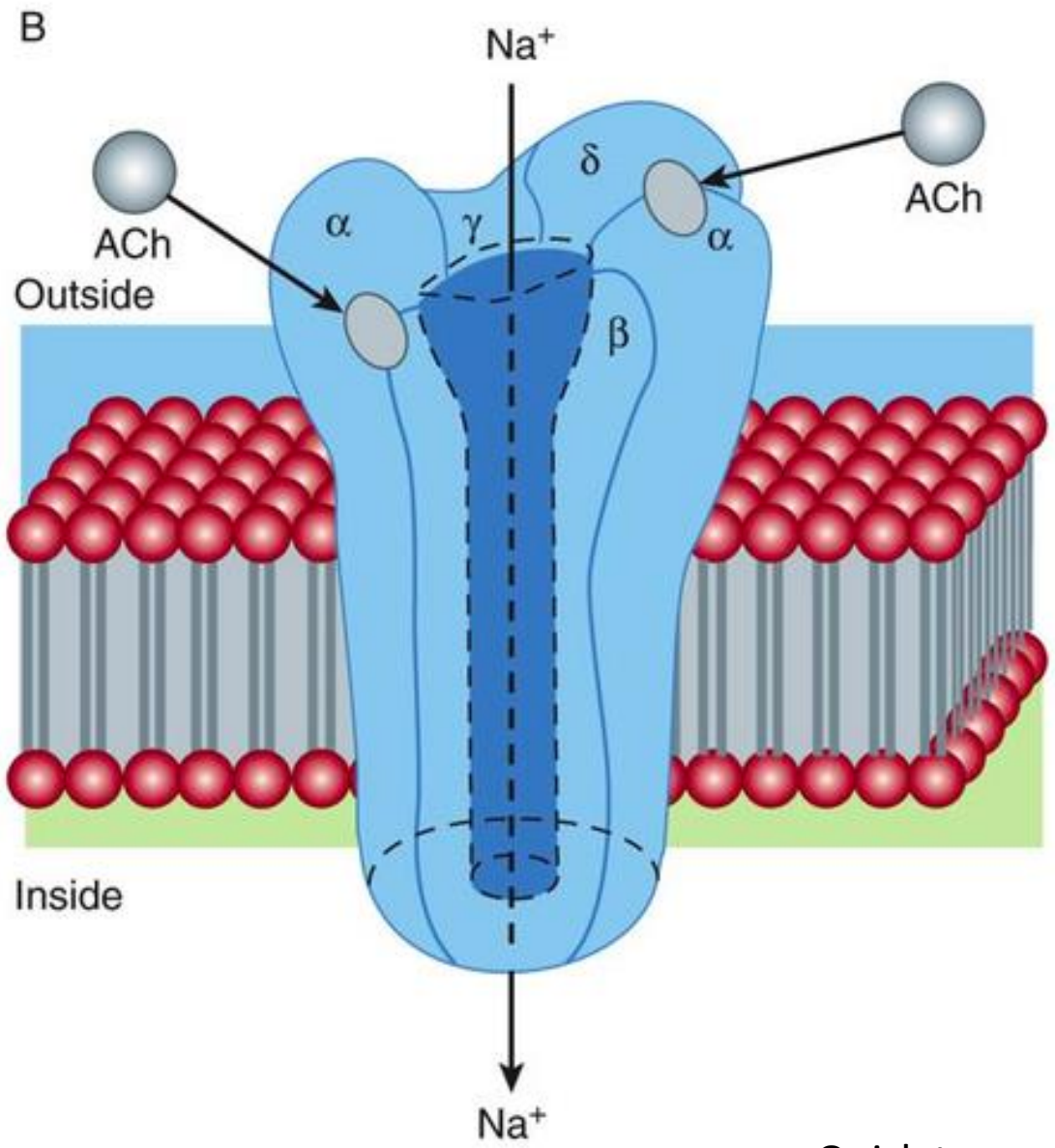
- They are located almost entirely near the mouths of the sub-neural clefts lying immediately below the dense bar areas, where the acetylcholine is emptied into the synaptic space.

Acetylcholine-gated channels

- Each receptor is a protein complex. The fetal acetylcholine receptor complex is composed of five subunit proteins, two alpha proteins and one each of beta, delta, and gamma proteins.

- In the adult, an epsilon protein substitutes for the gamma protein in this receptor complex.

Acetylcholine-gated channels



Quizlet.com

Acetylcholine-gated channels

- The channel remains constricted until two acetylcholine molecules attach respectively to the two alpha subunit proteins.

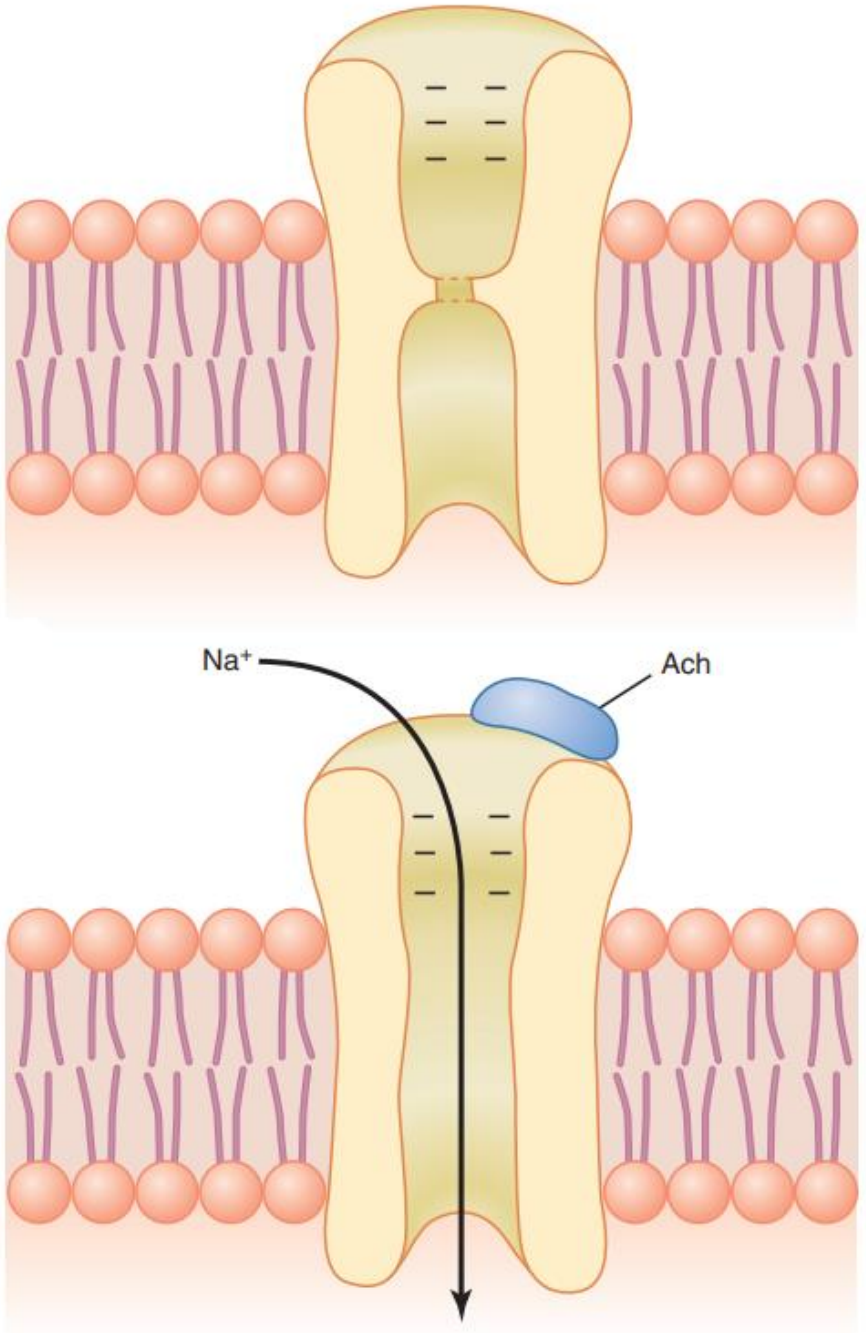
- This attachment causes a conformational change that opens the channel.

Acetylcholine-gated channels

- The acetylcholine-gated channel allow the important positive ions: Na+, K+, and Ca++ to move easily through the opening.

- Conversely, negative ions, such as Cl-, do not pass through because of strong negative charges in the mouth of the channel that repel these negative ions.

Acetylcholine-gated channels



Acetylcholine-gated channels

- In practice, far more sodium ions flow through the acetylcholine-gated channels than any other ions, for two reasons:

- First, there are only two positive ions in large concentration: Na+ in the ECF and K+ in the ICF.

- Second, the negative potential on the inside of the muscle membrane, −80 to −90 millivolts, pulls the positively charged sodium ions to the inside of the fiber.

Thank you