

Pitt Medical Neuroscience

Neurophysiology and Synaptic Transmission Modules

Module Listing

Please complete the following online neurophysiology modules during the first two weeks of class:

- **Module 1:** The neuron
- **Module 2:** Membrane potentials
- **Module 3:** Action potentials
- **Module 4:** Synaptic transmission
- **Module 5:** Glutamate receptors
- **Module 6:** Acetylcholine receptors
- **Module 7:** Inhibitory neurotransmitters
- **Module 8:** Monoamines
- **Module 9:** Effects of Ca²⁺ and Mg²⁺ on neuronal excitability

Learning Objectives

1. To review the basic structure of neurons
2. To review the electrophysiological properties of neurons, including the generation of the resting membrane potential and action potentials.
3. To review the process of synaptic transmission.
4. To list the major neurotransmitters used for signaling by the nervous system: glutamate, acetylcholine, GABA, glycine, norepinephrine, dopamine, and serotonin.
5. To understand the differences between metabotropic and ionotropic receptors.
6. To appreciate the differences in neuronal responses of glutamate binding to AMPA, kainate, and NMDA receptors.
7. To describe the process of long term potentiation in the nervous system.
8. To understand the basis of excitotoxicity.
9. To discern the differences in cellular responses of acetylcholine binding to nicotinic and muscarinic receptors.
10. To understand the differential distribution of glycine and GABA receptors in the nervous system, and the effects of agonists binding to these receptors.
11. To discuss the effects of allosteric modulators on GABA receptors.
12. To appreciate the locations of neurons that release the monoamines dopamine, norepinephrine, and serotonin.
13. To review the types and physiological roles of receptors that bind norepinephrine and epinephrine.
14. To understand how changes in plasma levels of calcium and magnesium alter neuronal excitability, and the physiological consequences of this altered excitability.

Neurophysiology Module 1

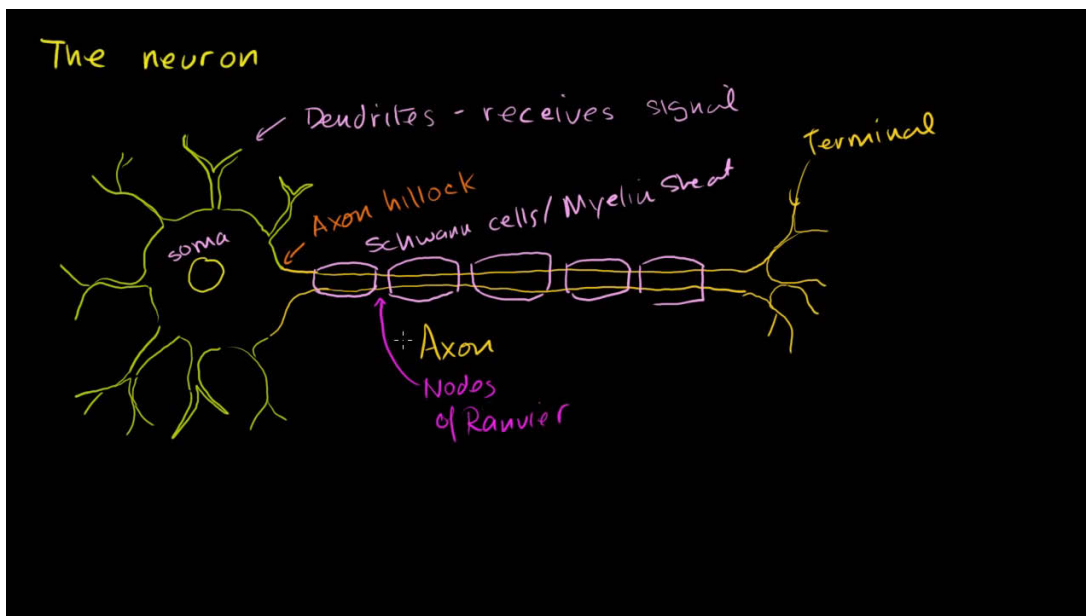
The Neuron

- [Introduction](#)
- [Anatomy and Types of Neurons](#)
- [Assessment](#)

Introduction

As an introduction, watch this movie from the KhanAcademy.

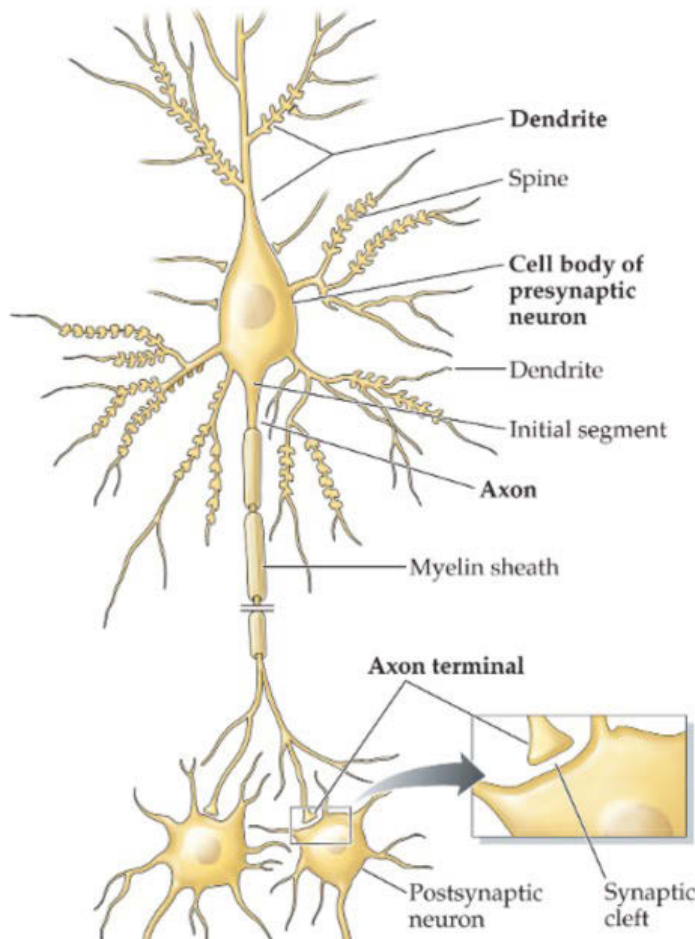
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Anatomy and Types of Neurons

Not all neurons are the prototypical cells described in the KhanAcademy video. In general, neurons receive inputs from other nerve cells on the dendrites and cell body, and transmit outputs to other neurons or effectors like muscle cells through an axon. Most neurons have multiple dendrites and one axon, which can branch near where it reaches its target. However, there are some exceptions.

To start, let's discuss the general classes of neurons, and their anatomy:

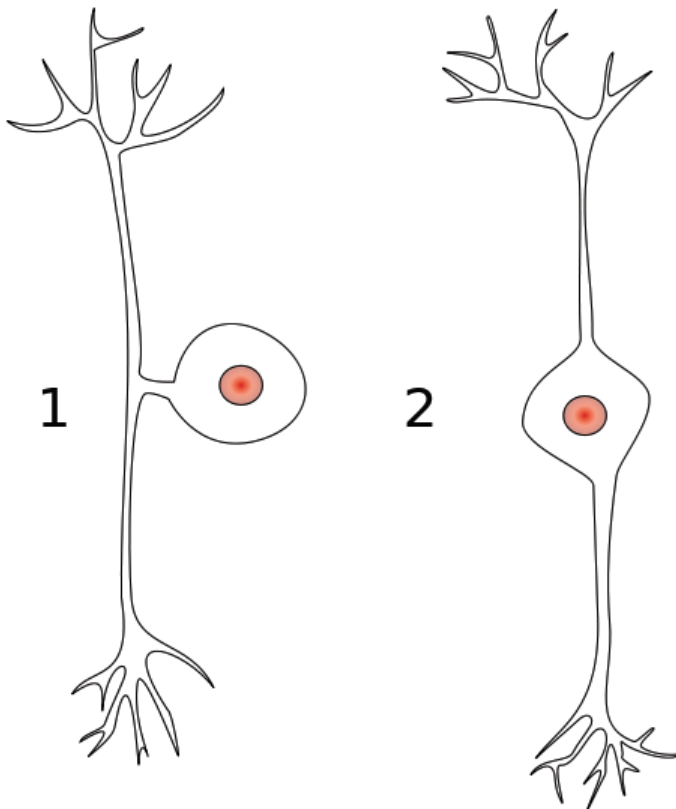


Interneurons are the most common cells in the central nervous system. The processes of interneurons always remain within the central nervous system, although some *projection (or relay) interneurons* may have long axons that extend for considerable distances (i.e., from the brain to the spinal cord).

Most interneurons are **multipolar neurons**, as they have many dendrites as well as an axon that branches to multiple targets. Thus, one interneuron can receive synaptic inputs on their dendrites and cell body from thousands of neurons, and in turn send outputs to many other interneurons, or perhaps to cells that provide outflow from the nervous system to peripheral targets like muscle or glands. Such output cells are discussed below. Interneurons are integrators, and the main components of the neural circuits that process information in the nervous system.

The neuron pictured on the left has **dendritic spines**. Dendritic spines are typically sites of excitatory synapses, where synaptic transmission makes it more likely that the neuron will generate an action potential. Inhibitory synapses are usually located on the shaft of the dendrites, the cell body, and the initial segment. Inhibitory synaptic transmission makes it less likely that a neuron will generate an action potential.

Sensory afferent neurons carry inputs from sensors in the periphery to the central nervous system. The term "afferent" means "carrying into," and usually describes the transmission of information towards the brain and spinal cord. The dendrites of sensory afferent neurons are often specialized to receive inputs from a peripheral sensory receptor (as in the vestibular and auditory systems), or may be a component of the peripheral sensory receptor (as in the skin and muscle). Usually, the cell bodies of sensory afferent neurons are coalesced in a **ganglion** outside the central nervous system.



Most sensory afferent neurons are **pseudounipolar** (neuron 1 to the left) or **bipolar** (neuron 2 to the left). Pseudounipolar neurons (neuron 1 to the left) have one projection from the cell body, which splits into two axons: one that extends into the periphery and one that extends into the central nervous system. Afferents that project into the spinal cord from skin and muscle are typically pseudounipolar. The cell bodies of these afferents are located in the **dorsal root ganglia** near the spinal cord, as will be discussed during the first week of class. The peripheral branch extends through a peripheral nerve, and is part of the sensory receptor in skin or muscle. The central branch projects through the **dorsal (posterior) root** into the spinal cord, and terminates on interneurons or **motoneurons** in the spinal cord, and may even project to the brainstem.

Some afferents entering the brainstem through the **cranial nerves** are also pseudounipolar.

Other sensory afferent neurons with projections through cranial nerves are bipolar (neuron 2 to the left). One branch from the cell body is effectively a dendrite, and extends into the periphery to make synaptic contact with sensory receptors. In other words, the sensory receptors deposit neurotransmitters onto receptors on the dendrite of the bipolar neuron. The other branch from the cell body is effectively an axon, and travels through a cranial nerve to the brainstem. Almost always, the cell bodies of bipolar neurons are in a ganglion outside the nervous system, although we will encounter one exception during the course.

Efferent neurons send their axons out of the central nervous system, to control effectors in the periphery. These include **motoneurons** that innervate muscle fibers and sympathetic and parasympathetic **preganglionic neurons** that regulate autonomic function.

Assessment: The Neuron

Please answer the questions below to assess how well you learned the material.

Dendritic spines are sites where neurons: *

- Release trophic neuropeptides
- Release neurotransmitter
- Receive excitatory inputs from other neurons
- Receive inhibitory inputs from other neurons

Pseudounipolar neurons: *

- Provide output signals from the central nervous system to motoneurons
- Have multiple dendrites emanating from the cell body
- Are the most common neuron type in the brain
- Often send a projection through the posterior roots of the spinal cord

Sensory afferent neurons: *

- Typically have their soma in the central nervous system
- Directly control the contraction of muscle fibers
- Can have their peripheral axon in either a spinal or cranial nerve
- Typically are multipolar neurons

Axons of interneurons: *

- Often provide direct outputs to muscle fibers
- Are always very short, and provide outputs to only nearby neurons
- Can provide outputs to multiple interneurons or efferent neurons
- Provide outputs to only a single interneuron

The Neuron: Self Assessment Questions

Dendritic spines are sites where neurons:

- Release neurotransmitter
- Receive inhibitory inputs from other neurons
- **Receive excitatory inputs from other neurons**
- Release trophic neuropeptides

Pseudounipolar neurons:

- Are the most common neuron type in the brain
- Have multiple dendrites emanating from the cell body
- **Often send a projection through the posterior roots of the spinal cord**
- Provide output signals from the central nervous system to motoneurons

Sensory afferent neurons:

- Typically are multipolar neurons
- Typically have their soma in the central nervous system
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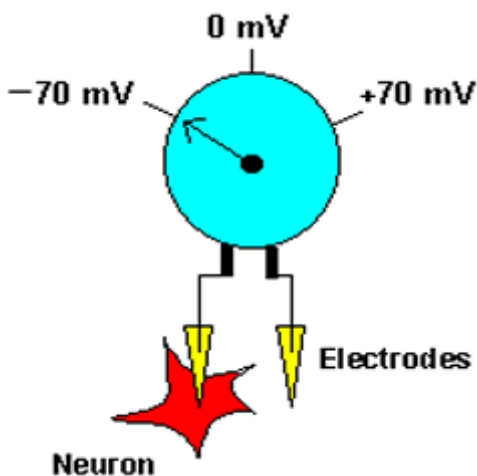
Neurophysiology Module 2

Membrane Potentials

- [Membrane Potentials](#)
- [Equilibrium Potentials](#)
- [Why is the Inside of a Neuron Negatively Charged?](#)
- [Membrane Potential is Dependent on Several Ions](#)
- [Assessment](#)

Ion Concentrations Across Membranes Generate Membrane Potentials

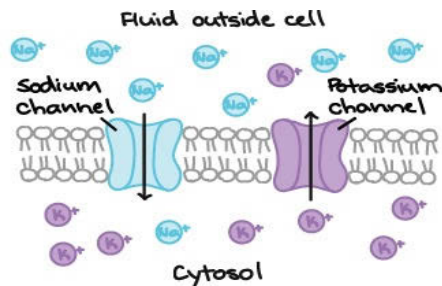
The lipid bilayer that forms the wall of a neuron (or glial cell) is not permeable to charged ions. However, there are a number of types of [ion channels](#) that allow ions to move down their concentration gradient across the membrane, and [ion transporters](#) that allow ions to move against their concentration gradient (from low concentration to high concentration). One of the best examples of an ion transporter is the [sodium-potassium pump](#) (also called Na⁺/K⁺ pump or Na⁺/K⁺ ATPase), which pumps potassium into a cell and sodium out of a cell, both against their concentration gradients, with the use of ATP to provide energy for the process. The actions of this pump sequester K⁺ inside of neurons and extrude Na⁺ from neurons (*in other words, the sodium potassium pump causes intracellular K⁺ to be high and intracellular Na⁺ to be low, relative to the extracellular fluid*).



The term [membrane potential](#) refers to the electrical potential difference across the membrane of a cell. To accurately measure the membrane potential, an investigator would need to place one electrode inside the cell and another outside, and compare the voltage on the two sides (*see figure to left*). The membrane potential is generated by the number of charged particles (positive and negative) on the two sides of the membrane. Most of these charged particles are ions, although some proteins inside cells are negatively charged, and contribute to producing the membrane potential.

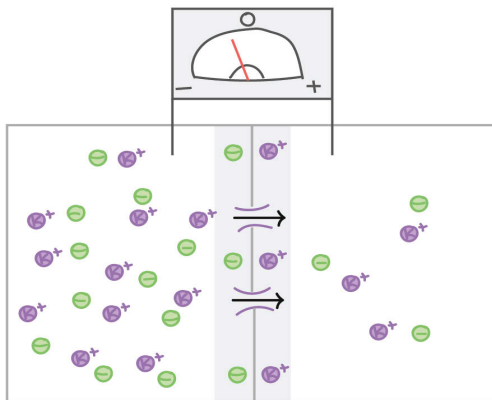
Virtually all cells have an interior that is negatively charged with respect to the outside.

Equilibrium Potentials



If ions were uncharged, then we would only need to worry about the concentration gradient to understand ion movements across a membrane. However, since ions are charged, they are attracted to ions with opposite electric charges (positive to negative, and vice versa), and repelled by ions of like charges. Positively charged ions are called **cations**, and negatively charged ions are called **anions**.

As an example, let's consider a membrane that is freely permeable to Na^+ and K^+ ions, but there are no other cations and no anions present. Since both ions have the same charge, then concentration gradient is the only factor that affects their movement.



Let's next consider a cell that has many K^+ ions inside and few outside (which is the normal case for neurons, due to the activity of the sodium-potassium pump), but the resting membrane potential is 0 due to the presence of negative ions balancing the positive ones.

If channels that allow K^+ to pass are opened, K^+ will move down its concentration gradient (from inside to outside the cell). As a result, there will be a loss of positive charge from the inside of the cell, so the inside will become negatively charged with respect to the outside.

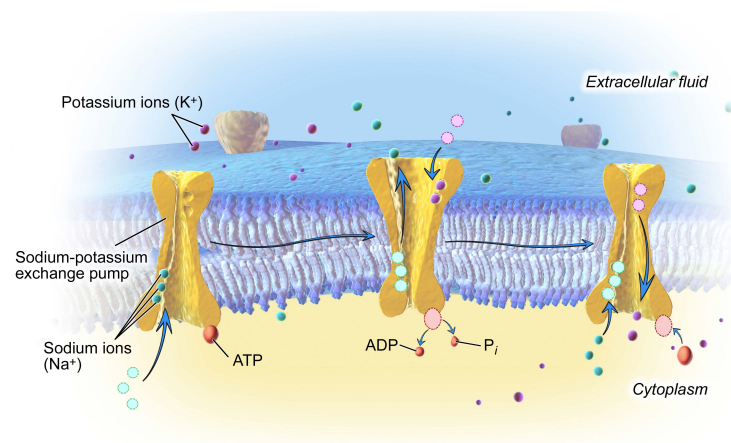
However, if an investigator placed an electrode outside of the cell and delivered a positive charge, the flow of K^+ from inside to outside the cell would be opposed, as the K^+ ions would be repelled by the positive charge that is being delivered. The charge that is needed to keep K^+ from diffusing from high concentration to low concentration when the K^+ channels open is called the **equilibrium potential**. The equilibrium potential is sometimes called a **reversal potential**, as it is the charge that is needed to prevent ions from moving down their concentration gradient.

As you might imagine, the exact charge that is needed to prevent the movement of ions down a concentration gradient can be calculated mathematically, with the use of the [Nernst equation](#). However, we will not use such mathematical approaches in this course.

One take-away from the Nernst equation is relevant to us: the charge that needs to be delivered to prevent the movement of ions is dependent on the difference in concentration of the ions across the membrane. If there is a large concentration difference, then a larger charge has to be delivered to oppose ionic movement than when the concentration gradient is small.

Let's apply these principles to the K^+ distribution across a membrane. With normal inside and outside concentrations of K^+ , a charge of -88 mV has to be present (inside relative to outside, or 88 mV more positive charge outside than inside) to keep K^+ from changing concentration across the membrane. This makes sense, as K^+ is a positive ion, and is attracted by a negative charge. If the charge inside the neuron (relative to the outside) was made extremely negative (let's say -100 mV), then K^+ would move against its concentration gradient and enter the cell.

I Don't Get it—Why is the Inside of a Neuron Negatively Charged?



From this discussion, it may be empirically difficult to visualize why the interior of a neuron is negatively charged. There are three reasons:

- The sodium-potassium pump removes three intracellular Na^+ ions for every two K^+ ions it lets in.
- Proteins that carry a negative charge are in high concentration inside a cell, and in low concentration outside.
- Neuronal membranes tend to be leakier for K^+ than for Na^+ . This causes a net loss of K^+ cations from the inside of the neuron, making it more negative. **This is the major factor.**

The Membrane Potential of Neurons is Dependent on Several Ions

Most neurons have channels that allow the passage of Na^+ , K^+ , and Cl^- . Thus, all of these ions contribute to the membrane potential of neurons.

As noted above, the [sodium-potassium pump](#) causes the intracellular K^+ levels and the extracellular Na^+ levels to be high, relative to the other side of the membrane. Since Na^+ is high outside the neuron, the concentration gradient favors the entry of Na^+ into the cell. The equilibrium potential for Na^+ is about 60 mV, as a positive internal charge would oppose the entry of Na^+ when Na^+ channels open (since cations are repelled by a positive charge).

The membrane potential for a resting neuron is between the equilibrium potentials for K^+ and Na^+ , usually about -70 mV. This is much closer to the equilibrium potential for K^+ than that of Na^+ . WHY? The main reason is that the resting neuronal membrane is leakier for K^+ than for Na^+ .

Why doesn't Cl^- contribute much to the resting membrane potential? The main reason is that most neurons don't actively transport Cl^- , so concentration gradients are the main factor that govern the movement of the ion. The equilibrium potential for Cl^- is also near the resting membrane potential of a neuron. Generally, Cl^- is higher outside the neuron than inside, as the negative intracellular potential repels the anion.

Assessment: Membrane Potentials

Please answer the questions below to assess how well you learned the material.

The resting membrane potential for a neuron: *

- is unrelated to the equilibrium potentials for particular ions
- Is closer to the equilibrium potential for sodium than the equilibrium potential for potassium
- Is between the equilibrium potentials for sodium and potassium
- Is mainly dependent on the presence of negatively charged proteins inside the cell

The resting membrane potential for a neuron: *

- Is mainly due to the leakiness of a membrane for potassium
- Is dependent only on the movement of sodium across the membrane
- Is near -85mV
- Is unrelated to the actions of the sodium-potassium pump

Changing the extracellular concentration of which ion would have the strongest effect on resting membrane potential: *

- Chloride
- Sodium
- Potassium
- Calcium

The movement of a particular ion across a membrane: *

- Is related to the concentration gradient for the ion across the membrane
- Is related to the number of channels that allow movement of the ion
- Is related to resting membrane potential
- Is related to resting membrane potential, number of ion channels, and concentration gradient for the ion

Membrane Potential: Self Assessment Questions

The resting membrane potential for a neuron:

- Is closer to the equilibrium potential for sodium than the equilibrium potential for potassium
- is unrelated to the equilibrium potentials for particular ions
- **Is between the equilibrium potentials for sodium and potassium**
- Is mainly dependent on the presence of negatively charged proteins inside the cell

The resting membrane potential for a neuron:

- Is unrelated to the actions of the sodium-potassium pump
- Is dependent only on the movement of sodium across the membrane
- Is near -85mV
- **Is mainly due to the leakiness of a membrane for potassium**

Changing the extracellular concentration of which ion would have the strongest effect on resting membrane potential:

- Calcium
- Sodium
- Chloride
- **Potassium**

The movement of a particular ion across a membrane:

- Is related to the number of channels that allow movement of the ion
- **Is related to resting membrane potential, number of ion channels, and concentration gradient for the ion**
- Is related to the concentration gradient for the ion across the membrane
- Is related to resting membrane potential

Neurophysiology Module 3

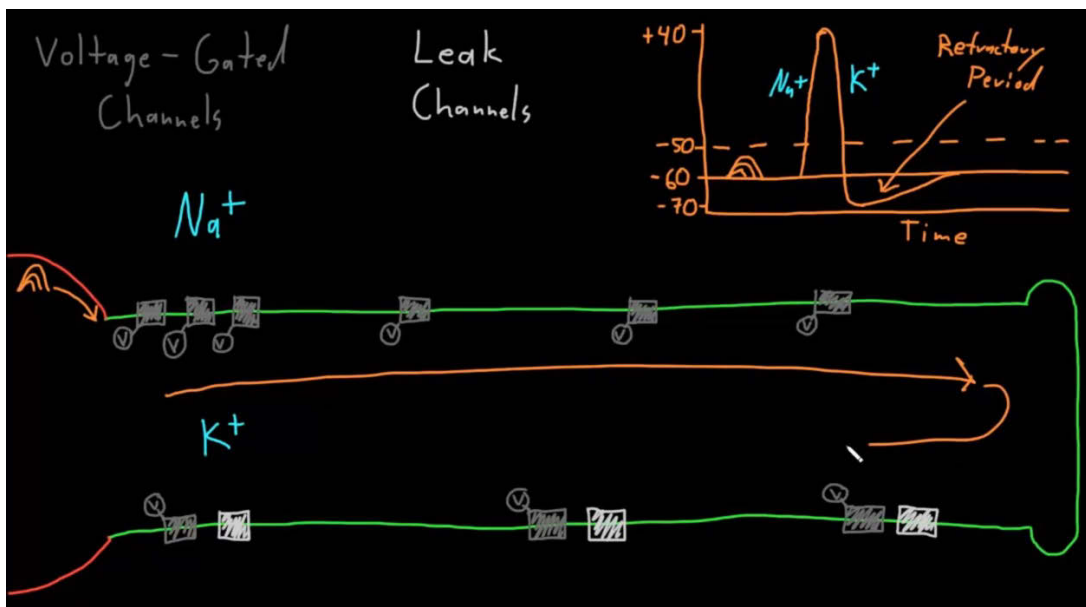
Action Potentials

- [Introduction](#)
- [Voltage Gated Channels](#)
- [Saltatory Conduction](#)
- [Unmyelinated Axons](#)
- [Some Neurons Are Weird](#)
- [Assessment](#)

Introduction

As an introduction, watch this movie from the KhanAcademy.

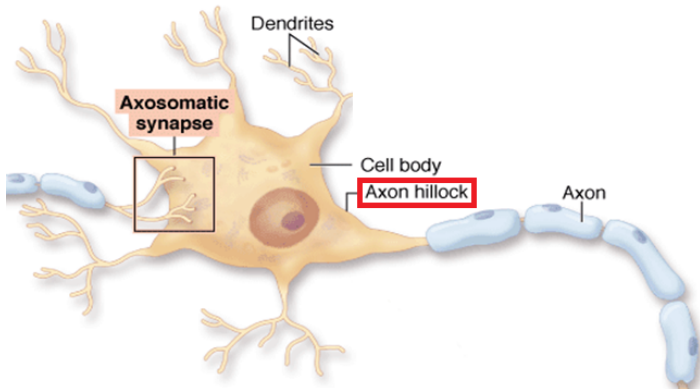
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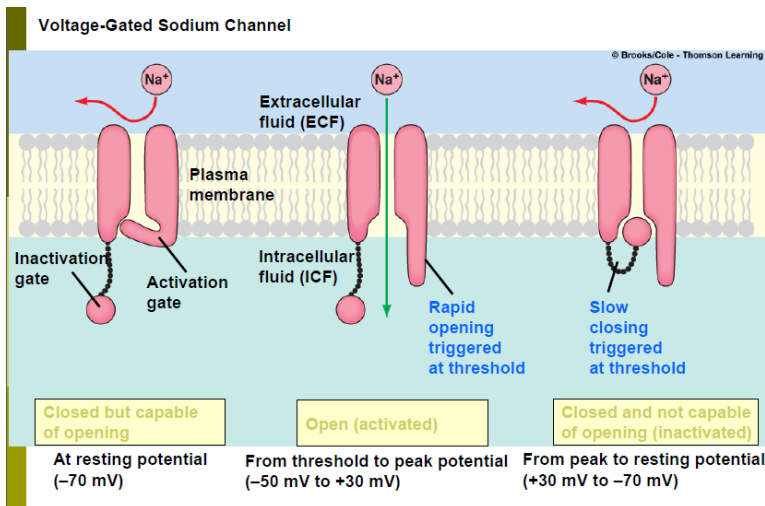
Opening of Voltage Gated Channels Produces Action Potentials

The subunits of *voltage-gated ion channels* change conformation in accordance with membrane potential. This can result in the opening of a pore that allows a specific ion to pass through the membrane.

Two types of voltage-gated channels play a role in producing action potentials: those that allow sodium to cross the membrane (voltage-gated *sodium channels*) and those that allow potassium to cross the membrane (*voltage-gated potassium channels*).

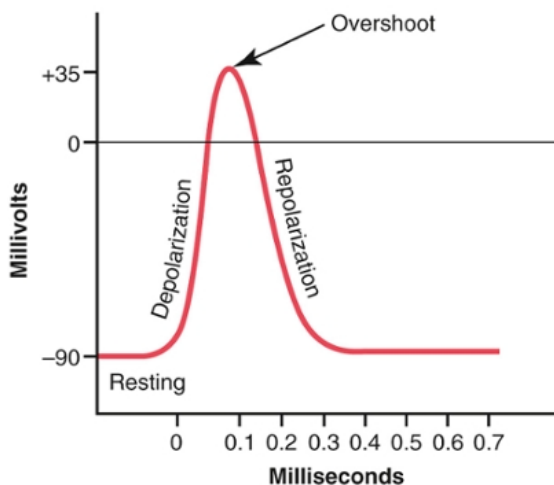


Voltage-gated channels are not usually present in the dendrites or the soma, but are concentrated in the initial segment of the axon (*axon hillock*). Both inhibitory and excitatory postsynaptic potentials are summed in the axon hillock. If the inside of the axon hillock is sufficiently depolarized (*becomes less negatively charged*), the Na^+ channels open and allow Na^+ to enter the neuron. Since Na^+ concentration is low inside the cell (due to the actions of the *sodium-potassium pump*) and the inside of the cell is negatively charged, Na^+ rushes from the outside to the inside of the cell.



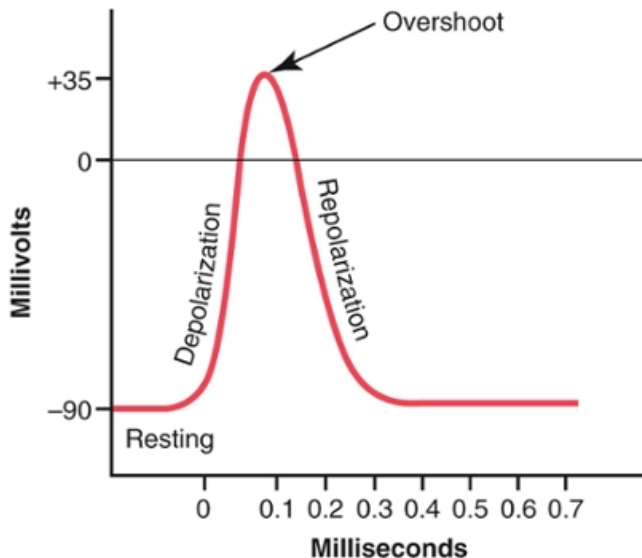
Voltage-gated Na^+ channels have two gates: an **activation gate** and an **inactivation gate**. The activation gate opens quickly when the membrane is depolarized, and allows Na^+ to enter. However, the same change in membrane potential also causes the inactivation gate to close. The closure of the inactivation gate is slower than the opening of the activation gate. As a result, the channel is open for a very brief time (*from the opening of the activation gate to the closure of the inactivation gate*).

Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to the original resting membrane potential level. Therefore, it is not possible for the sodium channels to open again without first repolarizing the nerve fiber.

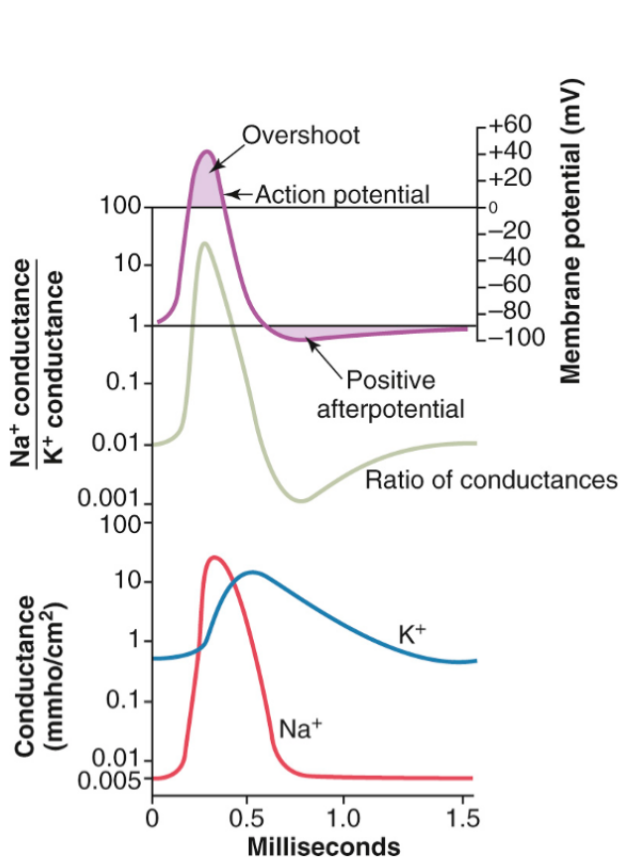


When the Na^+ channels are open at the axon hillock, the local membrane potential quickly becomes positive. It approaches the equilibrium potential for Na^+ , but does not reach it before the channels inactivate.

When the membrane at the axon hillock becomes depolarized, an opening of voltage-gated K^+ channels also occurs. Since K^+ is in high concentration inside the neuron,



K^+ diffuses outward through the channel. However, because of a delay in opening the K^+ channels, they open at about the same time that the Na^+ channels are closing because of inactivation. Thus, the decrease in sodium entry to the cell and the simultaneous increase in potassium exit from the cell combine to speed the [repolarization](#) process, leading to recovery of the resting membrane potential.



This figure summarizes the events that occur during and after the action potential. The bottom of the figure shows the changes in membrane conductance for Na^+ and K^+ ions. During the resting state, the conductance for K^+ ions is 50–100 times greater than the conductance for Na^+ ions. This is due to leakage of K^+ ions through the leak channels. At the onset of the action potential, Na^+ sodium channels open and allow up to a 5000-fold increase in Na^+ conductance. The inactivation process then closes the Na^+ channels. The onset of the action potential also triggers voltage gating of the K^+ channels, causing them to open at the time the Na^+ channels close. This produces a 30-fold increase in K^+ conductance. At the end of the action potential, the return of the membrane potential to the negative state causes the K^+ channels to close *slowly*.

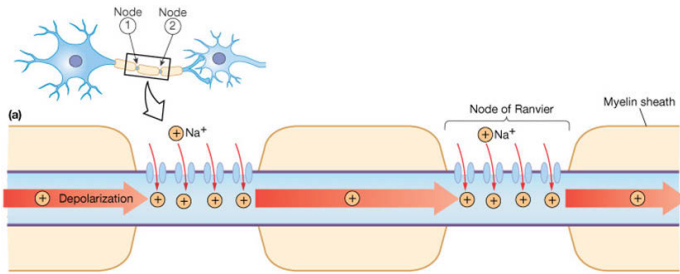
A common feature of action potentials is an [afterhyperpolarization](#). As noted in the [membrane potential module](#), the main factor that sets the resting membrane potential is the movement of K^+ ions through leak channels. When the voltage-gated K^+ channels are open, the conductance for K^+ is higher than during the resting state. As a result, the membrane potential approaches the equilibrium potential for K^+ (*is more negative than in the resting state*), resulting in the afterhyperpolarization. As soon as the voltage-gated K^+ channels close, the conductance for K^+ is reduced and the membrane potential returns to normal resting values.

Note that after the resting membrane potential is restored, a short period elapses before the inactivation gates of the voltage-gated Na^+ channels open. While the inactivation gate is closed, it is impossible for a new action potential to be elicited. This period is called the **absolute refractory period**.

As noted above, the voltage-gated K^+ channels close slowly after the membrane has been repolarized. Consequently, the K^+ conductance is higher (*and the neuronal membrane is more hyperpolarized*) at the end of the action than in the normal resting state. As a result, it is more difficult to generate the amount of

depolarization needed to open the activation gates. This period of higher K^+ conductance at the end of an action potential results in a **relative refractory period**, during which it is possible to elicit an action potential, although a strong excitation is needed to do so.

Saltatory Conduction in Myelinated Axons



Many neurons have **myelin** surrounding the axon. Myelin is a fatty white substance deposited by glial cells that insulates the axon, decreasing the leak of current through the axonal membrane. The voltage-gated channels described above are located between adjacent myelin sheaths. An unmyelinated area of membrane at the gaps between myelin sheaths, which contains voltage-gated channels, is called a **node of Ranvier**.

Myelination allows a bolus of sodium that enters through voltage-gated Na^+ channels to move quickly down the axon without leaking out very much. Another action potential occurs at the next node of Ranvier down the axon, refreshing the process. As such, the action potential appears to "leap" between the nodes of Ranvier, in a process called **saltatory conduction**.

Saltatory conduction allows electrical nerve signals to be propagated long distances at high rates without any degradation of the signal. In addition, the process is energy-efficient, as perturbations in the normal compartmentalization of Na^+ and K^+ only occur at the nodes of Ranvier. Bear in mind that after an action potential, the sodium-potassium pump has to restore the normal ionic balance across the membrane. Minimizing the need to do this reduces ATP expenditure.

Now you should be able to understand that the refractory period for axons described in the section above has a very practical physiological purpose: it assures that action potentials move in one direction down the axon. When an action potential is generated at one node of Ranvier, the previous node is still in a refractory period. Although sodium ions entering at a node diffuse in both directions down the axon, the previously-activated node cannot generate an action potential. This is key in assuring that an excitatory input to a neuron does not result in a reverberating series of action potentials.

Unmyelinated Axons Conduct Action Potentials Slowly

In contrast to myelinated axons, unmyelinated neurons must "refresh" the action potential in every successive patch of membrane. Thus, a repeated entry of Na^+ ions and efflux of K^+ ions occurs down the axon. The ionic redistribution is restored to the resting state by the sodium-potassium pump, but this requires a large amount of energy.

This may be the reason why unmyelinated axons have a small diameter. If an unmyelinated axon was of large diameter, the surface area would be large and many voltage-gated channels would be needed on the surface. When an action potential occurred, the movement of ions would be large, and a tremendous amount of ATP would be needed to fuel the activity of the sodium-potassium pump to restore ionic balance.

Two major factors govern how quickly an action potential moves down an axon:

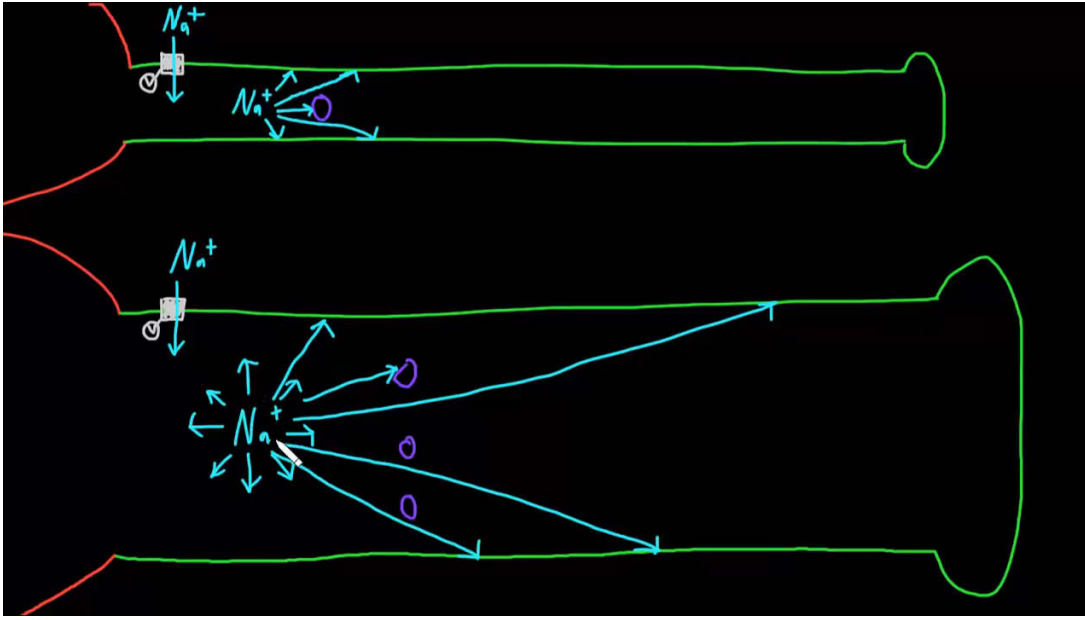
- its diameter
- how heavily myelinated it is

In general, the largest axons are also the most heavily myelinated, and propagate action potentials very rapidly. The smallest axons are unmyelinated and propagate action potentials slowly.

How do the amount of myelination and the diameter of an axon determine its conduction velocity?

Let's turn to the KhanAcademy for an explanation.

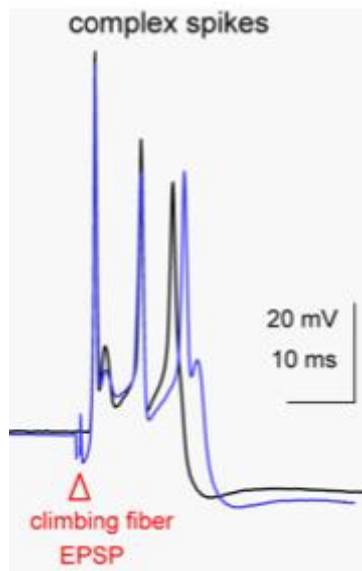
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Some Neurons Are Weird

Although the action potentials of most neurons resemble those described above, some neurons have action potentials with different properties.

As an example, cerebellar [Purkinje cells](#) produce complex spikes, which are very broad and complicated action potentials.



As shown to the left, the complex spike has a duration of almost 10 msec. A complex spike is characterized by an initial prolonged large-amplitude spike, followed by a high-frequency burst of smaller-amplitude action potentials. The duration of complex spikes is due to the presence of [P-type voltage-gated calcium channels](#), whose opening contributes to the generation of the action potential.

In general, [voltage-gated calcium channels](#) open and close slowly, resulting in a prolonged movement of ions. This generates a long-duration action potential.

Assessment: Action Potentials

Please answer the questions below to assess how well you learned the material.

During a demyelinating disease such as multiple sclerosis: *

- The conduction velocity of most axons increases
- Propagation of action potentials down an axon can fail
- Action potential propagation becomes more saltatory
- None of the above

Prior to the initiation of an action potential at the axon hillock: *

- The conductance of K^+ is higher than the conductance of Na^+
- The conductance of Na^+ is higher than the conductance of K^+
- There is no conductance of either Na^+ or K^+
- The inactivation gates of voltage-gated Na^+ channels are always closed

When is the conductance of K^+ in an axonal membrane highest? *

- Near the end of the afterhyperpolarization
- During the resting membrane potential
- During the depolarization phase of an action potential
- During the repolarization phase of the action potential

An unmyelinated axon: *

- Is typically larger in diameter than a myelinated axon:
- Typically has higher conduction velocities of action potentials than myelinated axons
- Is LESS energy efficient than myelinated axons
- Is capable of saltatory conduction of action potentials

Action Potential: Self Assessment Questions

During a demyelinating disease such as multiple sclerosis:

- The conduction velocity of most axons increases
- Action potential propagation becomes more saltatory
- **Propagation of action potentials down an axon can fail**
- None of the above

Prior to the initiation of an action potential at the axon hillock:

- The conductance of Na^+ is higher than the conductance of K^+
- The inactivation gates of voltage-gated Na^+ channels are always closed
- There is no conductance of either Na^+ or K^+
- **The conductance of K^+ is higher than the conductance of Na^+**

When is the conductance of K^+ in an axonal membrane highest?

- During the depolarization phase of an action potential
- Near the end of the afterhyperpolarization
- During the resting membrane potential
- **During the repolarization phase of the action potential**

An unmyelinated axon:

- Is typically larger in diameter than a myelinated axon:
- **Is LESS energy efficient than myelinated axons**
- Is capable of saltatory conduction of action potentials
- Typically has higher conduction velocities of action potentials than myelinated axons

Neurophysiology Module 4

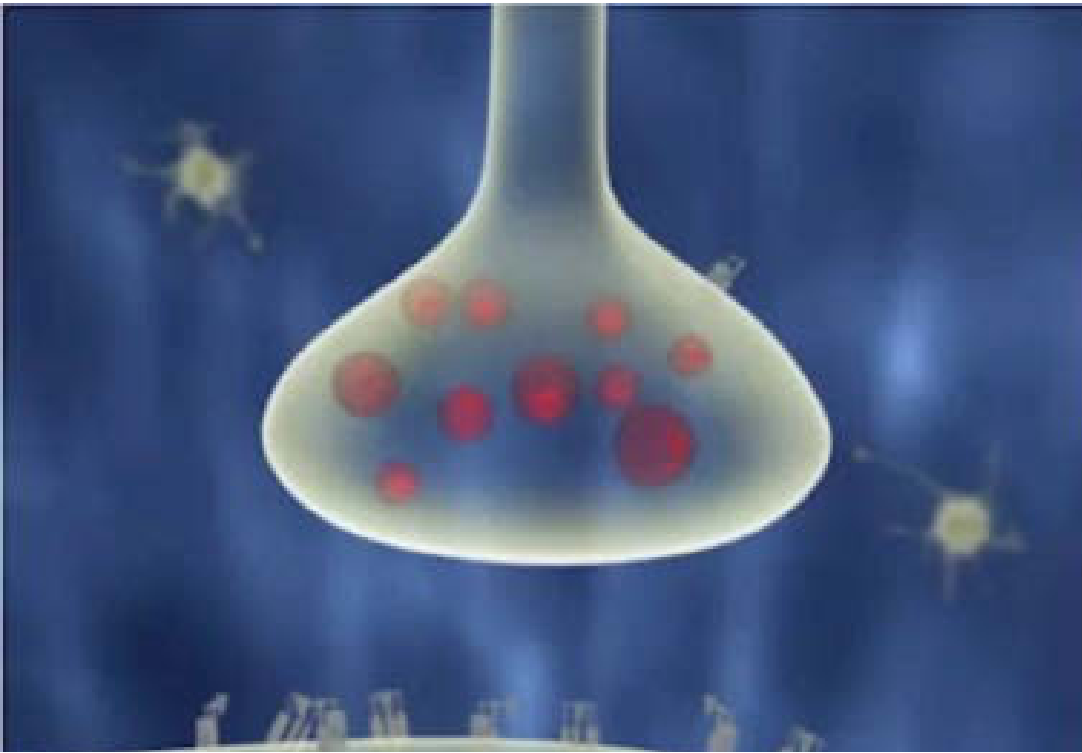
Synaptic Transmission

- [Introduction](#)
- [Release of Neurotransmitter from a Nerve Terminal](#)
- [Postsynaptic Actions of Neurotransmitters](#)
- [Excitatory and Inhibitory Neurotransmitters](#)
- [Postsynaptic Potentials](#)
- [Some Synapses Are Different](#)
- [Categories of Neurotransmitters](#)
- [Assessment](#)

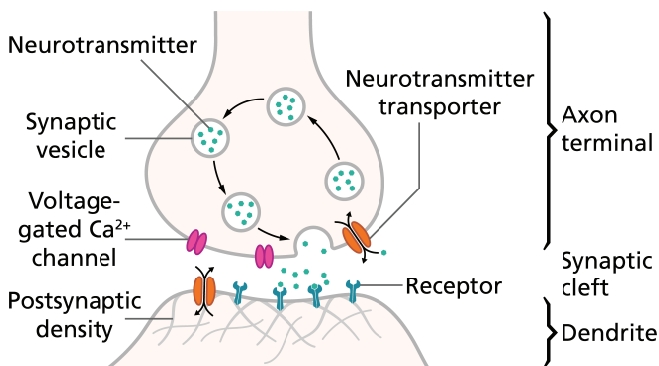
Introduction

As an introduction, watch this movie.

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Release of Neurotransmitter from a Nerve Terminal



Neurotransmitters are chemicals that transmit signals from one neuron to the next. Neurotransmitters are packaged into vesicles located in the nerve terminal. When an action potential depolarizes the nerve terminal, voltage-gated Ca^{2+} channels are opened, allowing Ca^{2+} to enter the terminal. When the calcium ions enter the presynaptic terminal, they bind with special protein molecules on the inside surface of the presynaptic membrane, called **release sites**. This binding in turn causes the release sites to open, allowing a few transmitter vesicles to release their transmitter into the synaptic cleft (*space between a nerve terminal and the dendrites or soma of another neuron*). The released neurotransmitter binds to receptors on the dendrite or soma of the postsynaptic neuron.

Let's make sure the terminology is clear:

- **Synapse**: a junction between two nerve cells, where information is transmitted chemically across a small gap (or synaptic cleft)
- **Presynaptic neuron**: the neuron that releases neurotransmitter at a synapse
- **Postsynaptic neuron**: the neuron with receptors for the released neurotransmitter

The nature of information processing by the nervous system requires that neuronal signaling occur over a very short temporal period. When an action potential reaches the nerve terminal, the neurotransmitter that is released

must have only a transient effect on the postsynaptic neuron. This is accomplished by removing the neurotransmitter from the synaptic cleft soon after it is released. There are two main mechanisms through which this is completed:

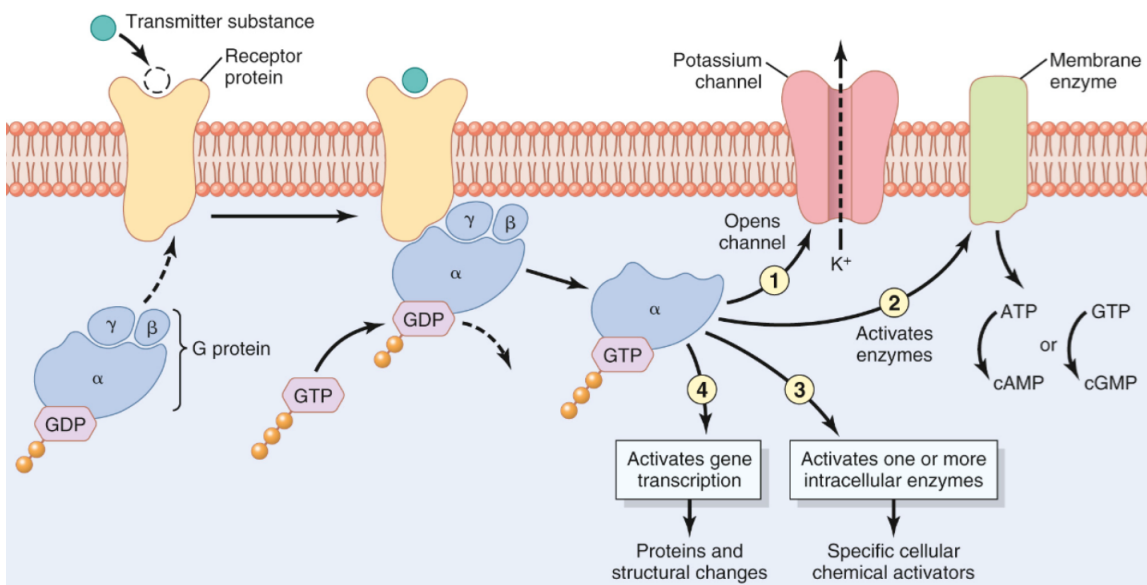
- Chemically degrading the neurotransmitter with an enzyme
- Reuptaking it into the presynaptic neuron

Postsynaptic Actions of Neurotransmitters

Neurotransmitters have one of two general effects when they bind to postsynaptic receptors:

- They directly cause the opening of an ion channel
- They activate a [second messenger system](#)

There are several types of [second messenger systems](#). One of the most common types entails the activation of [G proteins](#). In the example below, the inactive G protein complex in the cytosol consists of guanosine diphosphate (GDP) plus three components: an alpha (α) component that is the activator portion of the G protein, and beta (β) and gamma (γ) components that are attached to the alpha component. As long as the G protein complex is bound to GDP, it remains inactive. When the receptor is activated by a neurotransmitter, the receptor undergoes a conformational change, exposing a binding site for the G protein complex, which then binds to the receptor. This causes the α subunit to release GDP and simultaneously bind guanosine triphosphate (GTP) while separating from the β and γ portions of the complex. The separated α -GTP complex is then free to move within the cytoplasm and have a number of potential effects.



Although a particular second messenger system can cause different effects in different neurons, one or more of the following effects are induced (as indicated in the diagram above):

1. Specific ion channels are opened
2. [cAMP](#) or [cGMP](#) are activated, resulting in the activation or deactivation of enzymes
3. One or more enzymes are directly activated
4. Gene transcription is altered

Excitatory and Inhibitory Neurotransmitters

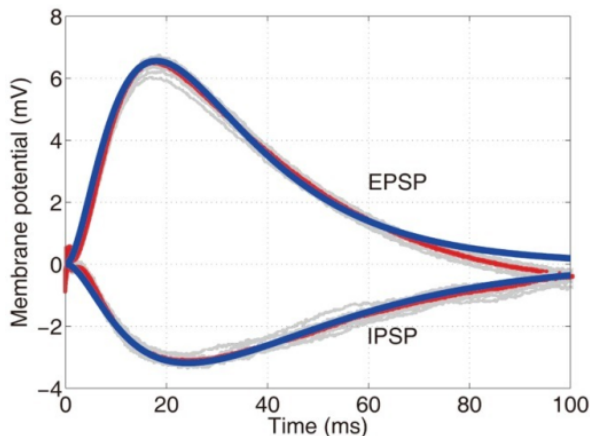
Although neurotransmitters can elicit a number of complex changes in the postsynaptic neuron, often these effects are categorized as excitatory or inhibitory. After all, the key aspect of neuronal signaling is the generation of action potentials, so it is logical to divide neurotransmitter effects into those that:

- increase the probability that an action potential will be produced at the axon hillock (***excitatory neurotransmitters***)
- decrease the probability that an action potential will be produced at the axon hillock (***inhibitory neurotransmitters***)

For example, an excitatory neurotransmitter could open a ligand-gated Na⁺ channel and cause depolarization of the neuron, decrease conductance through K⁺ channels, or induce the synthesis of additional ligand-gated Na⁺ channels. An inhibitory neurotransmitter could open Cl⁻ channels and cause hyperpolarization of the neuron, increase conductance through K⁺ channels, or induce the synthesis of additional K⁺ leak channels.

Postsynaptic Potentials

Although neurotransmitters can elicit complex postsynaptic effects, often they cause sudden changes in ionic movements across the membrane. These ionic movements produce the ***postsynaptic potentials*** that are added at the axon hillock; if the addition amounts to a sufficient depolarization, an action potential will occur.

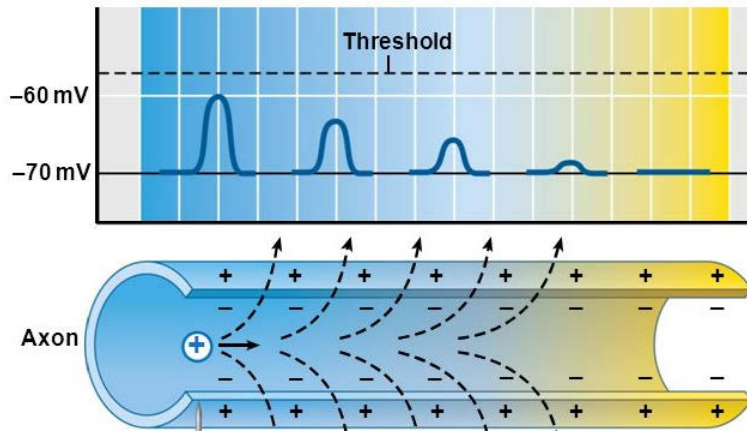


Excitatory postsynaptic potentials (EPSPs) occur when positive ions enter the neuron or negative ions leave. In most cases, the EPSP is a result of opening of cation channels that allow both Na⁺ and K⁺ to pass across the membrane. However, the conductance for Na⁺ usually predominates, such that a depolarization occurs in the neuron.

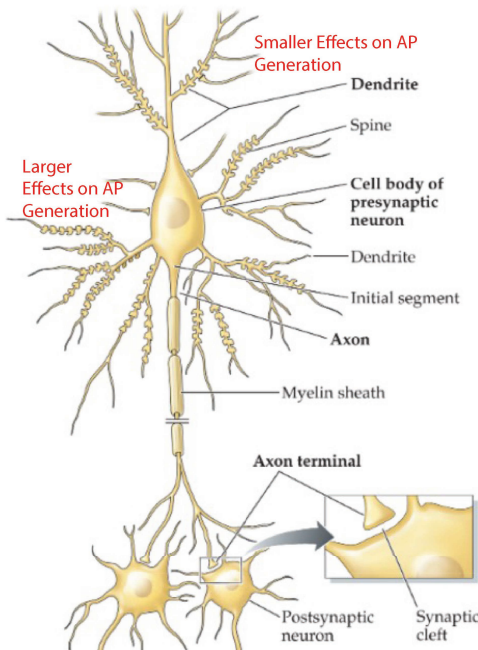
Inhibitory postsynaptic potentials (IPSPs) occur when negative ions (such as Cl⁻) enter the neuron or positive ions leave.

As an EPSP or IPSP propagates passively down a dendrite, it is altered by the physical properties of the neuronal membrane. This distorts the shape of an EPSP or an IPSP, so that if the electrical potential was recorded at a distance from the synapse where the potential was generated, it would look quite different than near the synapse. By use of ***cable theory***, the change in the properties of an EPSP or IPSP as it moves down a membrane can be modeled mathematically. However, this is certainly beyond the scope of this course.

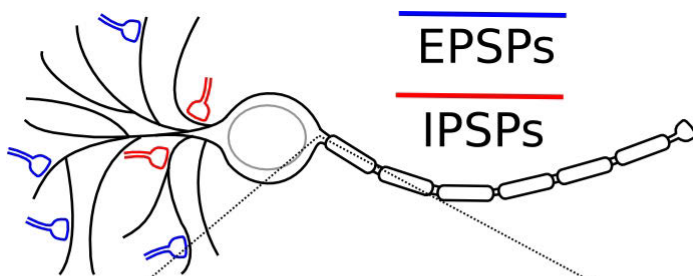
WHAT DO I NEED TO KNOW?



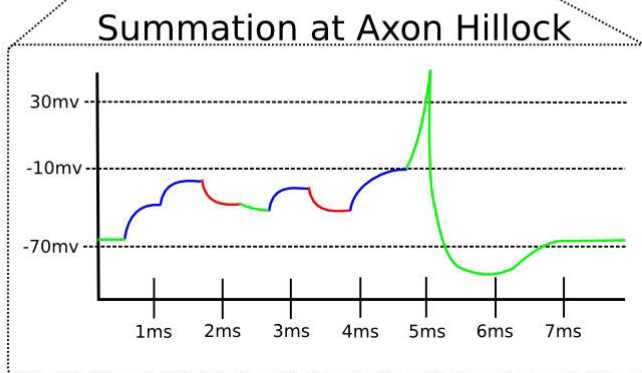
First, you should be aware that due to the membrane properties of a neuron, the amplitude of an EPSP or IPSP decreases as the potential propagates down the membrane, and the potential becomes more prolonged. Thus, if an EPSP is generated by Na⁺ ions entering a distal dendrite, then the depolarization (change in voltage) will be tiny by the time it reaches the axon hillock.



In other words, ions entering (or leaving) at a synapse on a distal dendrite will have little impact on the change in membrane potential at the axon hillock, and thus won't play very much of a role in determining whether the neuron will produce an action potential. In contrast, ions entering or leaving a neuron at a synapse on the soma will have a much bigger effect on the membrane potential at the axon hillock, and will play an appreciable role in determining whether the neuron produces an action potential.

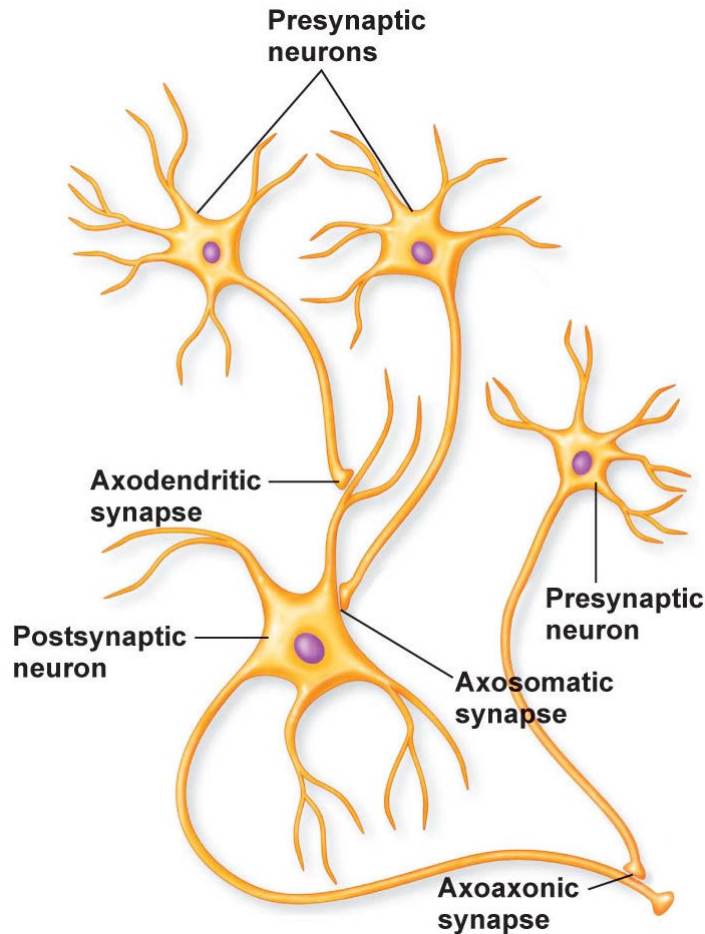


The axon hillock is constantly "summing" the thousands of EPSPs and IPSPs that are generated in the dendrites and soma. If this summation amounts to a depolarization of sufficient magnitude, the activation gates of the voltage-gated Na⁺ channels will open, an action potential will occur, and the neuron will release neurotransmitter onto the neurons it synapses upon. When the depolarization at the axon hillock is smaller than the threshold required to open the activation gates of the voltage-gated Na⁺ channels, the neuron will not communicate with other neurons down the line. Whether or not a neuron communicates with other neurons all comes down to the membrane potential at the axon hillock at a particular time.



Some Synapses Are Different

Most synapses are axo-dendritic (*i.e.*, the synapse is on a dendrite) or axo-somatic (*i.e.*, the synapse is on the neuronal soma), as described above. However, other synaptic configurations also exist. One such configuration is the axo-axonic synapse, where an axon of one neuron synapses on the axon of another neuron.



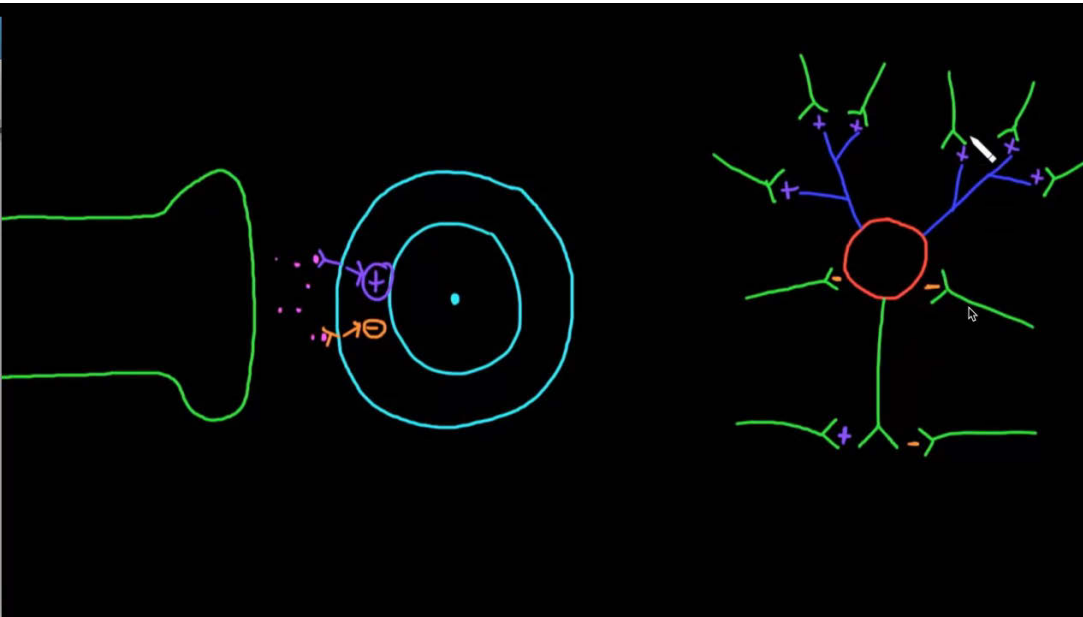
What is the function of an axoaxonic synapse? One common role of such synapses is producing **presynaptic inhibition**. The axoaxonic synapse can activate a second messenger system that affects the voltage-gated Ca^{2+} channels at the nerve terminal, so they allow less Ca^{2+} to enter the nerve terminal after an action potential occurs. As a result, the neuron releases less neurotransmitter following an action potential. Axoaxonic synapses thus provide a mechanism to regulate how much a neuron communicates to other neurons. Afferent fibers entering the spinal cord are subject to presynaptic inhibition via axoaxonic synapses.

A similar phenomenon is **presynaptic facilitation**. Second messenger systems triggered through axoaxonic synapses can cause more calcium to enter the nerve terminal when an action potential occurs, so a neuron releases more neurotransmitter. It is believed that presynaptic facilitation plays a key role in learning and memory.

Although we normally think of neurotransmitters binding to postsynaptic receptors, some nerve terminals have **autoreceptors** for the neurotransmitter they release. Often these autoreceptors play a homeostatic role, and serve to adjust the amount of neurotransmitter released subsequently. In other words, autoreceptors serve to assure that a nerve terminal is not releasing too much, or too little, neurotransmitter.

Lets review these concepts by watching a movie from the KhanAcademy.

If the movie does not play in this window, or you would like to see it in a window of alternate size, download it from [this link](#).



Categories of Neurotransmitters

The most common neurotransmitters are amino acids, particularly [glutamate](#), [GABA](#) (*gamma-aminobutyric acid*), and glycine. The actions of these amino acids will be discussed in subsequent modules. Glutamate is an excitatory neurotransmitter, and is released by most sensory afferents as well as neurons in the central nervous system. GABA and glycine are inhibitory neurotransmitters; glycine is mainly released from spinal cord neurons, whereas GABA is released from neurons in many brain areas. In fact, GABA is the most common inhibitory neurotransmitter present in the central nervous system.

Another very common neurotransmitter is [acetylcholine](#). Acetylcholine is released by neurons in many brain regions, as well as by motoneurons, sympathetic and parasympathetic preganglionic neurons, and parasympathetic postganglionic neurons. Acetylcholine is mainly an excitatory neurotransmitter, although there are some examples where it has an inhibitory role (*e.g., parasympathetic postganglionic nerve fibers that lower heart rate*).

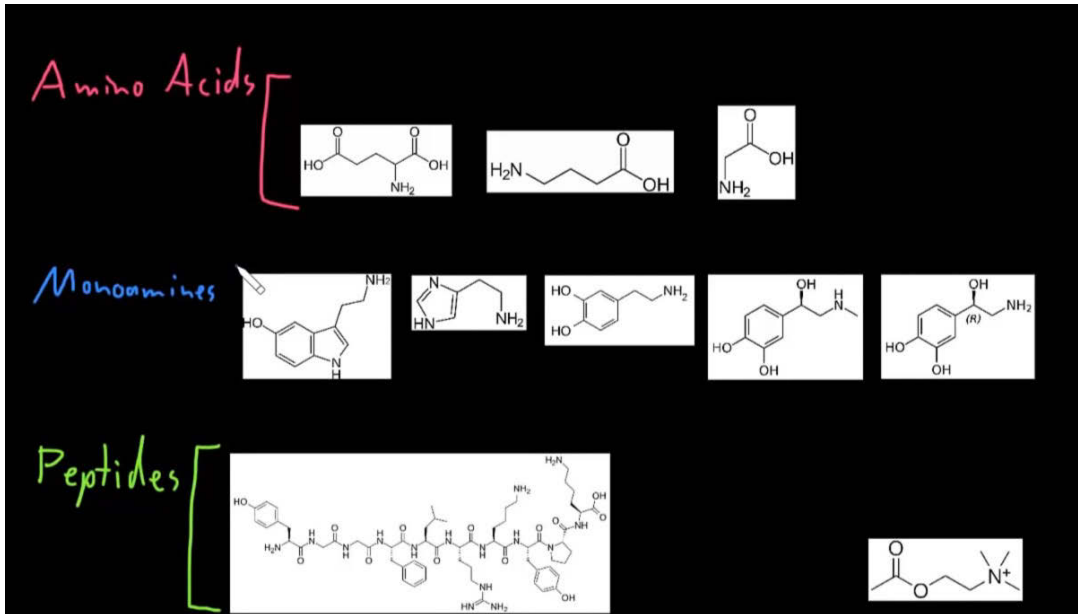
Another group of important neurotransmitters are the [monoamines](#), chemicals that contain one amino group that is connected to an aromatic ring by a two-carbon chain (-CH₂-CH₂-). The monoamine neurotransmitters include [dopamine](#), [norepinephrine](#), and [serotonin](#). Monoamine neurotransmitters typically bind to [G-protein coupled receptors](#), such that they can produce a wide variety of effects in the postsynaptic neuron. Many neurons that release monoamine neurotransmitters branch extensively, such that each neuron makes synapses on a large number of postsynaptic neurons. Many neurological and psychiatric diseases are related to the monoamine neurotransmitters.

[Nitric oxide](#) (NO) is released by nerve terminals in areas of the brain responsible for long-term behavior and memory. NO is different from other small-molecule transmitters, as it is very lipophilic and cannot be stored in the nerve terminal. Instead, it is synthesized as needed and then diffuses out of the presynaptic terminals to affect adjacent neurons. NO usually does not alter the membrane potential, but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes, or perhaps even longer. NO is also an important signaling molecule in the cardiovascular system, as you learned in the Cardiology Course.

A variety of [peptides](#) called neuropeptides can also act as neurotransmitters, but they usually have very specialized functions. For example, some hypothalamic neurons release peptides that control the release of hormones from the anterior pituitary. In some cases, a peptide hormone is co-released with one of the "classical" neurotransmitters discussed above.

Lets review these concepts by watching a movie from the KhanAcademy.

If the movie does not play in this window, or you would like to see it in a window of alternate size, download it from [this link](#).



Assessment: Synaptic Transmission

Please answer the questions below to assess how well you learned the material.

Receptors for a neurotransmitter: *

- Always activate a G protein after the ligand binds
- Always open an ion channel after the ligand binds
- Can be found on the nerve terminal that releases the neurotransmitter
- Are found on the soma and dendrites of a neuron, but never the axon

Inhibitory neurotransmitters: *

- Are usually monoamines, but never amino acids
- Are released in the spinal cord by sensory afferent fibers
- Sometimes cause the opening of Cl⁻ channels after binding to a postsynaptic receptor
- Typically trigger the opening of a Na⁺ channel in the postsynaptic neuron

EPSPs: *

- Result from the entry of Cl⁻ into a neuron
- Are always the same amplitude
- Change in amplitude as they propagate down a neuronal membrane
- Are present in dendrites, but never in the soma

Glutamate: *

- Causes the opening of Cl⁻ channels after binding to a postsynaptic receptor
- Is categorized as a monoamine
- Is released from the axons of motoneurons at the neuromuscular junction
- Increases the likelihood of an action potential after binding to a postsynaptic receptor

Synaptic Transmission: Self Assessment Questions

Receptors for a neurotransmitter:

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- Is released from the axons of motoneurons at the neuromuscular junction
- Causes the opening of Cl⁻ channels after binding to a postsynaptic receptor

Neurophysiology Module 5

Glutamate Receptors

- [Introduction](#)
- [Ionotropic Glutamate Receptors](#)
- [Long-Term Potentiation \(LTP\)](#)
- [Metabotropic Glutamate Receptors](#)
- [Excitotoxicity](#)
- [Clinical Neuropharmacology of Glutamate Transmission](#)
- [Assessment](#)

Introduction

As noted in the [synaptic transmission module](#), glutamate is an excitatory amino acid neurotransmitter. It is one of the most common signaling molecules used in synaptic transmission. This module discusses the types of receptors that the neurotransmitter glutamate binds to, and the effects that occur when such binding takes place.

Glutamate is released by normal synaptic mechanisms described in the [synaptic transmission module](#), and removed from the synaptic cleft by [glutamate transporters](#) on the presynaptic nerve terminal.

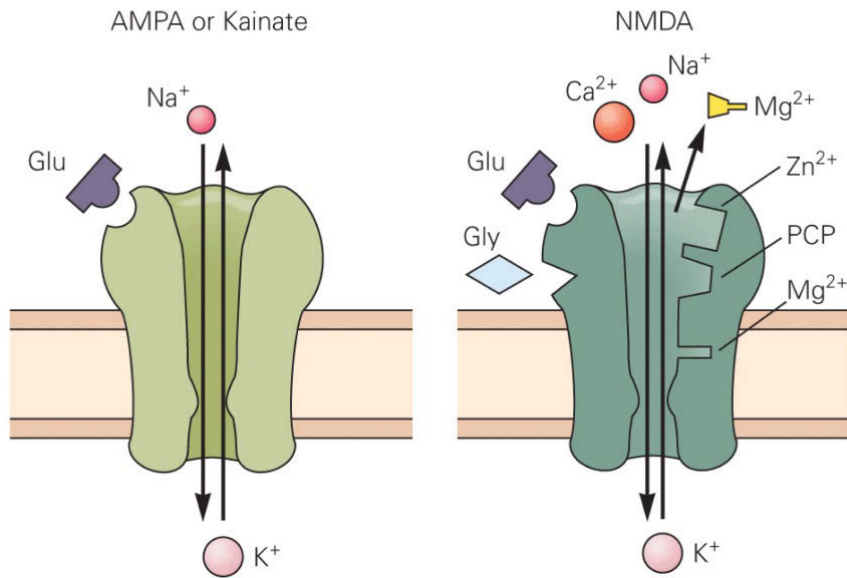
Ionotropic Glutamate Receptors

There are several subtypes of glutamate receptors. Receptors that bind a particular neurotransmitter such as glutamate are not all the same. In fact, binding of a neurotransmitter to one type of glutamate receptor can have vastly different effects than at another.

Typically, receptors with differing responses to the binding of a particular neurotransmitter also have different configurations, and affinities for that neurotransmitter. It thus may be possible for a particular drug to bind to one neurotransmitter receptor “subtype” and not another. This is how neurotransmitter subtypes are differentiated. Often a receptor subtype is named for a particular drug that binds selectively to it, but not other receptor subtypes for the same neurotransmitter.

Most glutamate receptors are ligand-gated ion channels, which are also called [ionotropic receptors](#). However, a few are [metabotropic receptors](#), meaning that binding of glutamate to the receptor activates a second messenger system.

A Ionotropic glutamate receptor

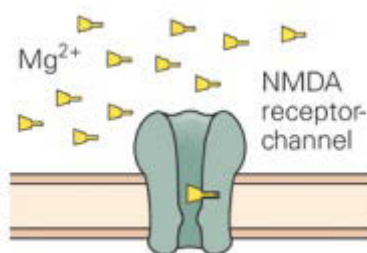


There are three subtypes of ionotropic glutamate receptors:

- The [AMPA](#) (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor
- The [kainate](#) receptor
- The [NMDA](#) (N-methyl-D-aspartate) receptor

The NMDA receptor is selectively blocked by the drug [APV](#) (2-amino-5-phosphonovaleric acid), whereas the AMPA and kainate receptors are both blocked by the drug [CNQX](#) (6-cyano-7-nitroquinoxaline-2,3-dione). Consequently, the AMPA and kainate receptor subtypes are sometimes collectively referred to as "non-NMDA" receptors.

When glutamate binds to either an AMPA or kainate receptor, a cation channel opens that allows both K⁺ to leave and Na⁺ to enter the cell. However, the driving force for Na⁺ to enter the cell predominates, as Na⁺ is attracted by the negative charge inside the cell, and is also moving down its concentration gradient. As a result, an [EPSP](#) occurs inside the neuron.



The NMDA receptor is unique among ligand-gated channels because its opening depends on both the presence of the [agonist](#) (activating ligand) and membrane voltage. At typical resting membrane potentials, the channel of the NMDA receptor is blocked by Mg²⁺ ions. However, when the membrane is depolarized (such as after glutamate binds to a nearby AMPA receptor), then binding of glutamate to the NMDA receptor can open it. This is because the positive membrane charge forces Mg²⁺ out of the channel through [electrostatic repulsion](#).

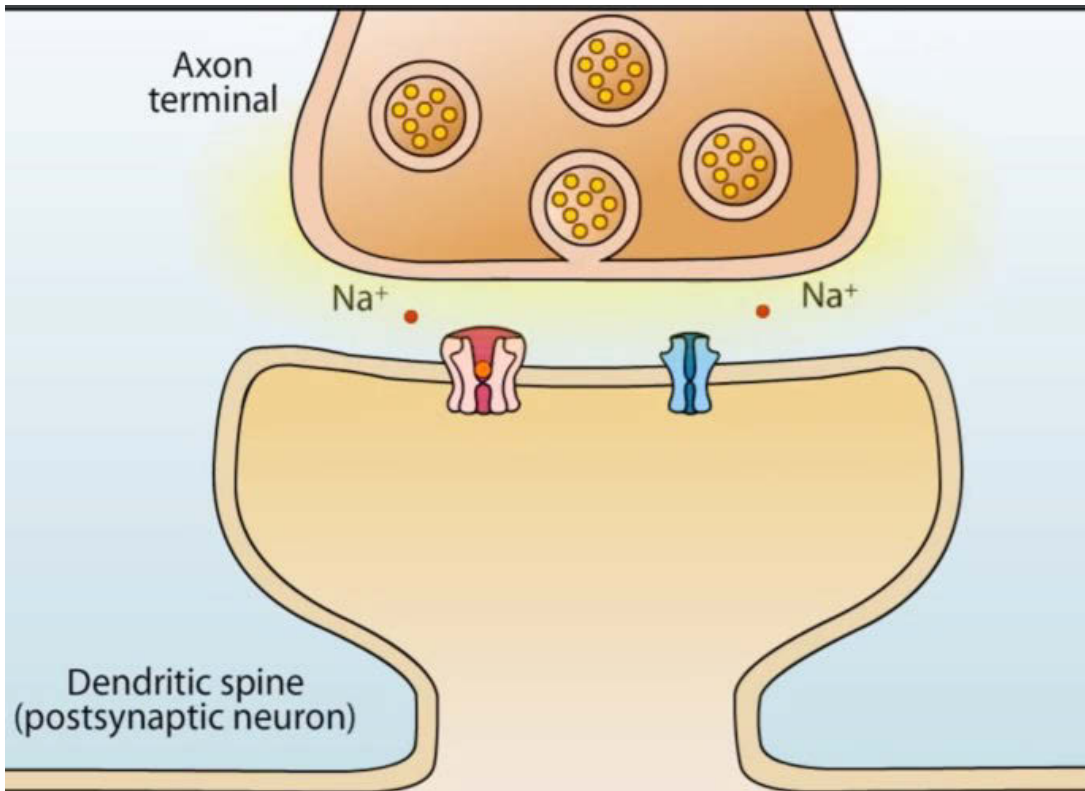
When the NMDA receptor channel is opened (by the combined binding of glutamate to the receptor and depolarization of the membrane), both Na⁺ and Ca²⁺ enter the neuron. The entering Ca²⁺ can activate various calcium-dependent signaling cascades, including [calcium-calmodulin-dependent protein kinases](#).

The NMDA receptor is also unusual in that it has a binding site for a "co-agonist," glycine. Both glycine and glutamate (and membrane depolarization) must be present for the NMDA receptor channel to open. However, glutamate is the actively controlled agonist for the receptor; glycine may simply be present in activating quantities in the synaptic cleft.

What about kainate receptors? Kainate receptors act much the same as AMPA receptors, but are less common in the brain. No specific function has been assigned to this subtype of glutamate receptors, although they certainly contribute to excitatory neurotransmission in the brain by generating EPSPs in postsynaptic neuron

Since this is complicated, let's review the material by watching a movie.

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Long-Term Potentiation (LTP)

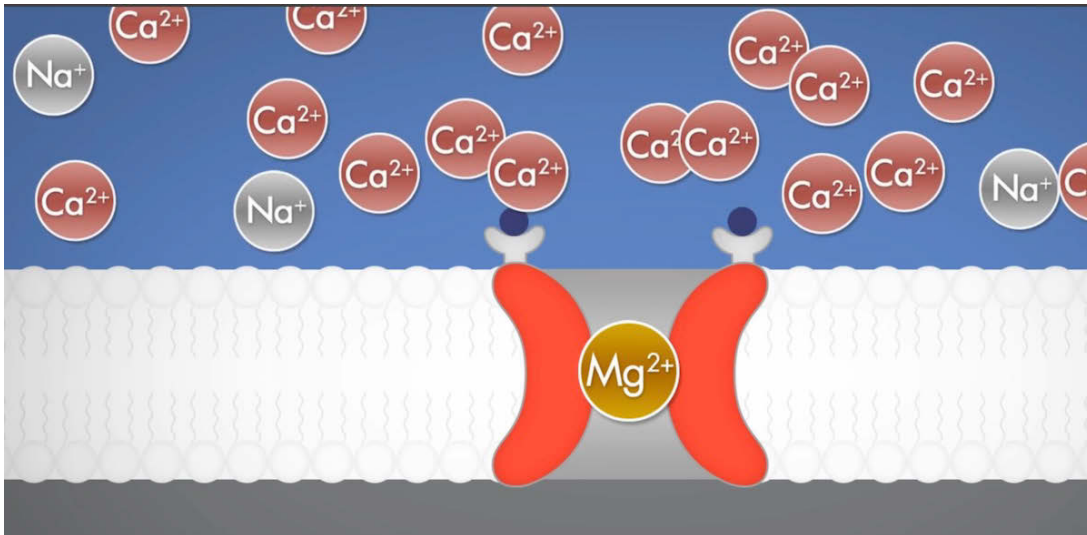
Long-term potentiation is persistent strengthening of synapses based on recent patterns of activity, and is believed to be an important component of learning and memory. NMDA receptors play a key role in generating long-term potentiation in many regions of the nervous system. As noted above, Ca²⁺ entering through an NMDA receptor can trigger an enzymatic cascade that phosphorylates AMPA receptors (increasing the probability they will open) or causes more AMPA receptors to be translocated to the neuronal membrane. As a result, subsequent releases of glutamate from the presynaptic neuron will cause larger EPSPs in the postsynaptic neuron, increasing the probability that it will generate an action potential. Often AMPA and NMDA receptors are located on the same **dendritic spine**, and synaptic strengthening through long-term potentiation can be localized to a particular spine or a collection of adjacently-positioned spines.

An opposite phenomenon is **long-term depression**, which is also often mediated via NMDA receptors. During long-term depression, AMPA receptors are dephosphorylated and fewer AMPA receptors are translocated to the neuronal surface. One function of long-term depression may be to clear old memories. Whether or not activation of an NMDA receptor induces long-term depression or potentiation may rest on the frequency of synaptic inputs, and consequently how much Ca²⁺ enters through the NMDA receptor channel. If synaptic inputs are frequent

and intracellular Ca^{2+} is high, then long-term potentiation occurs. If synaptic inputs are infrequent and intracellular Ca^{2+} is low, long-term depression will occur.

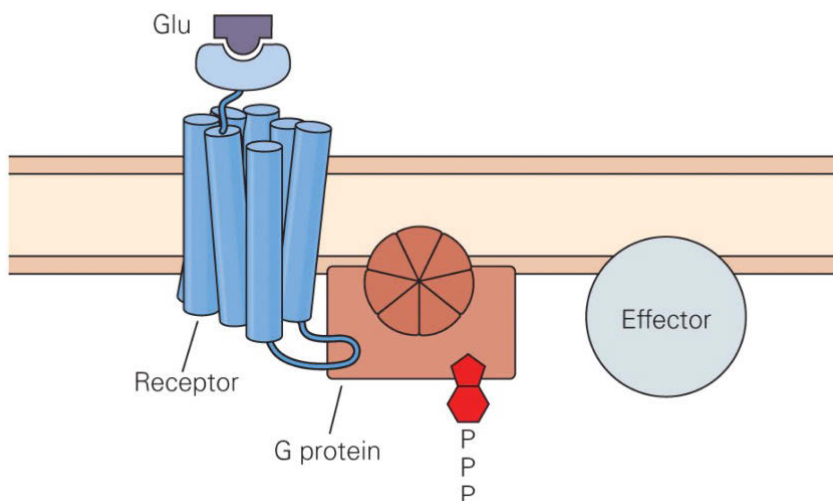
Let's review this important concept by watching a movie.

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Metabotropic Glutamate Receptors

B Metabotropic glutamate receptor



In addition to the ionotropic glutamate receptors described above, there are three groups of [metabotropic glutamate receptor](#) subtypes. Group 1 metabotropic glutamate receptors are postsynaptic, and apparently modulate the opening of the NMDA receptor. These receptors are usually located on the side of the [dendritic spine](#), away from where the glutamate is released. Thus, they are only activated following a huge presynaptic glutamate release, such that glutamate can diffuse farther than it normally does. When the Group 1 receptors are activated, NMDA receptors allow more Ca^{2+} to enter the neuron.

Group II and III metabotropic glutamate receptors are [autoreceptors](#) located presynaptically, and modulate how much glutamate is released by the presynaptic neuron during the next action potential. In general, activation of these receptors causes less glutamate to be released subsequently.

Excitotoxicity

Warning: glutamate can be harmful to a neuron's health!

Release of too much glutamate (or administration of too much glutamate agonist) can cause [excitotoxicity](#). Neurons can literally be "excited to death" following exposure to too much glutamate. Although the mechanisms of excitotoxicity are still debated, a predominant theory is that excitotoxicity relates to Ca²⁺ entry through NMDA receptor channels. When a neuron is continually exposed to glutamate, the cell membrane will be highly depolarized, and via the mechanisms described above an abnormal amount of Ca²⁺ will enter the cell through NMDA receptor channels. Over time, the effects on enzymatic processes induced by the excessive Ca²⁺ entry will cause neuronal death.

Excitotoxicity often happens after strokes and other events that cause neurons to die and rupture, releasing their intracellular contents. This causes excessive extracellular glutamate around the nearby neurons that survived the initial traumatic event, such that these nearby neurons eventually die because of excitotoxicity. This process can occur in a wave, with the death of a group of neurons causing subsequent excitotoxicity of their neighbors.

[Ischemia](#) of a brain can region also result in excitotoxicity, as there can be too little ATP synthesis to provide energy for glutamate reuptake into presynaptic terminals via the [glutamate transporters](#).

Clinical Neuropharmacology of Glutamate Transmission

Since glutamate is the predominant excitatory neurotransmitter in the nervous system, mutations that affect glutamate receptors are associated with a number of serious neurological diseases, including [epilepsy](#). A triggering event for many seizures is too much activation of glutamate receptors. However, since glutamate receptors are so ubiquitous in the nervous system, the efficacy of glutamate receptor antagonists for treating epilepsy is limited, since they cause many side effects. However, a few glutamate receptor antagonists have been approved for epileptic patients, including [Perampanel](#).

A number of drugs of abuse, including [Phencyclidine](#) (PCP), also known as "angel dust," [ketamine](#), and [methadone](#) are NMDA receptor antagonists. For example, PCP binds to a site in the NMDA receptor channel pore, thereby partially occluding the movement of ions. These drugs also have other pharmacological actions, but their effects highlight the importance of NMDA receptors in cognitive function.

Assessment: Glutamate Receptors

Please answer the questions below to assess how well you learned the material.

When glutamate binds to an NMDA receptor: *

- An EPSP always occurs
- An IPSP occurs
- Ca²⁺ always enters the postsynaptic neuron
- An EPSP may occur, depending on the resting membrane potential when glutamate binds to the receptor

Kainate receptors: *

- Are autoreceptors, present on the presynaptic nerve terminal
- Are examples of metabotropic receptors
- Allow both K⁺ and Na⁺ to cross a neuronal membrane
- Allow both Na⁺ and Ca²⁺ to enter a neuron

Metabotropic glutamate receptors: *

- Are located in close proximity to NMDA receptors on a dendritic spine
- Cannot open unless the membrane is already depolarized
- Are often found on the presynaptic terminal
- Always trigger the opening of ion channels when glutamate binds

Long term potentiation: *

- Is facilitated by injection of CNQX to block AMPA receptors
- Occurs when the postsynaptic neuron is hyperpolarized
- Is dependent on entry of Ca²⁺ through NMDA receptor channels
- Occurs when a presynaptic neuron releases glutamate at irregular intervals

Glutamate Receptors: Self Assessment Questions

When glutamate binds to an NMDA receptor:

- An IPSP occurs
- Ca^{2+} always enters the postsynaptic neuron
- An EPSP may occur, depending on the resting membrane potential when glutamate binds to the receptor
- An EPSP always occurs

Kainate receptors:

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Metabotropic glutamate receptors:

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Neurophysiology Module 6

Cholinergic Receptors

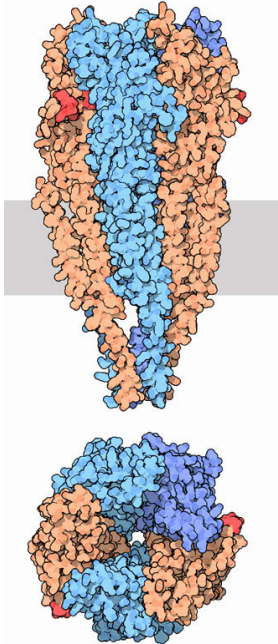
- [Introduction](#)
- [Nicotinic Receptors](#)
- [Muscarinic Receptors](#)
- [Messing with Cholinergic Neurotransmission](#)
- [Assessment](#)

Introduction

There are two major subtypes of acetylcholine (cholinergic) receptors: *nicotinic* and *muscarinic* receptors. Both nicotinic and muscarinic receptors are present in the central nervous system. In addition, acetylcholine is used as a neurotransmitter by neurons that constitute the *peripheral nervous system*, including *motoneurons*, sympathetic and parasympathetic *preganglionic neurons*, and parasympathetic *postganglionic neurons*.

Acetylcholine also differs from most neurotransmitters, in that it is **NOT** reuptaken into the neuron that released it. Instead, acetylcholine is broken down by an enzyme, *acetylcholinesterase*, which is present in abundance at cholinergic synapses.

Nicotinic Receptors



All nicotinic receptors are **ionotropic**: binding of acetylcholine to the receptor results in the opening of an ion channel. Nicotinic receptors are comprised of 5 subunits, arranged symmetrically around a central pore. At least 12 building blocks and 17 subtypes of nicotinic receptors have been discovered. One of these subtypes is located at the neuromuscular junction and another is located in autonomic ganglia, where sympathetic or parasympathetic preganglionic neurons synapse with postganglionic neurons. The other subtypes are located in the central nervous system, and can be either presynaptic or postsynaptic.

The pharmacology of the two subtypes of nicotinic receptors in the periphery (the **autonomic ganglion subtype** and the **neuromuscular junction subtype**) is much simpler than that of the multiplicity of subtypes in the central nervous system. However, one of the brain subtypes (**alpha-4 beta-2 nicotinic receptor**) is of note, as it is the main mediator of nicotine dependence.

The three nicotinic receptor subtypes highlighted above (**ganglion-type**, **muscle-type**, **alpha-4 beta-2**) are a cation channel that allows both Na⁺ and K⁺ to move through the membrane when acetylcholine binds. The entry of Na⁺ predominates, so an EPSP occurs in the postsynaptic neuron.

Nicotinic receptors are so named because they bind **nicotine**, which serves as an agonist. In reality, the potency of nicotine as an agonist is less at the neuromuscular junction than in autonomic ganglia and many nicotinic receptors in the brain.

What you need to know: There are some fairly specific nicotinic receptor agonists and **antagonists** (receptor blockers) with selective effects on synaptic transmission to muscle or in the autonomic nervous system. Here are some examples:

Nicotinic Receptor	Selective Agonist	Selective Antagonist
Muscle Type	<i>Suxamethonium chloride</i> (succinylcholine)	<i>Pancuronium bromide</i>
Ganglion Type	<i>Dimethylphenylpiperazinium</i>	<i>Trimetaphan</i>

Muscarinic Receptors

Unlike nicotinic receptors, muscarinic receptors are **metabotropic**: they are linked with G proteins. As such, binding of acetylcholine to a muscarinic receptor can elicit a host of effects in the postsynaptic neuron. Muscarinic receptors are so named because they bind **muscarine**, a product of some mushrooms.

Muscarinic receptors are located on the peripheral targets of the parasympathetic nervous system (like smooth muscle cells and secretory cells), a limited number of targets of the sympathetic nervous system (e.g., sweat glands), and in the central nervous system.

There are 5 major subtypes of muscarinic receptors: M1-M5. All of these subtypes are found in the central nervous system, and the M1-M3 subtypes are found in the periphery (on the targets of parasympathetic and a few sympathetic postganglionic neurons).

Many peripheral tissues have more than one muscarinic receptor subtype, such that it is difficult to predict the effects of applying acetylcholine (or a muscarinic receptor antagonist) to a particular tissue. It is thus also difficult to provide an agonist or antagonist for a muscarinic receptor that does not produce effects in many tissues.

That being said, one can draw some generalities about the different subtypes of muscarinic receptors, which are summarized in the table below:

Subtype	Effects and Localization
M1	Agonist causes a slow EPSP and a decrease in K ⁺ conductance Located in salivary glands, GI tract
M2	Agonist causes an increased K ⁺ conductance and a decrease in Ca ²⁺ conductance Located in the heart (slows heart rate and conduction of electrical potentials)
M3	Many effects through G protein. Located in salivary glands, eye (accommodation), GI tract, Internal urinary sphincter

What you need to know: Most muscarinic agonists and antagonists have effects on multiple receptor subtypes. In addition, most tissues contain more than one muscarinic receptor subtype. Thus, altering a specific physiological function with a drug that acts on muscarinic receptors is difficult.

For example, the muscarinic receptor antagonist *atropine* induces dry mouth, large pupils, urinary retention, constipation, and a fast heart rate (it acts at many sites to produce many effects).

Messing with Cholinergic Neurotransmission

A variety of pharmacological approaches can be used to alter cholinergic neurotransmission, in addition to the delivery of cholinergic agonists and antagonists. These approaches include:

1. Use of *acetylcholinesterase inhibitors*. Such drugs delay the breakdown of acetylcholine, so the effects of the neurotransmitter persist over a longer time. Examples include *neostigmine* (used to treat *myasthenia gravis*, an autoimmune disease that results in loss of functional nicotinic receptors at the neuromuscular junction).
2. Use of *Botulinum toxins*. Such drugs interfere with the activity of proteins that are critical for the binding of vesicles containing acetylcholine to the membrane at the nerve terminal. Thus, the toxins prevent release of acetylcholine from the presynaptic terminal. They are injected into particular facial muscles as a cosmetic treatment (paralyzing facial muscles can eliminate wrinkles), or are used to relax spastic muscles.

Assessment: Cholinergic Receptors

Please answer the questions below to assess how well you learned the material.

Which of the following statements about cholinergic neurotransmission is correct? *

- Peripheral tissues innervated by the parasympathetic nervous system contain only one muscarinic receptor subtype
- Muscarinic receptors are not present in the central nervous system
- Different subtypes of nicotinic receptors are present in the neuromuscular junction and autonomic ganglia
- There are only three subtypes of nicotinic receptors

Which of the following drugs can be used to enhance skeletal muscle contractions? *

- Neostigmine
- Pancuronium bromide
- Botulinum toxin
- Suxamethonium chloride

Following the binding of acetylcholine to nicotinic receptors in the peripheral nervous system: *

- The membrane is hyperpolarized
- A channel opens that allows K^+ and Na^+ to cross the membrane
- A G-protein is activated
- A channel opens that allows Na^+ and Ca^+ to cross the membrane

Muscarinic receptors are located in: *

- Autonomic ganglia
- Sweat glands
- The neuromuscular junction
- None of the above

Cholinergic Receptors: Self Assessment Questions

Which of the following statements about cholinergic neurotransmission is correct?

- Muscarinic receptors are not present in the central nervous system
- There are only three subtypes of nicotinic receptors
- Peripheral tissues innervated by the parasympathetic nervous system contain only one muscarinic receptor subtype
- **Different subtypes of nicotinic receptors are present in the neuromuscular junction and autonomic ganglia**

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- The membrane is hyperpolarized
- A G-protein is activated
- **A channel opens that allows K⁺ and Na⁺ to cross the membrane**

Muscarinic receptors are located in:

- Autonomic ganglia
- **Sweat glands**
- The neuromuscular junction
- None of the above

Neurophysiology Module 7

Inhibitory Neurotransmitters

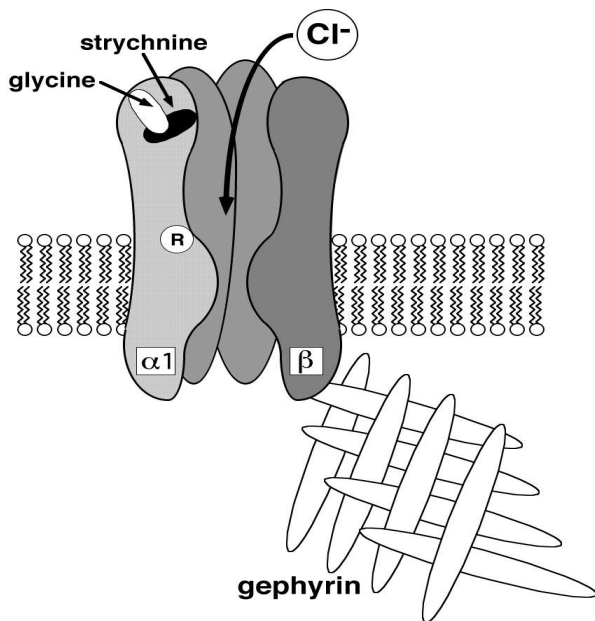
- [Introduction](#)
- [Glycine Receptors](#)
- [GABA_A Receptors](#)
- [GABA_B Receptors](#)
- [Assessment](#)

Introduction

The two major inhibitory neurotransmitters released by neurons are amino acids: **GABA** (*gamma-aminobutyric acid*) and glycine. All [glycine receptors](#) are ionotropic receptors. Most GABA receptors, which belong to the [GABA_A receptor subtype](#), are also ionotropic receptors. However, a minority of GABA receptors, which belong to the [GABA_B receptor](#) subtype, are metabotropic, as they activate G-proteins.

Both GABA and glycine are reuptaken from the synaptic cleft by transporters on the axon terminal.

Glycine Receptors



The binding of glycine to its receptor results in the opening of a Cl⁻ channel. Chloride is usually in much higher concentration outside of neurons, and thus opening a Cl⁻ channel allows Cl⁻ to move down its concentration gradient and hyperpolarize the membrane, resulting in an [IPSP](#). All glycine receptors are relatively simple [ligand-gated ion channels](#).

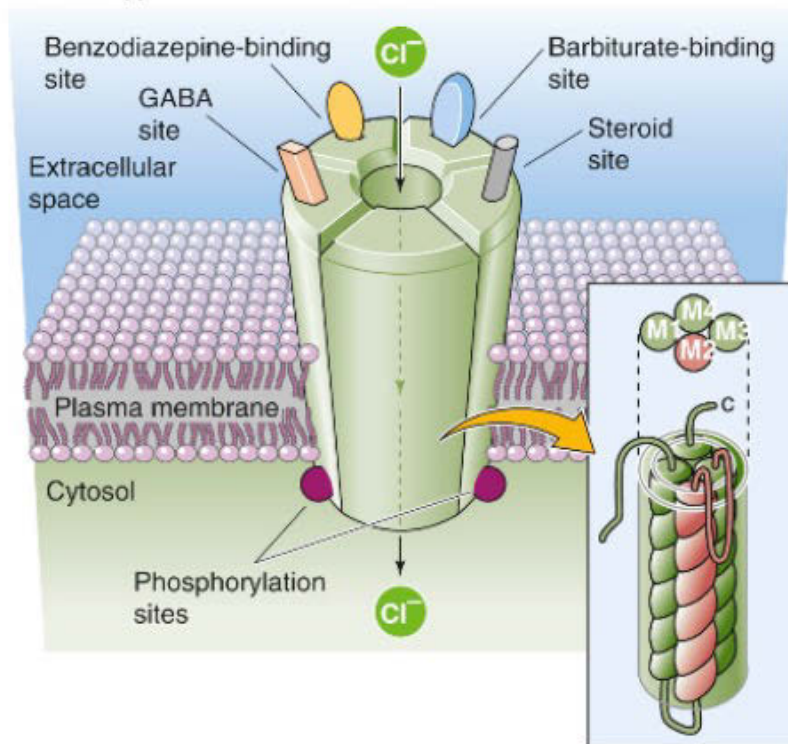
Both glycine and GABA_A receptors are anchored to the postsynaptic cytoskeleton by the protein [gephyrin](#). Downregulation of this protein can affect inhibitory neurotransmission in the nervous system, resulting in neurons that are hyperexcitable, which can lead to disease states. For example, patients with [temporal lobe epilepsy](#) have abnormally low levels of gephyrin in their temporal lobes.

Glycine receptors are mainly located in the spinal cord and brainstem.

Strychnine is a fairly selective **glycine receptor antagonist**. There are no good selective agonists for glycine receptors other than glycine.

GABA_A Receptors

E GABA_A RECEPTOR CHANNEL

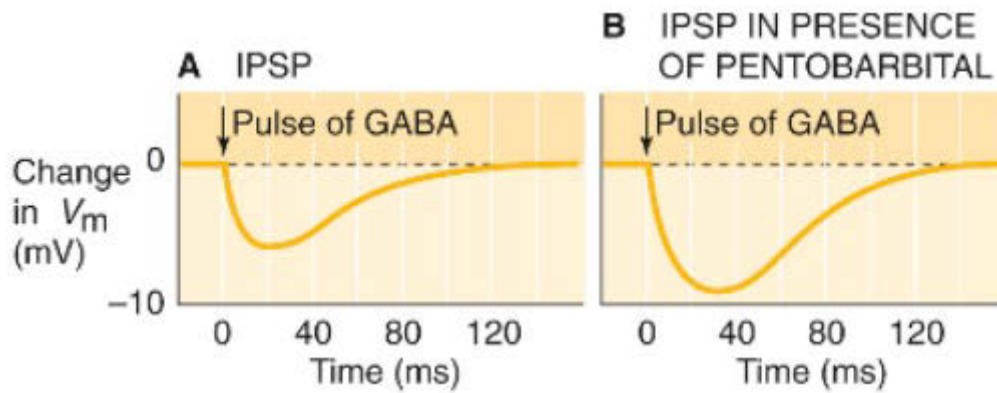


GABA_A receptors have many characteristics in common with glycine receptors:

- Binding of agonist to the receptor opens a Cl⁻ channel, resulting in an IPSP in the postsynaptic neuron.
- The receptor is anchored to the membrane via gephyrin.

GABA_A receptors are located on the dendrites and cell bodies of neurons throughout the nervous system.

A large number of common drugs exert their actions by binding to either the main receptor site of the GABA_A receptor, or bind to another part of the receptor causing a change in conformation. The latter drugs are called **allosteric modulators**, and fall into two classes: those that amplify the effects of agonist binding to the receptor (**positive allosteric modulator**) and those that reduce the effects of ligand binding to the receptor (**negative allosteric modulator**).



In the case of the GABA_A receptor, a **positive allosteric modulator** results in more Cl⁻ moving into the postsynaptic neuron when GABA binds to the receptor, and a **negative allosteric modulator** results in less Cl⁻ moving into the postsynaptic neuron. In the example to the left, the positive allosteric modulator [pentobarbital](#) (a [barbiturate](#)) results in a larger IPSP when GABA binds to the GABA_A receptor.

Some examples of agonists and antagonists of GABA_A receptors, as well as allosteric modulators, are provided below:

- Agonist: [muscimol](#)
- Antagonist: [bicuculline](#)
- Positive allosteric modulator: [benzodiazepines](#), [barbiturates](#), [zolpidem](#) (ambien)
- Negative allosteric modulator: [flumazenil](#)

The effects of these drugs are as you would predict from GABA's role as the main inhibitory neurotransmitter in the nervous system. Positive allosteric modulators increase inhibition of neurons, resulting in sedation, hypnosis, and amnesia. These drugs also act as [anticonvulsants](#). Negative allosteric modulators would have the opposite effect, and thus are not widely used in medicine. For example, flumazenil (*a negative allosteric modulator of GABA_A receptors*) is only used to reverse the effects of benzodiazepines. The GABA_A receptor antagonist bicuculline causes hyperexcitability of neurons, and thus produces seizures. This drug is provided to laboratory animals to mimic epilepsy.

GABA_B Receptors

GABA also acts on G protein-coupled [GABA_B receptors](#). GABA_B [autoreceptors](#) are located presynaptically at GABAergic synapses, and are also located on terminals that release glutamate. Binding of GABA to presynaptic GABA_B receptors results in diminished opening of voltage-gated Ca²⁺ channels at the nerve terminal, and less release of neurotransmitter following an action potential.

However, most GABA_B receptors are postsynaptic. Binding of GABA to the postsynaptic GABA_B receptors results in increased conductance of K⁺, causing hyperpolarization of the postsynaptic neuron, such that it is less likely to generate an action potential.

The drug [baclofen](#) is a GABA_B agonist. It is used to treat [spasticity](#), a condition that will be discussed in this course.

Assessment: Inhibitory Neurotransmitters

Please answer the questions below to assess how well you learned the material.

Benzodiazepines: *

- Decrease Cl⁻ conductance through GABA_A receptors
- Bind to the same site on GABA_A receptors as GABA
- Bind to GABA_B receptors
- Increase Cl⁻ conductance through GABA_A receptors when GABA binds to the receptor

Which of the following statements about GABA_A antagonists is correct?

*

- GABA_A antagonists are commonly used to treat epilepsy
- GABA_A antagonists increase Na⁺ conductance into a neuron
- GABA_A antagonists elicit epilepsy-like seizures when provided to experimental animals
- Examples of GABA_A antagonists include barbiturates

Which of the following statements about GABA receptors is correct? *

- All are metabotropic receptors
- All are ionotropic receptors
- They can be present on the presynaptic or postsynaptic membrane of the synapse
- They are present in the brainstem and spinal cord, but not cerebral cortex

Glycine receptors: *

- Are abundant in the spinal cord and brainstem but not cerebral cortex
- Increase Cl⁻ conductance when they bind strychnine
- Are mainly located on nerve terminals
- Are mainly located in the peripheral nervous system

Inhibitory Neurotransmitters: Self Assessment Questions

Benzodiazepines:

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Neurophysiology Module 8

Monoamines

- [Introduction](#)
- [Serotonin](#)
- [Norepinephrine](#)
- [Dopamine](#)
- [Summation](#)
- [Assessment](#)

Introduction

The monoamines are neurotransmitters that contain one amino group that is connected to an aromatic ring by a two-carbon chain (-CH₂-CH₂-). Typically, the monoamines activate G proteins to exert their effects at the synapse, although there is one exception described below.

Monoaminergic systems, the networks of neurons that utilize monoamine neurotransmitters, are involved in the regulation of cognitive processes such as emotion, arousal, and certain types of memory.

The monoamines are normally separated into three groups:

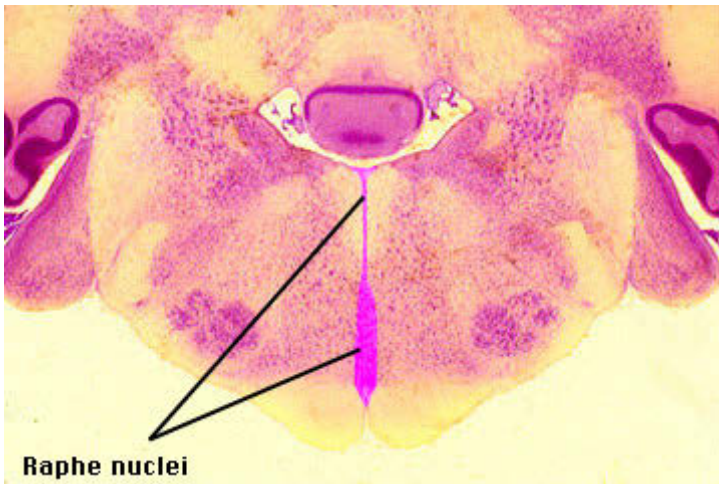
Group	Characteristics	Members
<i>Histamine</i>	Derived from decarboxylation of the amino acid histidine	Histamine
<i>Catecholamines</i>	Have a catechol (<i>benzene with two hydroxyl side groups at carbons 1 and 2</i>) and a side-chain amine	<i>Epinephrine, Dopamine, Norepinephrine</i>
<i>Tryptamines</i>	Contain an indole ring structure, so structurally similar to the amino acid tryptophan	<i>Serotonin, Melatonin</i>

All of the molecules listed above are used as neurotransmitters by the central nervous system, but we will focus on the following three with the most important roles: dopamine, norepinephrine, and serotonin.

All of the monoamines are reuptaken into the presynaptic nerve terminal through [monoamine transporters](#). Each of the monoamines we will focus on has its own transporter, but since dopamine and norepinephrine are similar molecules, the norepinephrine transporter can reuptake dopamine, and vice versa. Many drugs used to treat mental health disorders, as well as recreational drugs such as cocaine, have their actions on the monoamine transporters. For example, most modern antidepressant drugs work on the principle of blocking these re-uptake transporters.

There are many, many subtypes of monoamine receptors, and thus we will only focus on generalities. These receptors are both presynaptic and postsynaptic.

Serotonin

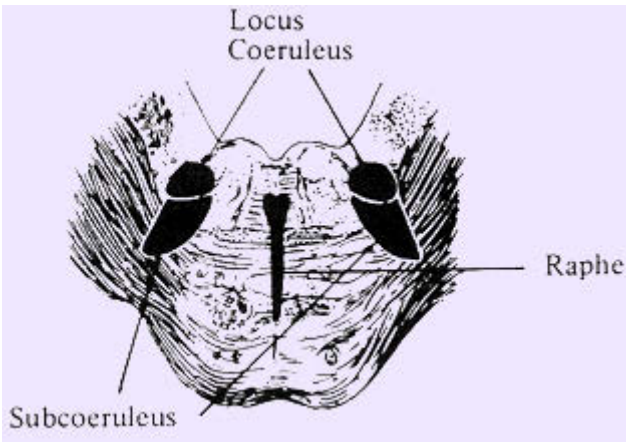


Neurons that synthesize serotonin (also called 5-hydroxytryptamine, or 5-HT) are mainly located in nuclei at the midline of the brainstem, called the [raphe nuclei](#) (raphe means "seam" in Greek). Generally, the raphe nuclei in the caudal brainstem (in the [medulla](#)) project to the brainstem and spinal cord, while the rostral raphe nuclei (in the [pons](#) and [midbrain](#)) project to much of the [diencephalon](#) and [telencephalon](#).

The axons of the raphe nucleus neurons branch extensively, and provide inputs to neurons scattered throughout the brain and spinal cord. Hence, a relatively small number of cells have widely branching axons that affect many postsynaptic targets. In addition, there are 7 subtypes of [serotonin receptors](#) (labeled 5HT1-5HT7), with a further division within subtypes. Since activating each subtype has different intracellular effects mediated through G-proteins, the actions of serotonin in the nervous system are very, very complex. However, some of the behaviors mediated through serotonergic neurotransmission should be highlighted:

- Pain control. Activation of serotonin neurons with projections to the spinal posterior horn alters pain sensation
- Nausea. Drugs that block the [5-HT₃](#) receptor such as [ondansetron](#) are highly effective in treating most forms of nausea, except that associated with [motion sickness](#). Curiously, the 5-HT₃ receptor is one of the few monoamine receptors that is ionotropic; binding of serotonin to the 5HT₃ receptor opens a cation channel.
- Sleep
- Mood (hence, [serotonin reuptake inhibitors](#) are commonly used to treat depression).

Norepinephrine



Norepinephrine is synthesized by most sympathetic postganglionic neurons as well as groups of neurons in the brainstem whose axons branch extensively. The largest of the norepinephrine-producing cell groups is located in a nucleus in the pons called *locus coeruleus*. Locus coeruleus neurons contain *melanin* crystals, such that the nucleus appears as a black dot in brainstem sections through the pons.

Norepinephrine binds to two main subtypes of metabotropic receptors: α and β . The α subtype can be divided into the $\alpha-1$ and $\alpha-2$ subtypes. The β subtype can be divided into $\beta-1$, $\beta-2$ and $\beta-3$ receptors, although $\beta-3$ receptors are mainly in peripheral tissues (not the CNS) and are less important than the other subclasses.

The actions of norepinephrine binding to these receptors is summarized in the table below:

Receptor	Effects of binding to the receptor
$\alpha 1$	Activates <i>phospholipase C</i> , resulting in an increase in intracellular Ca^{2+}
$\alpha 2$	Decreases cAMP by inhibiting adenylate cyclase
β (all subtypes)	Increases cAMP by activating adenylate cyclase

Based on this information, it appears that binding of ligand to $\alpha 2$ and β receptors would have opposite effects. While it is true that effects of transmitter binding to $\alpha 1$ and β receptors produces excitatory responses, whereas binding of norepinephrine to $\alpha 2$ causes inhibitory responses, there is a complication. In the central nervous system, $\alpha 2$ receptors are mostly presynaptic *autoreceptors*, such that ligand binding to the receptor reduces norepinephrine release from the nerve terminal. In contrast, $\alpha 1$ and β receptors are usually postsynaptic.

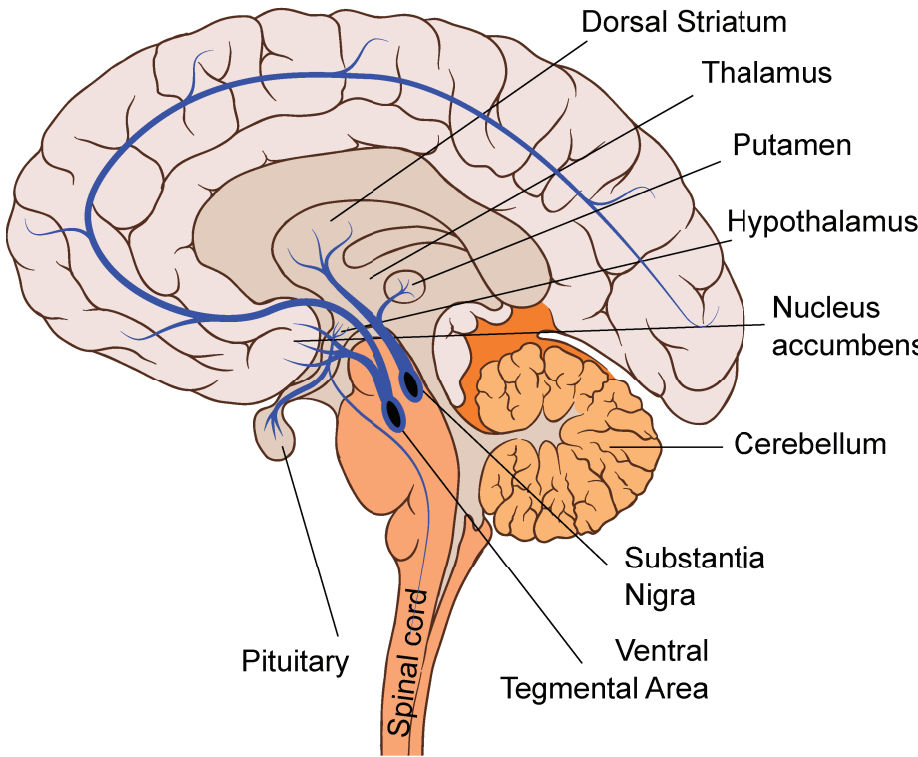
In the autonomic nervous system lecture later in the course, we will discuss the effects of norepinephrine (and epinephrine) binding to peripheral α and β receptors on physiological processes. In the central nervous system, binding of norepinephrine to these receptors results in changes in arousal, attention, cognition, and emotions.

Dopamine

Dopamine is mainly a neurotransmitter of the central nervous system, although some peripheral tissues (e.g., *cells in the kidney*) also use dopamine as a signaling molecule. There are 5 main subtypes of dopamine receptors (D1-D5), all of which exert their effects by activating G-proteins. Most dopamine receptors are postsynaptic, but some are presynaptic (autoreceptors).

Most dopaminergic neurons are located in two midbrain areas, substantia nigra pars compacta and the ventral tegmental area.

Neurons in substantia nigra pars compacta project to regions of the basal ganglia called the striatum, parts of the brain that are involved in movement control.



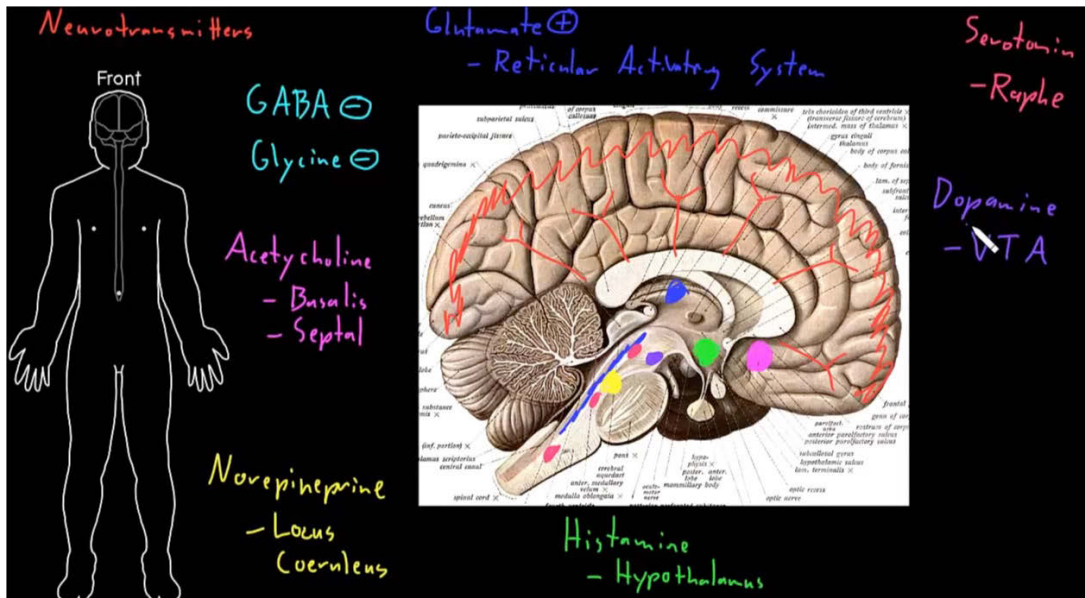
Degeneration of these connections (nigro-striatal pathway) results in Parkinson's disease. These connections will be discussed during the second week of the class.

Dopamine-producing neurons in the ventral tegmental area project to prefrontal cortex, and structures of the limbic system. These connections are a fundamental part of the brain's reward system, and also have roles in cognition. Changes in dopaminergic transmission in this pathway can result in psychiatric diseases, including schizophrenia and attention deficit hyperactivity disorder. These connections will be discussed during this course, and in the psychiatry course.

Summation

Now that we have discussed a bunch of neurotransmitters, let's review what they do by watching a movie from the KhanAcademy.

If the movie does not play in this window, or you would like to see it in a window of alternate size, download it from [this link](#).



Assessment: Monoamines

Please answer the questions below to assess how well you learned the material.

Which of the following statements about dopamine is correct? *

- Dopamine is inactivated by an enzyme in the synaptic cleft
- Dopamine is mainly synthesized by neurons located in the medulla
- Drugs that affect dopamine release or reuptake have been used to treat Parkinson's disease and schizophrenia
- Dopamine mainly binds to ionotropic receptors

Which of the following statements about monoamines is correct? *

- Neurons producing monoamines generally have branching axons that affect many postsynaptic target neurons
- Monoaminergic neurons are exclusively located in the central nervous system
- Receptors for monoamine neurotransmitters are exclusively postsynaptic
- Most cell bodies of monoamine-producing neurons are located in cerebral cortex

Serotonin (5HT) receptors: *

- Are entirely presynaptic
- Are present in cerebral cortex, but not the spinal cord
- Can only be divided into only two subtypes
- When activated, can modulate pain sensitivity

Alpha-2 receptors: *

- Are frequently autoreceptors
- Bind neurotransmitter released by neurons with cell bodies in the raphe nuclei
- Are located in autonomic ganglia
- Are exclusively localized to the brainstem

Monoamines: Self Assessment Questions

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Neurophysiology Module 9

Effects of Ca²⁺ and Mg²⁺ on Neuronal Excitability

- [Calcium](#)
- [Magnesium](#)
- [Assessment](#)

Calcium

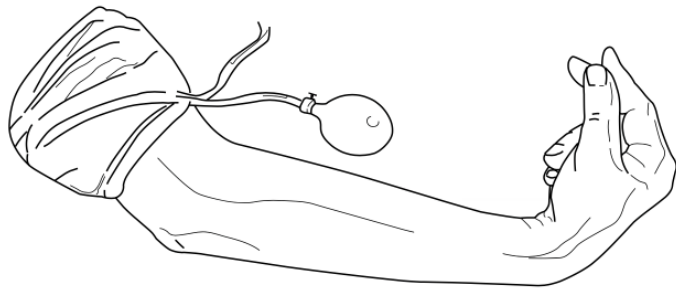
[Calcium](#) (Ca²⁺) is a prevalent element in the body, and comprises about 1.2 Kg of our weight. Although 99% of this Ca²⁺ is found in bones, the small amount of Ca²⁺ found in the extracellular fluid is critically important. Ca²⁺ is an important physiologic mediator, and participates in muscle contraction, neuronal function, and regulation of enzymatic processes. It is critical to maintain constant levels of plasma Ca²⁺, and thus a number of physiological mechanisms participate in this regulatory process.

In previous courses, you have learned about the renal and endocrine mechanisms that regulate blood Ca²⁺ levels. A number of pathophysiological conditions can lead to elevated blood calcium ([hypercalcemia](#)) or reduced blood calcium ([hypocalcemia](#)). This module focuses on the effects of hypercalcemia and hypocalcemia on neuronal excitability and neuromuscular activity.

Since Ca²⁺ entry into a nerve terminal causes neurotransmitter release, you might think that hypercalcemia would result in exaggerated neurotransmitter release and neuronal hyperactivity. In contrast, the effects are the opposite.

High Ca²⁺ levels ([hypercalcemia](#)) can block sodium movement through voltage-gated sodium channels, causing reduced depolarization and impaired action potential generation. This explains the fatigue, cognitive impairments, muscle weakness, low muscle tone, and sluggish reflexes in muscle groups during hypercalcemia. Severe hypercalcemia is considered a medical emergency: coma and cardiac arrest can result due to the effects of Ca²⁺ on sodium entry into cardiac myocytes and neurons.

In contrast, low Ca²⁺ levels ([hypocalcemia](#)) facilitate sodium transport, as the normal inhibition by Ca²⁺ of sodium movement through voltage-gated sodium channels is lost. Thus, low Ca²⁺ levels result in hyperexcitability of excitable cells, such as neurons. At plasma Ca²⁺ ion concentrations about 50 percent below normal, the peripheral nerve fibers become so excitable that they begin to discharge spontaneously, initiating trains of nerve impulses that pass to the peripheral skeletal muscles to elicit [tetanic muscle contraction](#).



A diagnostic indicator of hypocalcemia is **Trousseau's sign**. Trousseau's sign presents as carpopedal spasms following inflation of a sphygmomanometer cuff above systolic blood pressure. Occlusion of the brachial artery causes flexion of the wrist and metacarpophalangeal joints, hyper-extension of the fingers, and flexion of the thumb on the palm, producing a characteristic posture. The proposed mechanism for Trousseau's sign is increased excitability of the nerves in the arm and forearm by hypocalcemia, such that the nerves fire when subjected to Ischemia after inflating the cuff.

Another indicator of hypocalcemia is **Chvostek's sign**, which is elicited by tapping the cheek over the path of the facial nerve. In hypocalcemia patients, the facial muscles on the same side of the face will contract momentarily, as the tap will stimulate hyperexcitable motor axons.

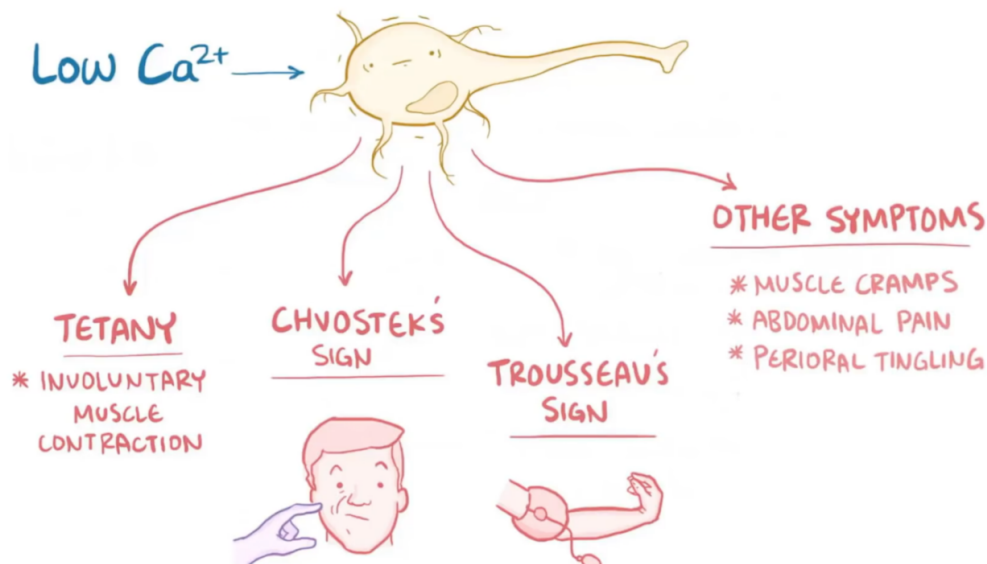
A rarer consequence of hypocalcemia is seizures.

The table below summarizes the typical effects of hypercalcemia and hypocalcemia on excitable membranes.

Condition	Characteristics
<u>Hypercalcemia</u>	Fatigue, cognitive impairments, muscle weakness, low muscle tone, sluggish reflexes
<u>Hypocalcemia</u>	<u>Tetany</u> , <u>Trousseau's sign</u> , <u>Chvostek's sign</u>

This movie provides more insights into the effects of hypercalcemia and hypocalcemia on excitable membranes.

If the movie does not play in this window, or you would like to see it in a window of alternate size, download it from [this link](#).



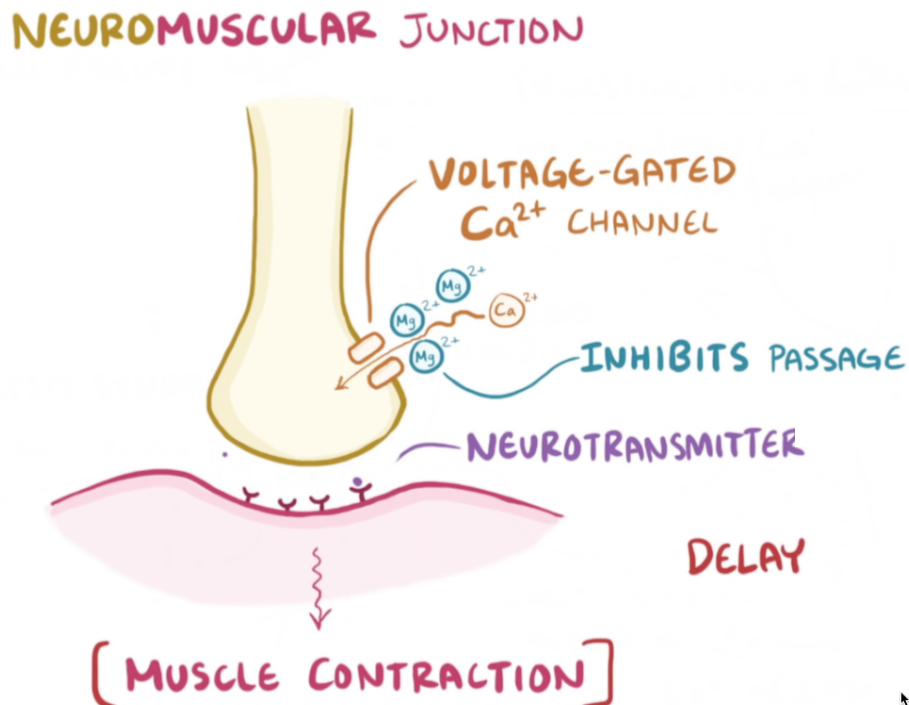
Magnesium

Another ion that can affect neuronal and muscle excitability is [magnesium](#). Plasma magnesium levels are affected by changes in gastrointestinal and renal absorption of the ion, as well as a number of metabolic disorders you will discuss in subsequent courses. High levels of magnesium ([hypermagnesemia](#)) block Ca²⁺ movement through voltage-gated Ca²⁺ channels, particularly those of the peripheral nervous system, such as terminals of motoneurons and sympathetic and parasympathetic nervous system neurons. As a consequence, neurotransmission at these terminals is reduced, resulting in slowed muscle contraction, decreased or absent muscle reflexes, impaired breathing (*due to decreased neurotransmission at the diaphragm*), and lowered blood pressure (*due to effects on the sympathetic nervous system*).

If magnesium levels are too low ([hypomagnesemia](#)), the normal inhibition of Ca²⁺ movement through voltage-gated Ca²⁺ channels dissipates, so neurotransmission increases. This is particularly prominent at the neuromuscular junction, resulting in [tetany](#) and muscle spasms.

This movie provides more insights into the effects of hypermagnesemia and hypomagnesemia on excitable membranes.

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Assessment: Ca²⁺ and Mg²⁺

Please answer the questions below to assess how well you learned the material.

Trousseau's sign: *

- Is an indicator of hypocalcemia or hypomagnesemia
- Is an indicator of hypercalcemia or hypermagnesemia
- Is an indicator of hypocalcemia or hypermagnesemia
- Is an indicator of hypercalcemia or hypomagnesemia

Tetany is the involuntary contraction of muscles. The most common cause of tetany is: *

- Insufficient blood supply to muscles
- Hyperkalemia
- Hypercalcemia
- Hypocalcemia

Which of the following statements is correct? *

- The effects of hypercalcemia are mainly due to increased influx of Ca²⁺ through voltage-gated Ca²⁺ channels
- High magnesium levels inhibit the movement of Ca²⁺ through voltage-gated Ca²⁺ channels
- Infusion of magnesium into a patient would likely cause an increase in blood pressure
- Magnesium can inhibit the movement of sodium through voltage-gated sodium channels

Hypomagnesemia is a frequent complication of cisplatin or aminoglycoside treatment. In a patient with hypomagnesemia: *

- Blood pressure is typically low
- Positive Chvostek's and Trousseau's signs can be observed
- The patient's signs and symptoms will resemble those of a patient with hypercalcemia
- Muscle paralysis is likely

Ca²⁺ and Mg²⁺: Self Assessment Questions

Trousseau's sign:

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- Is an indicator of hypocalcemia or hypermagnesemia
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