Pitt Medical Neuroscience Fall 2025

Neurophysiology and Synaptic Transmission Modules

Module Listing

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 provide an overview of the principal pathological conditions that impair neurotransmission at the neuromuscular junction, as well as to examine the mechanisms of action of commonly employed paralytic agents.
11. To understand the differential distribution of glycine and GABA receptors in the nervous system, and the effects of agonists binding to these receptors.
12. To discuss the effects of allosteric modulators on GABA receptors.
13. To appreciate the locations of neurons that release the monoamines dopamine, norepinephrine, and serotonin.
14. To review the types and physiological roles of receptors that bind norepinephrine and epinephrine.
15. To understand how changes in plasma levels of calcium and magnesium alter neuronal excitability, and the physiological consequences of this altered excitability.

Help!

If you need help learning the materials on this site, send a question via the help page.

Printable Version

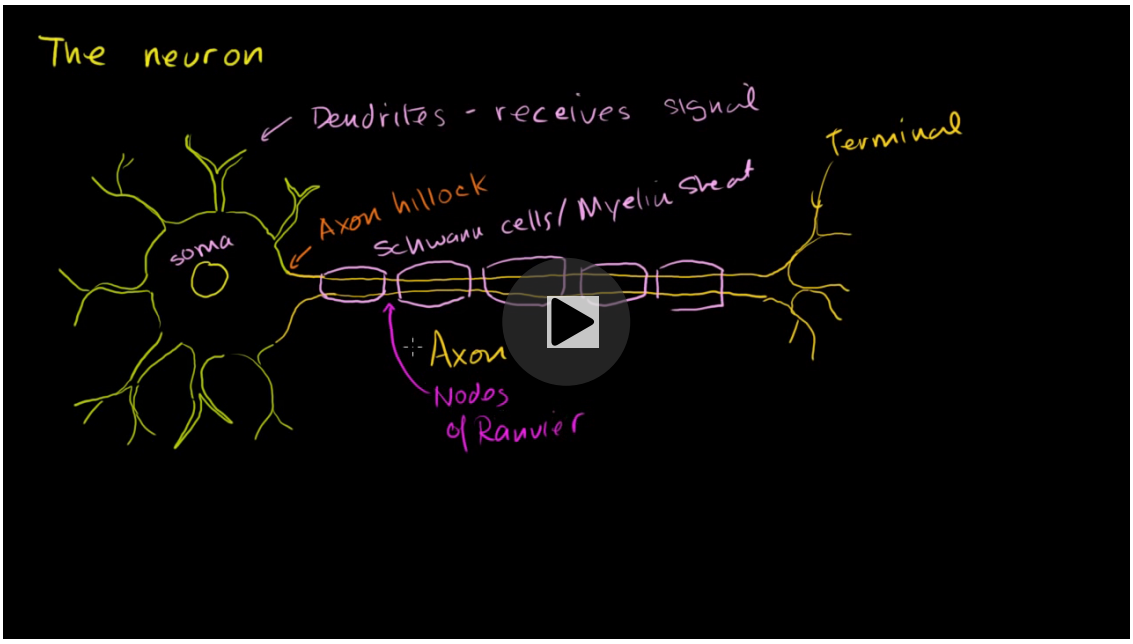
A printable version of this module can be downloaded from this link. Note that the printout does not contain the active hyperlinks, formatting, or movies included in the online module.

Neurophysiology Module 1

The Neuron

Introduction

As an introduction, watch this 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.

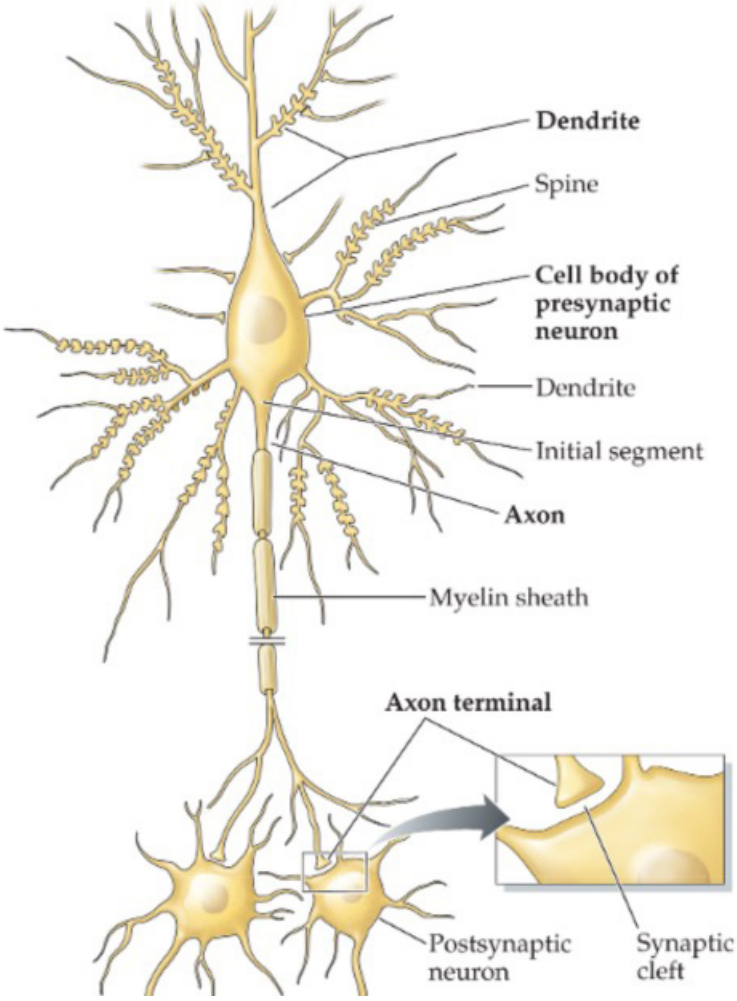


Anatomy and Types of Neurons

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:

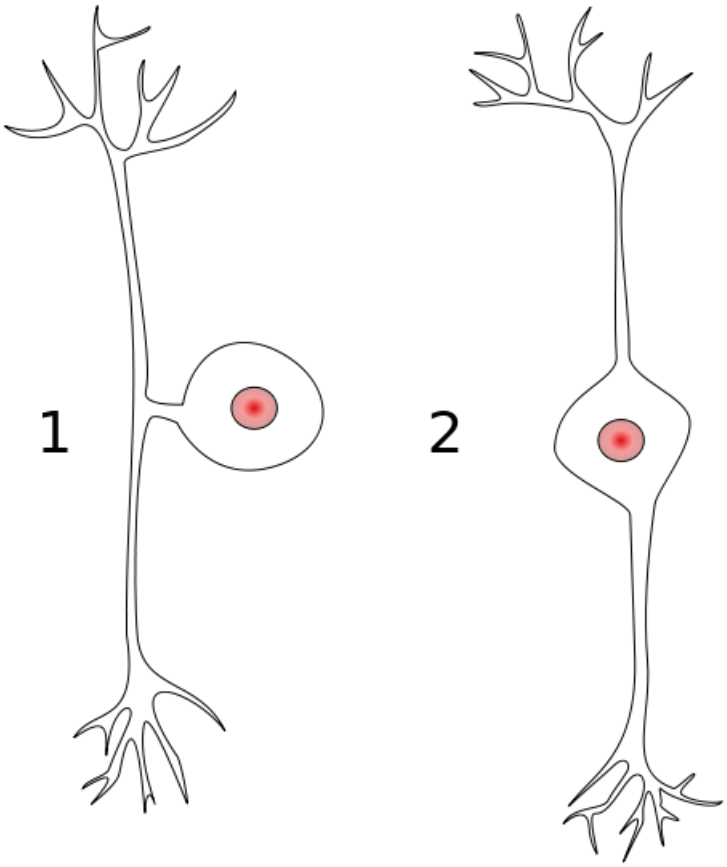


Interneurons are the most common cells in the central nervous system. The processes of interneurons always remain within the central nervous system, although some ***projection (or relay) interneurons*** may have long axons that extend for considerable distances (i.e., from the brain to the spinal cord).

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.



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

Pseudounipolar neurons: *

- Provide output signals from the central nervous system to motoneurons
- 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

Sensory afferent neurons: *

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

Axons of interneurons: *

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

Pitt Medical Neuroscience

Fall 2025

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

As noted in the module, excitatory inputs often come through dendritic spines, whereas inhibitory inputs usually come from synaptic connections on dendritic shafts and the cell body

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

Virtually all afferent fibers to the spinal cord and some afferents coursing in cranial nerves are pseudounipolar neurons. A peripheral branch is associated with a receptor, while a central branch enters the central nervous system through the posterior roots or a cranial nerve.

Sensory afferent neurons:

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

As noted in the previous question, the peripheral branch of a sensory afferent is associated with a receptor, while a central branch enters the central nervous system through the posterior roots or a cranial nerve.

Axons of interneurons:

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

By definition, the axons of interneurons remain within the central nervous system. They can be either short or long, and can branch to innervate many target neurons (including motoneurons and preganglionic neurons).

Next Module: Membrane Potentials

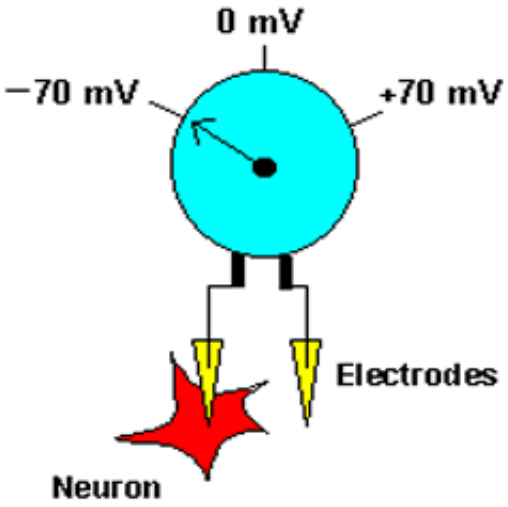
Return to the Neuron Module

Neurophysiology Module 2

Membrane Potentials

Ion Concentrations Across Membranes Generate Membrane Potentials

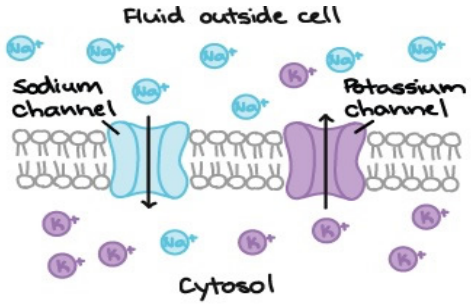
The lipid bilayer that forms the wall of a neuron (or glial cell) is not permeable to charged ions. However, there are a number of types of ***ion channels*** that allow ions to move down their concentration gradient across the membrane, and ***ion transporters*** that allow ions to move against their 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.

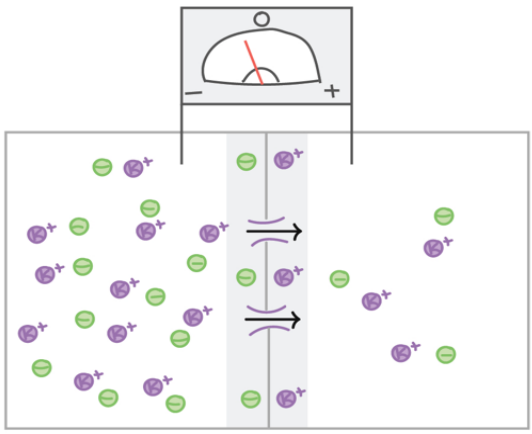
Virtually all cells have an interior that is negatively charged with respect to the outside.

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.

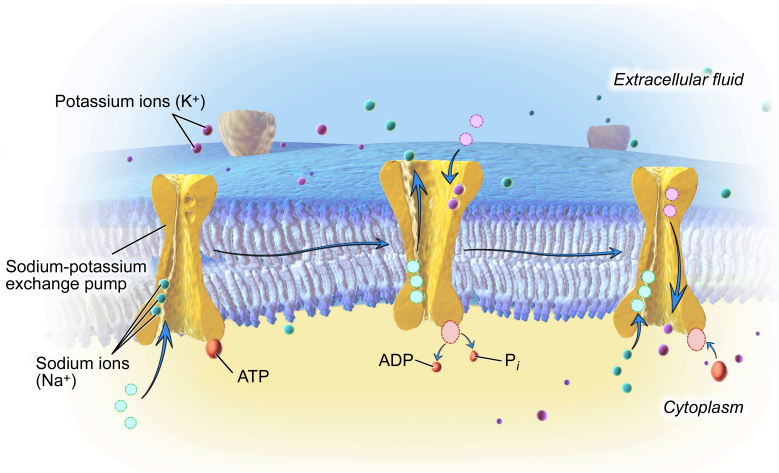
However, if an investigator placed an electrode outside of the cell and delivered a positive charge, the flow of K+ from inside to outside the cell would be opposed, as the K+ ions would be repelled by the positive charge that is being delivered. The charge that is needed to keep K+ from diffusing from 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 mainly dependent on the presence of negatively charged proteins inside the cell
- Is between the equilibrium potentials for sodium and potassium
- Is closer to the equilibrium potential for sodium than the equilibrium potential for potassium
- is unrelated to the equilibrium potentials for particular ions

The resting membrane potential for a neuron: *

- Is dependent only on the movement of sodium across the membrane
- Is mainly due to the leakiness of a membrane for potassium
- 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: *

- Sodium
- Chloride
- Calcium
- Potassium

The movement of a particular ion across a membrane: *

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

Pitt Medical Neuroscience

Fall 2025

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

Both sodium and potassium ions contribute to generating the resting membrane potential, and thus the resting membrane potential is between the equilibrium potentials of these two ions. However, the resting membrane potential is closer to the equilibrium potential for K+, as the membrane is leakier for this ion.

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

The resting membrane potential is near -70mV (not -85mV), and its generation is strongly dependent on the distribution of ions generated by the sodium potassium pump. The resting membrane has limited permeability for sodium. However, it is leaky for potassium, and this movement of K+ ions plays a key role in producing the resting membrane potential

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

- Calcium
- Sodium
- Chloride
- Potassium

Since the membrane is leakiest for potassium, changes in the extracellular concentration of potassium have the strongest effects on membrane potential.

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

All the factors indicated above contribute to ion movement. Without channels, an ion cannot cross the membrane. The movement is facilitated by a high concentration gradient across the membrane, and ionic movement is related to the charge across the membrane.

Next Module: Action Potentials

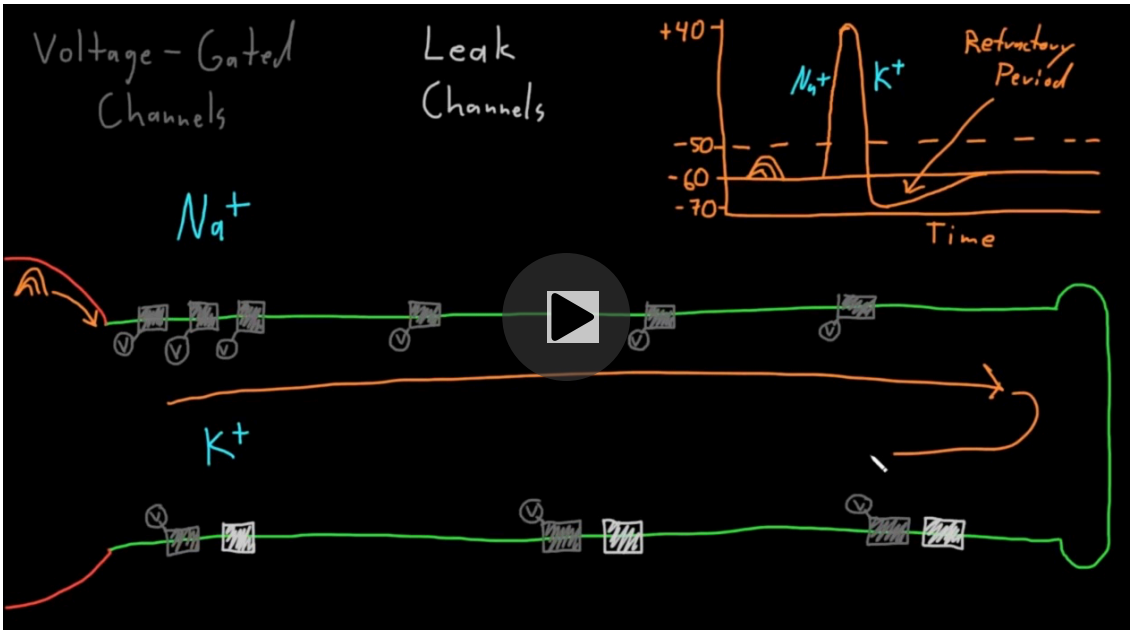
Return to the Membrane Potential Module

Neurophysiology Module 3

Action Potentials

Introduction

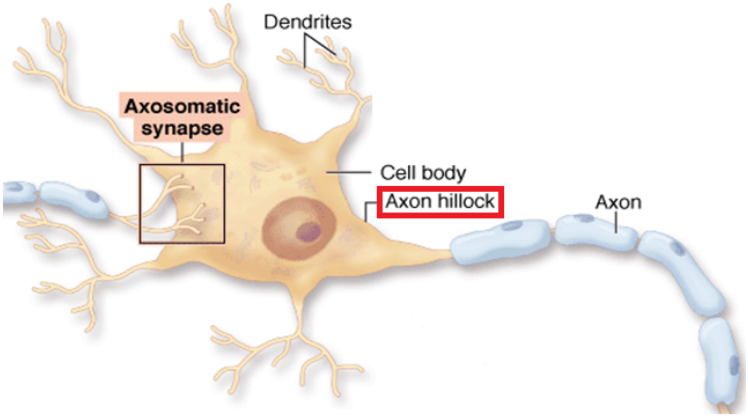
As an introduction, watch this movie from the KhanAcademy.
If the movie does not play in this window, or you would like to see it in a window of alternate size, download it from ***this link***.



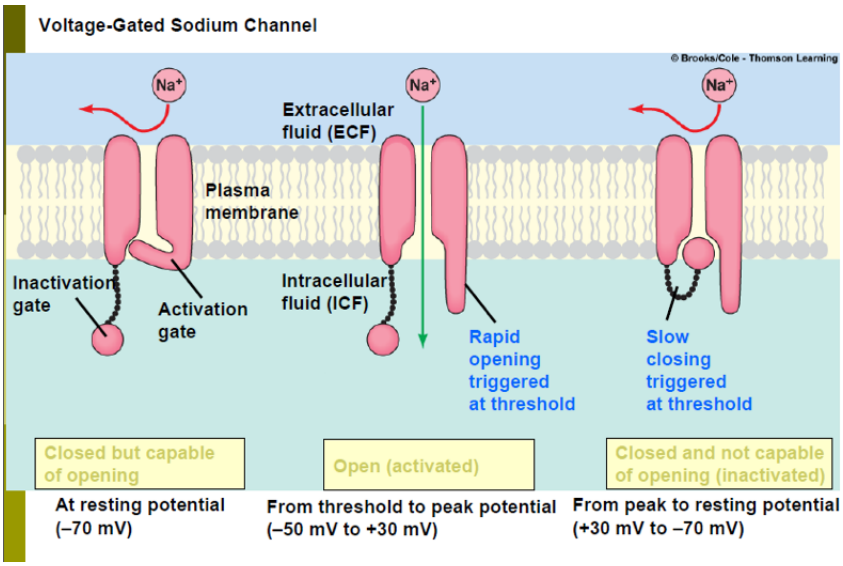
Opening of Voltage Gated Channels Produces Action Potentials

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***).



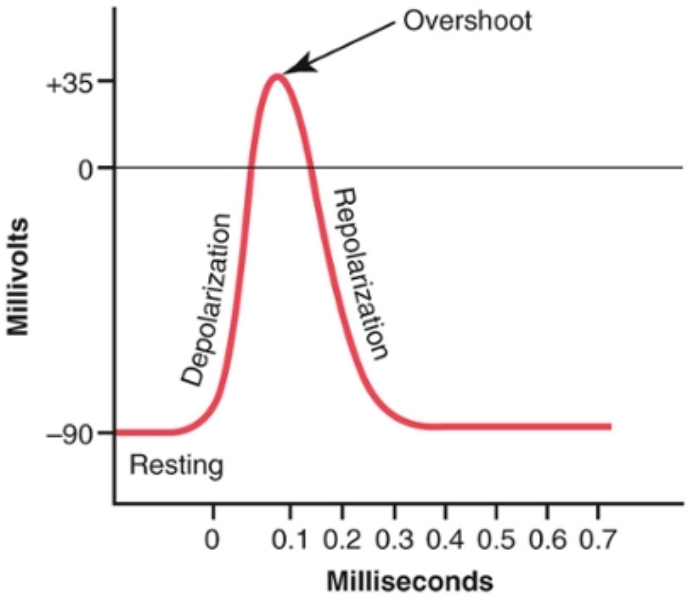
Voltage-gated channels are not usually present in the dendrites or the soma, but are concentrated in the initial segment of the axon (***axon hillock***). Both inhibitory and excitatory postsynaptic potentials are summed in the axon hillock. If the inside of the axon hillock is sufficiently depolarized *(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)*.

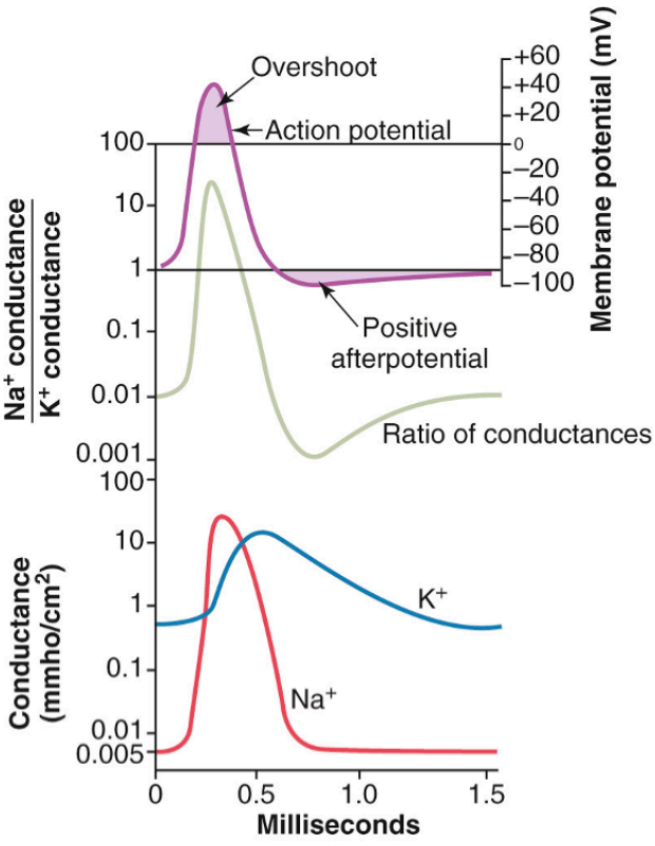
Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to the original resting membrane potential level. Therefore, it is not possible for the sodium channels to open again without first repolarizing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



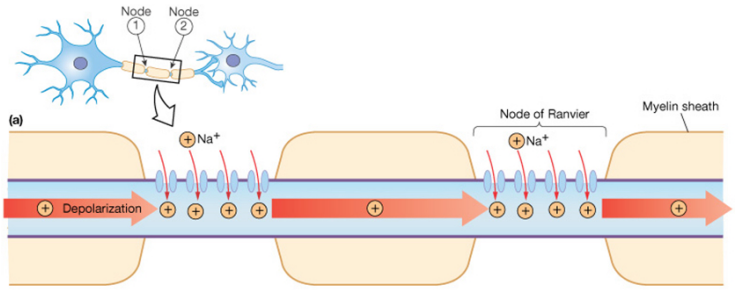
This figure summarizes the events that occur during and after the action potential. The bottom of the figure shows the changes in membrane conductance for Na+ and K+ ions. During the resting state, the conductance for K+ ions is 50–100 times greater than the conductance for Na+ ions. This is due to leakage 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 need 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 downs an axon:

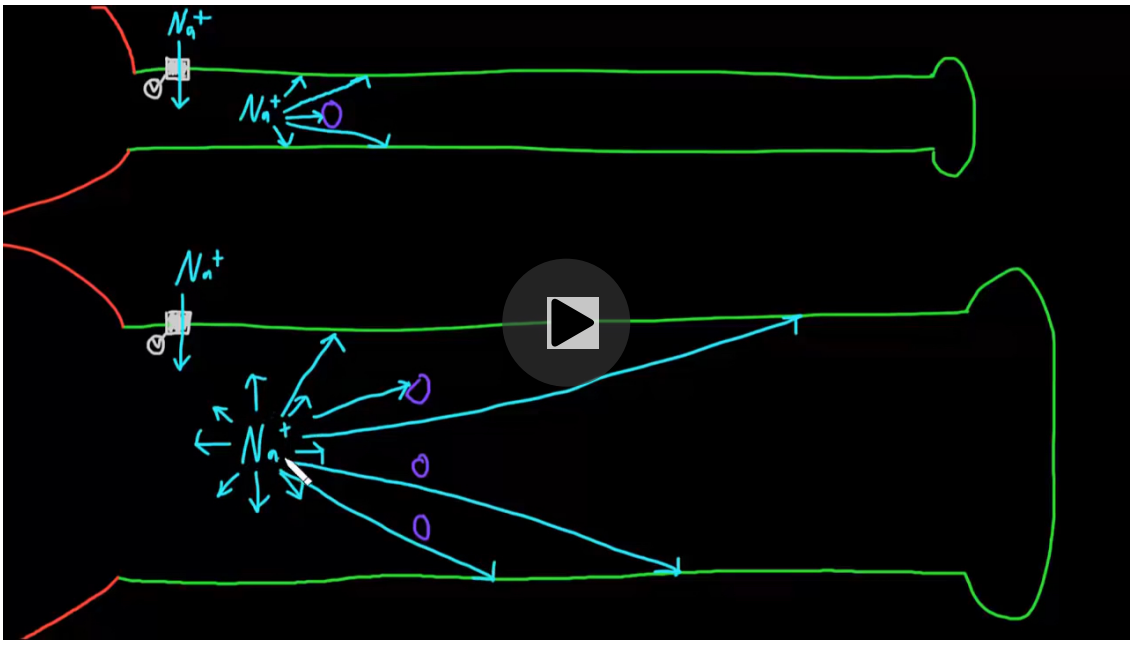
- its diameter
- how heavily myelinated it is

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.

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***.

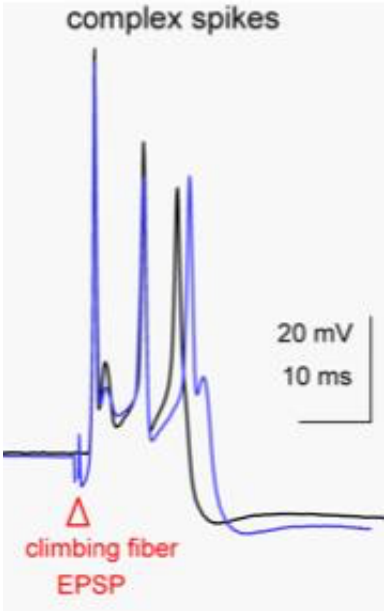


Some Neurons Are Weird

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 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+
- The conductance of Na+ is higher than the conductance of K+

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

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

An unmyelinated axon: *

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

Pitt Medical Neuroscience

Fall 2025

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

A demyelinating disease transforms myelinated axons into unmyelinated axons. In a myelinated axon, action potentials occur only at the nodes of Ranvier, and in unmyelinated axons the action potential needs to be refreshed in each successive patch of membrane. Thus, when an axon is demyelinated, the patches of voltage-gated channels may be spaced too far apart to propagate an action potential.

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+

At the resting membrane potential, there is little conductance of Na+ across the membrane but the conductance of K+ through the leak channels is appreciable. The inactivation gates of the Na+ channels would be open unless an action potential recently occurred.

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

The conductance of K+ is highest when the greatest number of K+ channels is open. During the repolarization phase, both the voltage-gated K+ channels and the leak channels are available to remove K+ from the neuron. At the end of the hyperpolarization, some of the voltage-gated K+ channels have already closed, decreasing K+ conductance.

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

Unmyelinated axons are small in diameter, and have slow conduction velocities. The propagation of action potentials is not saltatory, as the action potential has to be renewed in each successive patch of membrane. As a result, a high level of activity of the sodium-potassioum pump is needed to restore ionic balance after an action potential moves down the axon, making the process energetically inefficient.

Return to: Action Potentials Module

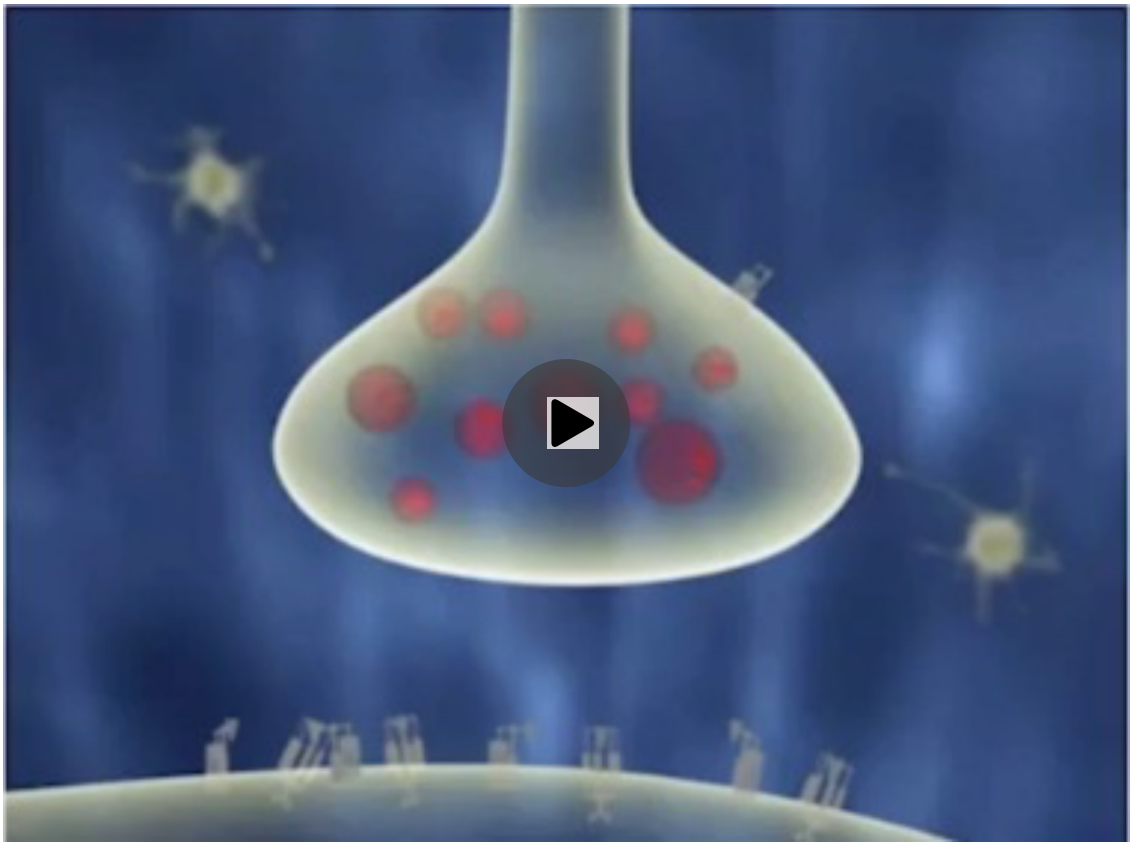
Next module: Synaptic Transmission

Neurophysiology Module 4

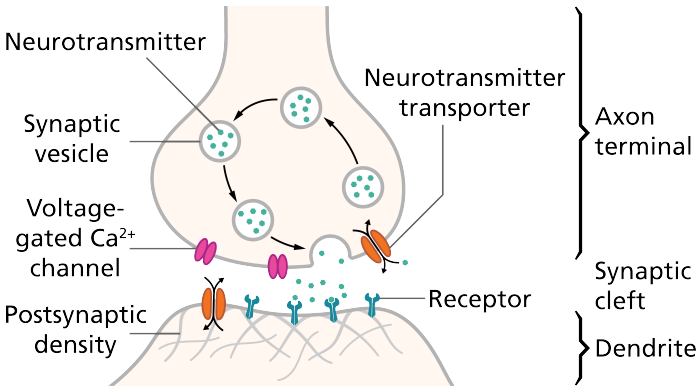
Synaptic Transmission

Introduction

As an introduction, watch this movie.
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***.



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 Ca2+ channels are opened, allowing Ca2+ 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:

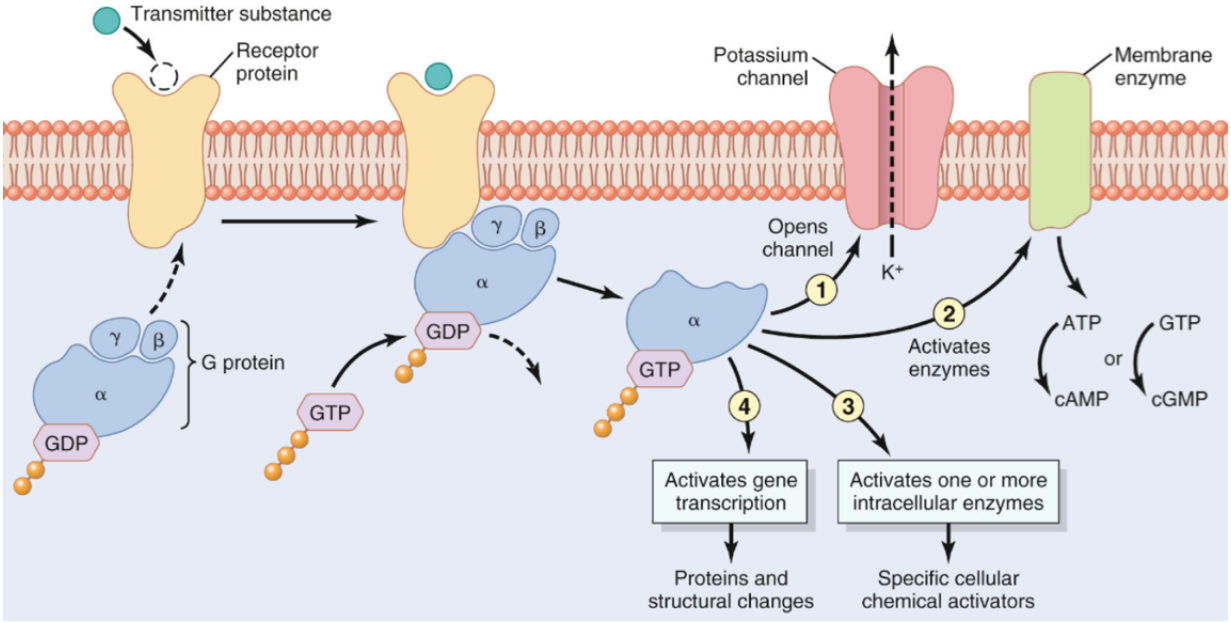
- Chemically degrading the neurotransmitter with an enzyme
- Reuptaking it into the presynaptic neuron

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

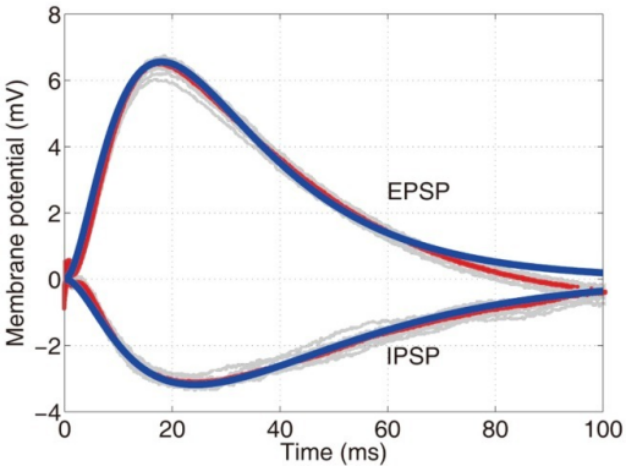
Although neurotransmitters can elicit a number of complex changes in the postsynaptic neuron, often these effects are categorized as excitatory or inhibitory. After all, the key aspect of neuronal signaling is the generation of action potentials, so it is logical to divide neurotransmitter effects into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

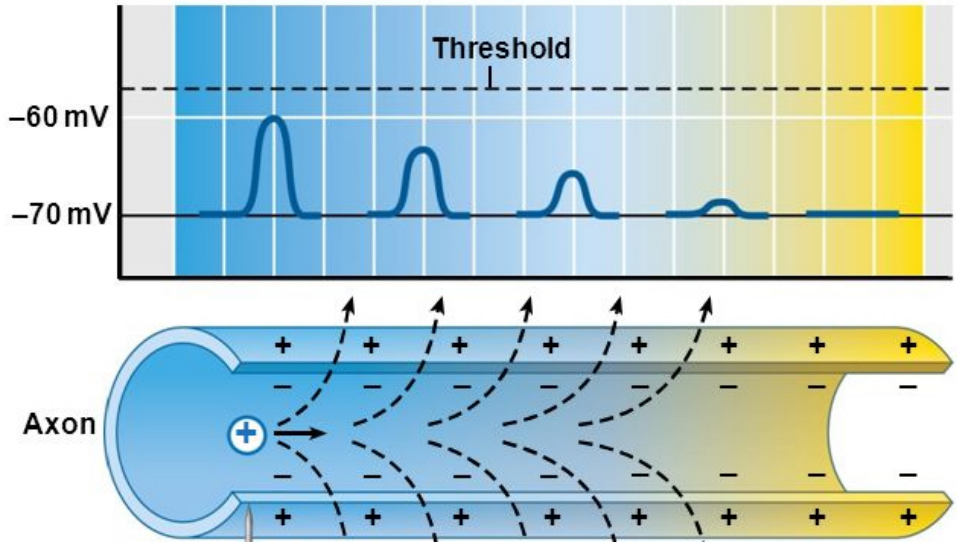


Excitatory postsynaptic potentials (EPSPs) occur when positive ions enter the neuron or negative ions leave. In most cases, the EPSP is a result of opening of cation channels that allow both Na+ and K+ to pass across the membrane. However, the conductance for Na+ usually predominates, such that a depolarization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

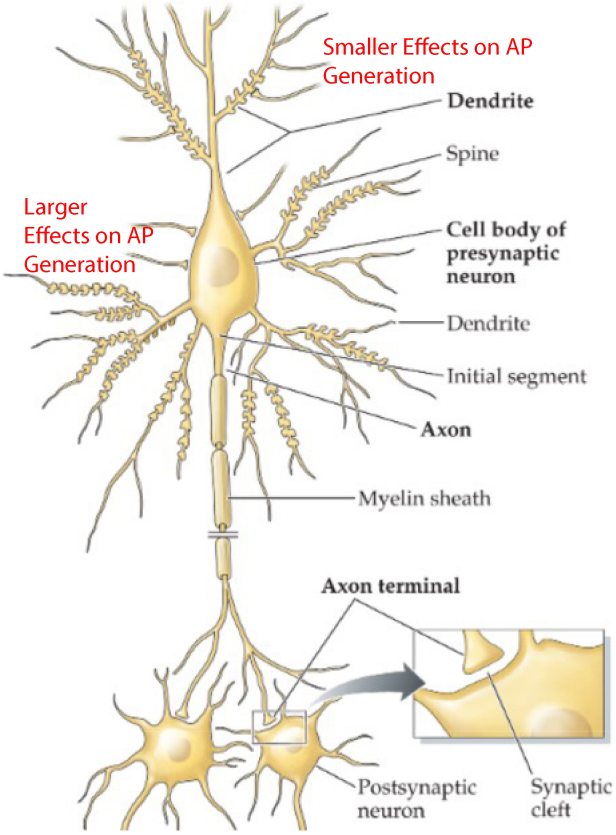
Inhibitory postsynaptic potentials (IPSPs) occur when negative ions (such as Cl-) enter the neuron or positive ions leave.

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 that 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.

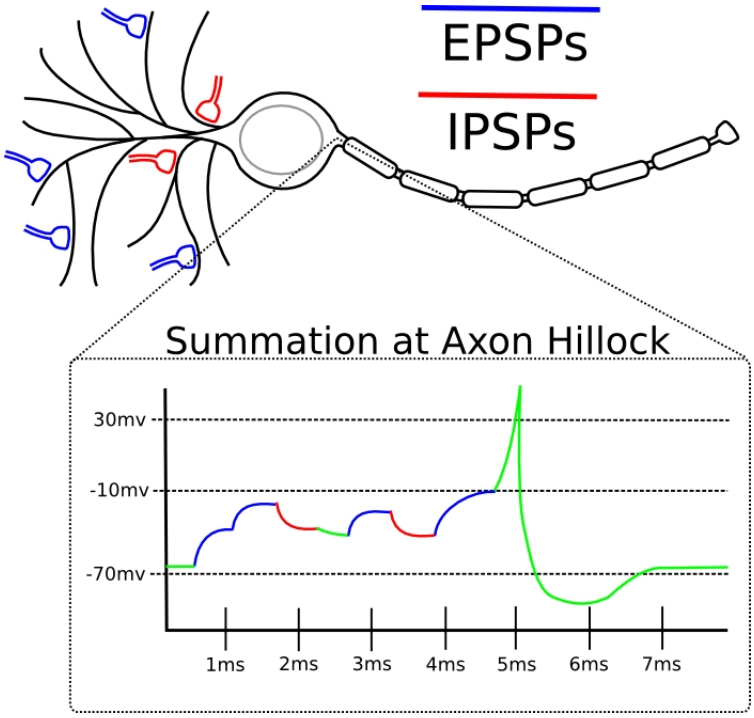
WHAT DO I NEED TO KNOW?



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.



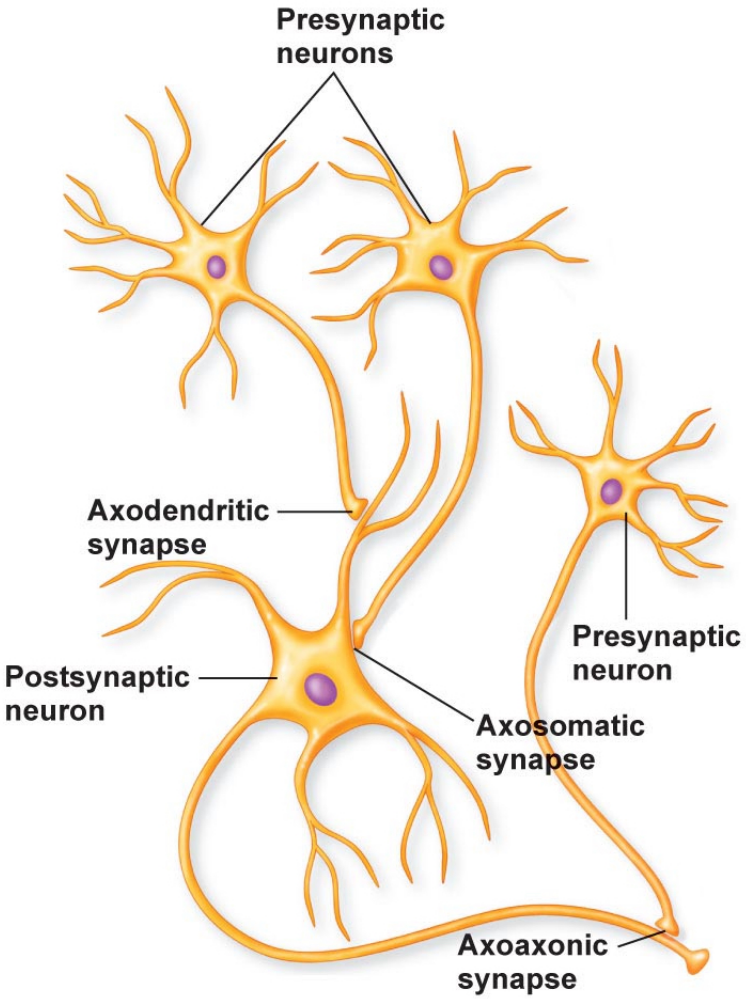
In other words, ions entering (or leaving) at a synapse on a distal dendrite will have little impact on the change in membrane potential at the axon hillock, and thus won't play very much of a role in determining whether the neuron will produce an action potential. In contrast, ions entering or leaving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

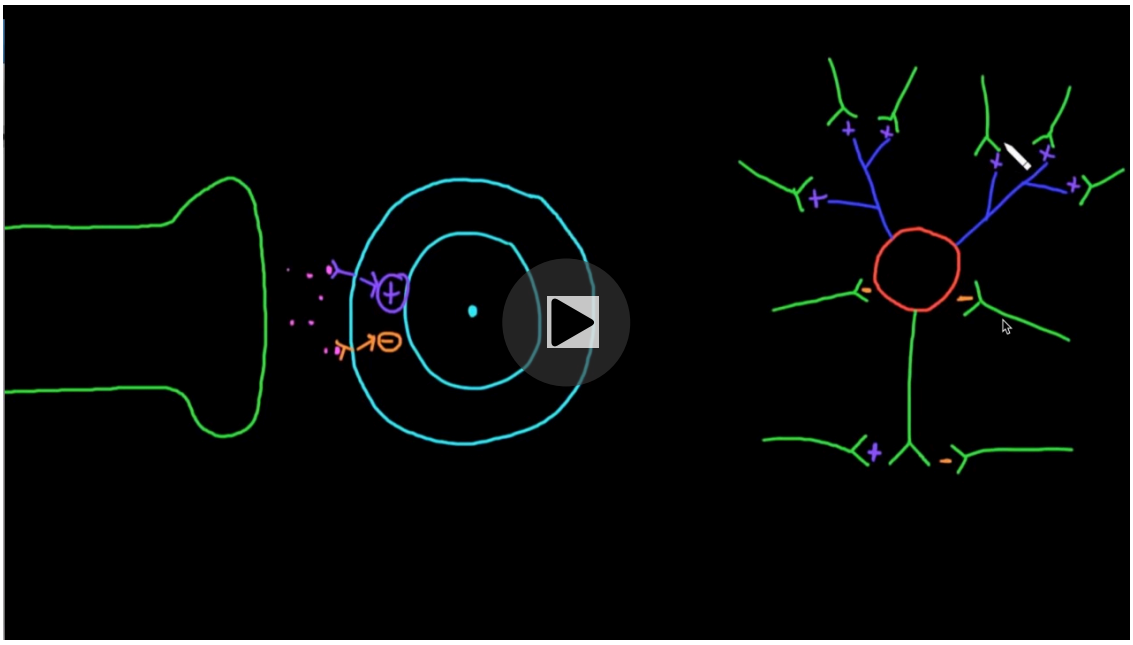


What is the function of an axoaxonic synapse? One common role of such synapses is producing **presynaptic inhibition**. The axoaxonic synapse can activate a second messenger system that affects the voltage-gated Ca2+ channels at the nerve terminal, so they allow less Ca2+ to enter the nerve terminal 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)*.

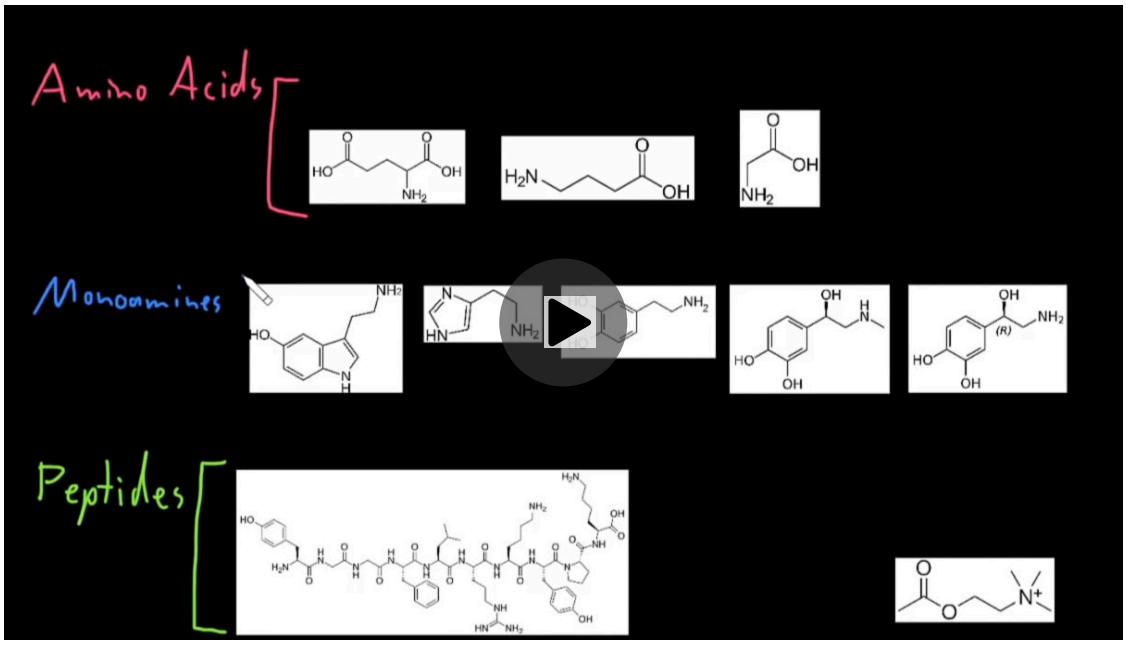
Another group of important neurotransmitters are the ***monoamines***, chemicals that contain one amino group that is connected to an aromatic ring by a two-carbon chain (-CH2-CH2-). The monoamine neurotransmitters include ***dopamine***, ***norepinephrine***, and ***serotonin***. Monoamine neurotransmitters 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
- Are found on the soma and dendrites of a neuron, but never the axon
- Can be found on the nerve terminal that releases the neurotransmitter
- Always open an ion channel after the ligand binds

Inhibitory neurotransmitters: *

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

EPSPs: *

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

Glutamate: *

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

Pitt Medical Neuroscience

Fall 2025

Synaptic Transmission: Self Assessment Questions

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

After a ligand binds to a neurotransmitter receptor, either a second messenger system (like a G protein) can be activated OR an ion channel can be opened. The receptors can be found on the soma, dendrites OR axon. They can also be found on the nerve terminal that releases the neurotransmitter; such receptors are called autoreceptors.

Inhibitory neurotransmitters:

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

The most common inhibitory neurotransmitters are amino acids, such as GABA and glycine. Inhibitory neurotransmitters would never open a Na+ channel, as this would result in depolarization of a neuron (and excitation). Virtually all sensory afferent fibers release an excitatory neurotransmitter (particularly glutamate), and not inhibitory neurotransmitters. However, inhibitory neurotransmitters may open a Cl- channel, which would cause a hyperpolarization of the neuron.

EPSPs:

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

EPSPs could not result from Cl- entry into a neuron; this would cause an IPSP. EPSPs become attenuated in amplitude as they propagate down the membrane; only action potentials are "all or nothing" in amplitude. EPSPs can be elicited in either the soma or dendrites.

Glutamate:

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

Glutamate is an excitatory amino acid neurotransmitter. It is released from many CNS neurons and sensory afferents, but NOT motoneurons (which release acetylcholine). It could not open Cl- channels, as this would hyperpolarize the neuronal membrane.

Return to Synaptic Transmission Module

Next Module: Glutamate Receptors

Neurophysiology Module 5

Glutamate Receptors

Introduction

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

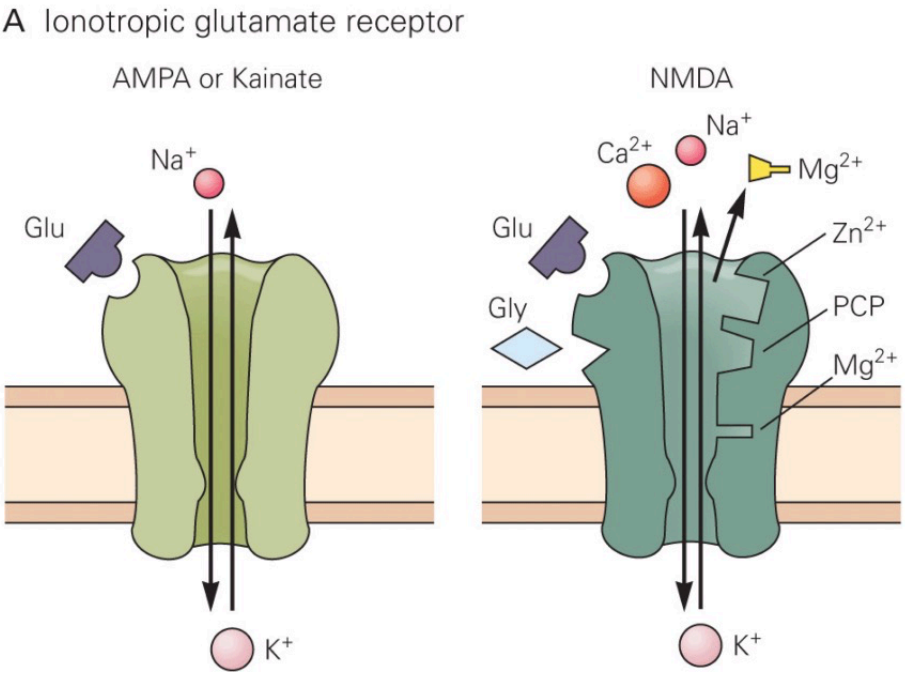
Glutamate is released by normal synaptic mechanisms described in the ***synaptic transmission module***, and removed from the synaptic cleft by ***glutamate transporters*** on the presynaptic nerve terminal.

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

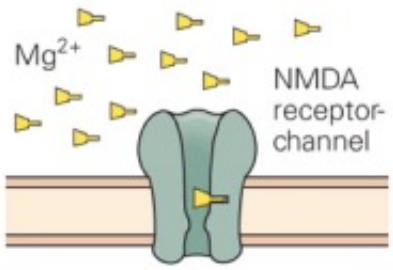


There are three subtypes of ionotropic glutamate receptors:

- 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***.

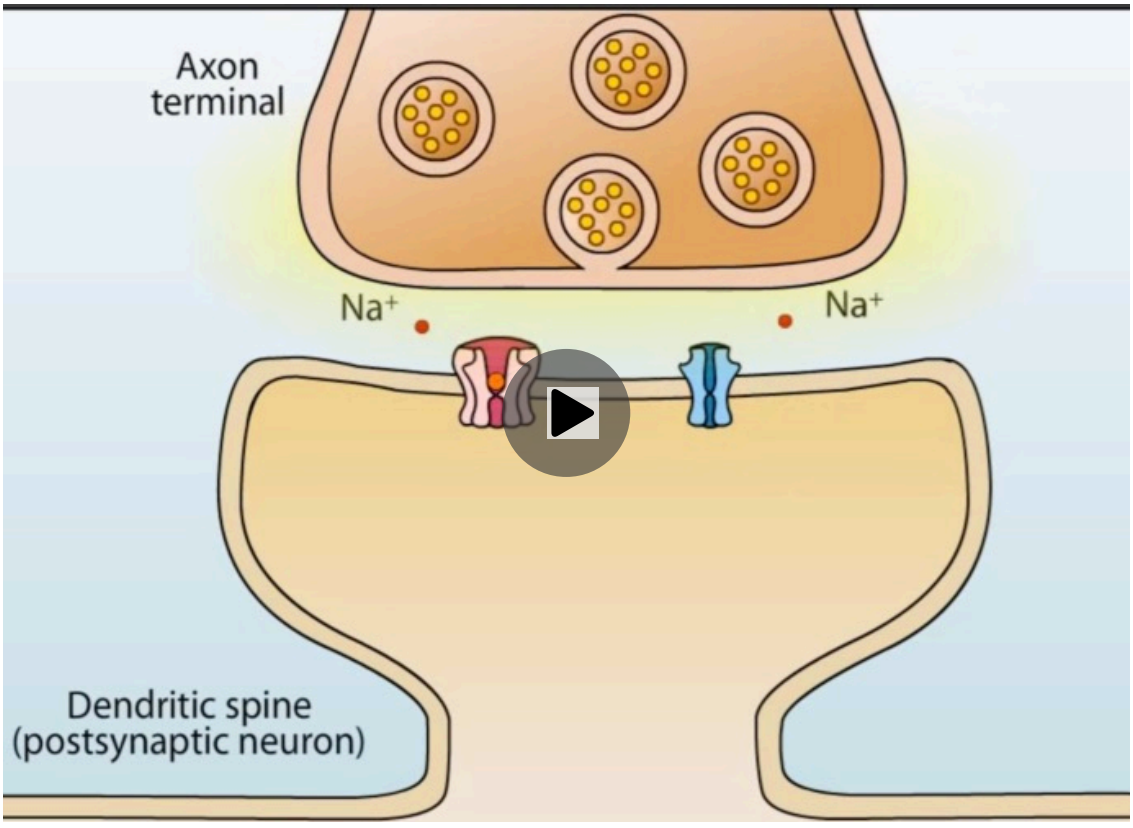
When the NMDA receptor channel is opened (by the combined binding of glutamate to the receptor and depolarization of the membrane), both Na+ and Ca2+ enter the neuron. The entering Ca2+ can activate

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 neurons.

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

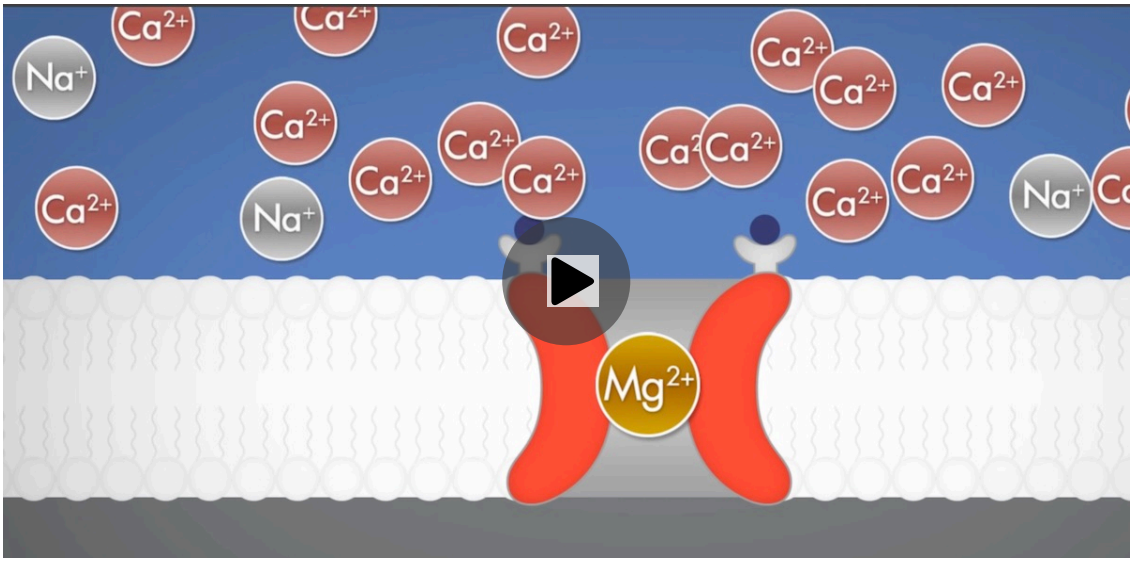


Long-Term Potentiation (LTP)

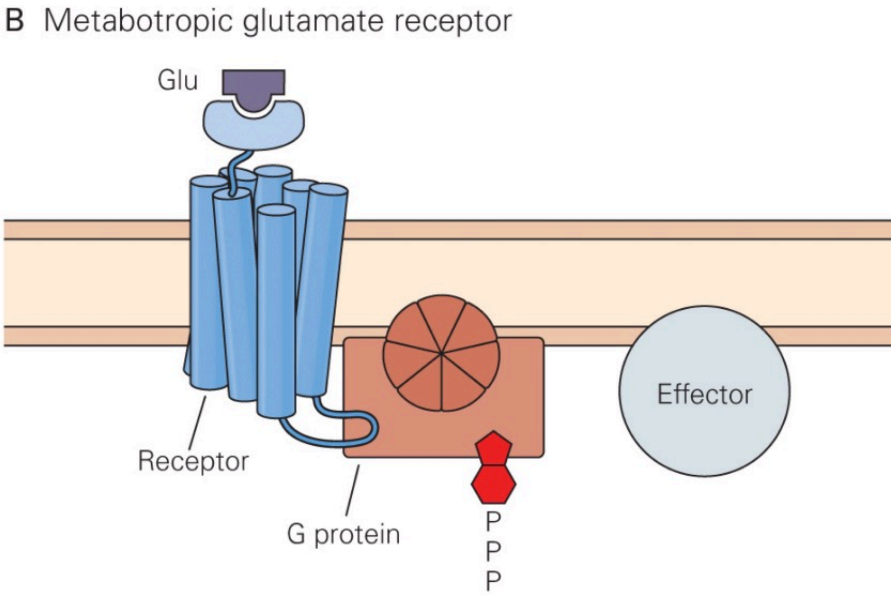
Long-term potentiation is persistent strengthening of synapses based on recent patterns of activity, and is believed to be an important component of learning and memory. NMDA receptors play a key role in generating long-term potentiation in many regions of the nervous system. As noted above, Ca2+ entering 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 synpatic inputs, and consequently how much Ca2+ enters through the NMDA receptor channel. If synaptic inputs are frequent and intracellular Ca2+ is high, then long-term potentiation occurs. If synaptic inputs are infrequent and intracellular Ca2+ is low, long-term depression will occur.

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



Metabotropic Glutamate Receptors



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

Kainate receptors: *

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

Metabotropic glutamate receptors: *

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

Long term potentiation: *

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

Pitt Medical Neuroscience

Fall 2025

-

Glutamate Receptors: Self Assessment Questions

When glutamate binds to an NMDA receptor:

- 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
- An EPSP always occurs

The NMDA receptor allows both Na+ and Ca2+ ions to enter a neuron, but the receptor channel only opens if the membrane is depolarized when glutamate binds to the receptor. The entry of Na+ will produce an EPSP.

Kainate receptors:

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

Binding of glutamate to a kainate receptor opens a cation channel that allows Na+ to enter and K+ to leave the neuron. Usually kainate receptors are postsynaptic, and are always ionotropic receptors.

Metabotropic glutamate receptors:

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

Metabotropic glutamate receptors can be located on the edge of a dendritic spine postsynaptially (away from the other receptors) or on the presynaptic teminal. Binding of glutamate to the receptors activates a second messenger system.

Long term potentiation:

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

Long term potentiation occurs when substantial amounts of Ca2+ enter a neuron through an NMDA receptor. For this to occur, the presynaptic terminal must release a considerable amount of glutamate, to cause AMPA receptors to depolarize the postsynaptic membrane. Thus, blocking AMPA receptors would not allow an adequate depolarization to occur to provide for opening on NMDA receptors.

Return to Glutamate Receptor Module

Next Module: Cholinergic Receptors

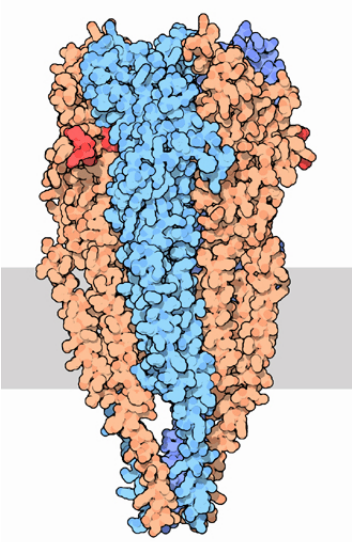
Neurophysiology Module 6

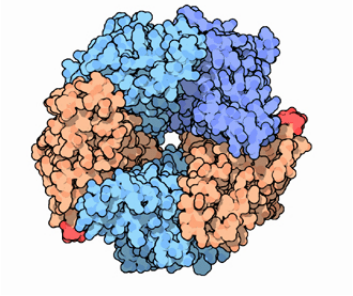
Cholinergic Receptors

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	***Suxamethonium chloride*** *(succinylcholine)*	***Pancuronium bromide***
Ganglion Type	***Dimethylphenylpiperazinium***	***Trimetaphan***

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 Ca2+ 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).

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? *

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

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

- 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
- The membrane is hyperpolarized

Muscarinic receptors are located in: *

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

Pitt Medical Neuroscience

Fall 2025

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

Both nicotinic and muscarinic receptors are present in the central and peripheral nervous system. There are many subtypes of nicotinic receptors, with distinct types in the neuromuscular junction and autonomic ganglia. However, most peripheral tissues contain multiple subtypes of muscarinic receptors, each associated with distinct postsynaptic signaling pathways.

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

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

Nicotinic receptors are ionotropic; binding of acetylcholine to the receptor opens an in channel that allows Na+ and K+ to move across the membrane. The entry of Na+ predominates, so an EPSP occurs in the postsynaptic neuron.

Muscarinic receptors are located in:

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

Muscarinic receptors are located in peripheral targets innervated by parasympathetic postganglionic neurons, and some sympathetic postganglionic fibers. One of the sympathetic targets with cholinergic innervation is sweat glands.

Return to Cholinergic Receptors Module

Next Module:Neuromuscular Junction

Neurophysiology Module 7

Neuromuscular Junction

Introduction

The neuromuscular junction is a specialized peripheral cholinergic synapse that provides communication between a motoneuron and a skeletal muscle fiber. Due to its unique structural and functional properties, this synapse is particularly susceptible to a range of pathological conditions, which are outlined in the sections below. Additionally, synaptic transmission at the neuromuscular junction can be influenced by a range of pharmacological agents that exert paralytic effects.

Paralytic Drugs: Nondepolarizing and Depolarizing Muscle Relaxants

Paralytic drugs, also known as muscle relaxants, are commonly used in clinical settings to induce muscle relaxation during surgical procedures and facilitate intubation. These drugs are divided into two major classes: nondepolarizing agents and depolarizing agents.

Nondepolarizing Paralytic Drugs

Nondepolarizing agents work by competitively inhibiting the binding of acetylcholine (ACh) to nicotinic receptors at the neuromuscular junction. By blocking ACh from binding, these agents prevent the depolarization of the muscle cell membrane, thereby inhibiting muscle contraction. Commonly used nondepolarizing agents include:

- Pancuronium
- Vecuronium
- Rocuronium
- Atracurium

These drugs generally have a longer duration of action compared to depolarizing agents and are often used for procedures that require extended muscle relaxation. The effects of nondepolarizing agents can be reversed using acetylcholinesterase inhibitors, such as neostigmine or edrophonium. These inhibitors increase the concentration of ACh at the neuromuscular junction, allowing it to outcompete the nondepolarizing agents and restore muscle function.

Depolarizing Paralytic Drugs

In contrast, depolarizing paralytic drugs such as succinylcholine act as agonists for nicotinic receptors. They initially bind to these receptors, causing an initial depolarization and muscle contraction. However, continued exposure leads to desensitization of the receptors and a sustained depolarized state.

Drugs such as succinylcholine act in two phases:

- *Phase 1 (Depolarization):* Succinylcholine binds to nicotinic receptors, causing them to open and allow sodium ions to enter the muscle cell. This results in an initial muscle contraction.
- *Phase 2 (Desensitization):* The postsynaptic membrane does not fully repolarize because the nicotinic receptor remains open, leading to a prolonged influx of sodium ions. As a result, the inactivation gates of voltage-gated sodium channels remain closed, preventing further action potentials and leading to muscle paralysis.

Succinylcholine has a rapid onset and a short half-life, resulting in a brief duration of action. This makes it ideal for procedures that require quick muscle relaxation, such as rapid sequence intubation. However, unlike nondepolarizing agents, the effects of depolarizing agents are not easily reversed, and their use can be associated with certain complications, such as hyperkalemia (due to continued potassium efflux from muscle fibers) or malignant hyperthermia in susceptible individuals.

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors lead to an accumulation of acetylcholine at synapses, which can result in effects similar to those of depolarizing paralytics, as the excess acetylcholine continuously activates nicotinic receptors at the neuromuscular junction.

In addition to causing muscle paralysis at the neuromuscular junction, acetylcholinesterase inhibitors lead to an accumulation of acetylcholine at muscarinic synapses, which overstimulates the parasympathetic nervous system. This overstimulation can result in symptoms such as bradycardia, bronchoconstriction, excessive salivation, and gastrointestinal disturbances.

Some pesticides commonly used in agriculture, such as organophosphates and carbamates, function as acetylcholinesterase inhibitors. These compounds can cause muscle paralysis and excessive stimulation of muscarinic receptors, leading to toxic effects in both humans and animals.

Highly toxic organophosphate nerve agents such as Sarin have been weaponized for military purposes. Sarin is considered a weapon of mass destruction and its production and stockpiling are banned under the Chemical Weapons Convention due to its potency and potential for mass casualties.

Clinical Management of Acetylcholinesterase Inhibitor Toxicity

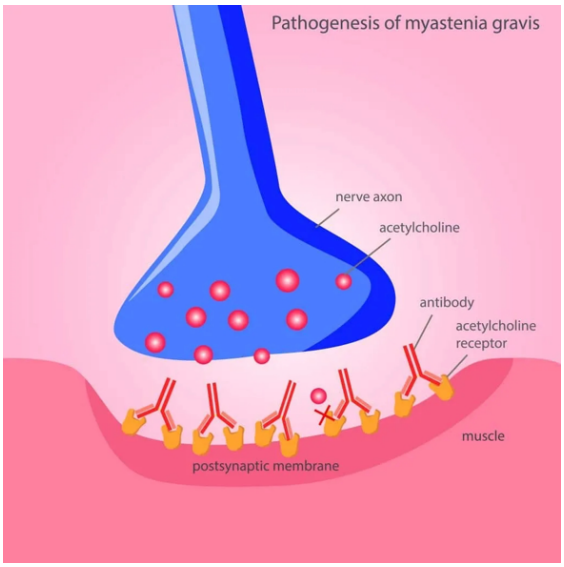
Patients experiencing toxicity from acetylcholinesterase inhibitors can be treated with:

- Atropine, which competes with acetylcholine for muscarinic receptors, reducing the effects of excess acetylcholine on the parasympathetic nervous system.

- Pralidoxime (2-PAM), which reactivates acetylcholinesterase by cleaving the bond between the enzyme and the organophosphate, restoring normal enzyme function.

Common Neuromuscular Diseases

Myasthenia Gravis



Myasthenia Gravis (MG) is an autoimmune neuromuscular disorder characterized by a type II hypersensitivity reaction. This condition results in the production of autoantibodies against acetylcholine (ACh) receptors at the neuromuscular junction, leading to impaired synaptic transmission and muscle weakness.

The pathogenesis of MG involves two main mechanisms:

1. *Antibody-Mediated Receptor Blockade*: Autoantibodies directly block ACh receptors, preventing acetylcholine binding and subsequent muscle activation.
2. *Complement-Mediated Damage*: The binding of antibodies triggers the complement cascade, leading to the destruction of the postsynaptic membrane and further reduction in the number of functional ACh receptors.

The hallmark of MG is fluctuating muscle weakness that worsens with activity and improves with rest. This is due to the decreased number of functional ACh receptors and the depletion of acetylcholine in the presynaptic cleft over time.

- *Ocular Symptoms*: Extraocular muscle weakness often manifests as ptosis and diplopia, as ocular muscles are in constant use and have a lower density of ACh receptors.
- *Brainstem Symptoms*: Patients may experience difficulty chewing, dysphagia, and dysarthria due to the involvement of bulbar muscles.
- *Limb Weakness*: Proximal limb weakness is common, affecting the muscles of the shoulders and hips, and may present as difficulty in performing tasks such as climbing stairs or lifting objects.
- *Generalized Weakness*: In severe cases, generalized muscle weakness can affect respiratory muscles, leading to respiratory insufficiency and crisis.

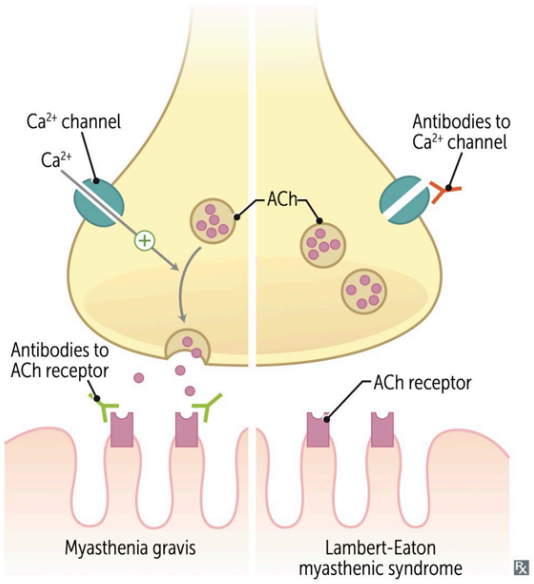
Symptoms of Myasthenia Gravis typically worsen with sustained muscle use and progress throughout the day. This phenomenon, known as fatigability, occurs as the presynaptic supply of acetylcholine becomes insufficient to compete with the receptor-blocking antibodies, leading to a decrease in muscle response.

Diagnosing Myasthenia Gravis involves clinical evaluation, serological testing (for presence of antibodies against the ACh receptor), and electrophysiological studies (MG patients shows a decremental response in muscle action potentials with repetitive stimulation).

Treatments for MG include:

- Long-acting Acetylcholinesterase Inhibitors such as Pyridostigmine (Mestinon)
- Immunosuppressive Therapies, including corticosteroids and non-steroidal Immunosuppressants like azathioprine and mycophenolate mofetil
- Plasmapheresis
- Intravenous Immunoglobulin
- Monoclonal Antibodies, including Rituximab (Rituxan) and Eculizumab (Soliris)
- Thymectomy: Approximately 10% of MG patients have a thymoma, and thymectomy is recommended for these individuals to remove the tumor and alleviate symptoms. Even for those without a thymoma, thymectomy can be beneficial. Studies have shown that removing the thymus can reduce the severity of MG symptoms, decrease the need for immunosuppressive medications, and improve overall outcomes by modulating the immune response.

Lambert-Eaton Myasthenic Syndrome



Lambert-Eaton Myasthenic Syndrome (LEMS) is a rare disorder that affects neuromuscular junction transmission, primarily manifesting as muscle weakness. This condition is characterized by the presence of antibodies directed against the presynaptic voltage-gated calcium channels (VGCCs) on motoneuron terminals. These antibodies disrupt the normal calcium flux necessary for the release of acetylcholine.

There are two main types of LEMS: paraneoplastic and non-paraneoplastic. Paraneoplastic LEMS is the more common form and is often associated with small cell lung cancer (SCLC). In this type, the expression of functional VGCCs on the surface membrane of SCLC cells, along with numerous other neural antigens, is believed to be responsible for most, if not all, cases. This connection makes LEMS an important paraneoplastic syndrome to consider in patients with suspected or known malignancies.

In contrast, non-paraneoplastic LEMS occurs without an associated malignancy, and the specific trigger for the development of VGCC antibodies in these cases remains unknown. The clinical presentation of LEMS differs from Myasthenia Gravis (MG) in several ways. Initial limb weakness is more common in LEMS, while extraocular muscle weakness, a hallmark of MG, is less frequently observed.

Treatment for LEMS differs from that of MG. Acetylcholinesterase inhibitors, commonly used in MG, are only marginally effective for LEMS. The primary treatment for LEMS is Amifampridine (3,4-diaminopyridine). Aminopyridines like Amifampridine are beneficial because they block potassium channels, significantly prolonging the depolarization of the presynaptic nerve terminal membrane. This action enhances calcium entry, thereby improving the release of acetylcholine and alleviating muscle weakness.

This table from First Aid compares the characteristics of MG and LEMS:

Neuromuscular junction diseases

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome
FREQUENCY	Most common NMJ disorder	Uncommon
PATHOPHYSIOLOGY	Autoantibodies to postsynaptic ACh receptor	Autoantibodies to presynaptic Ca^{2+} channel → ↓ ACh release; L comes before M
CLINICAL	Fatigable muscle weakness—ptosis; diplopia; proximal weakness; respiratory muscle involvement → dyspnea; bulbar muscle involvement → dysphagia, difficulty chewing Spared reflexes Worsens with muscle use	Proximal muscle weakness, autonomic symptoms (dry mouth, constipation, impotence) Hyporeflexia Improves with muscle use
ASSOCIATED WITH	Thymoma, thymic hyperplasia	Small cell lung cancer
AChE INHIBITOR ADMINISTRATION	Reverses symptoms (pyridostigmine for treatment)	Minimal effect

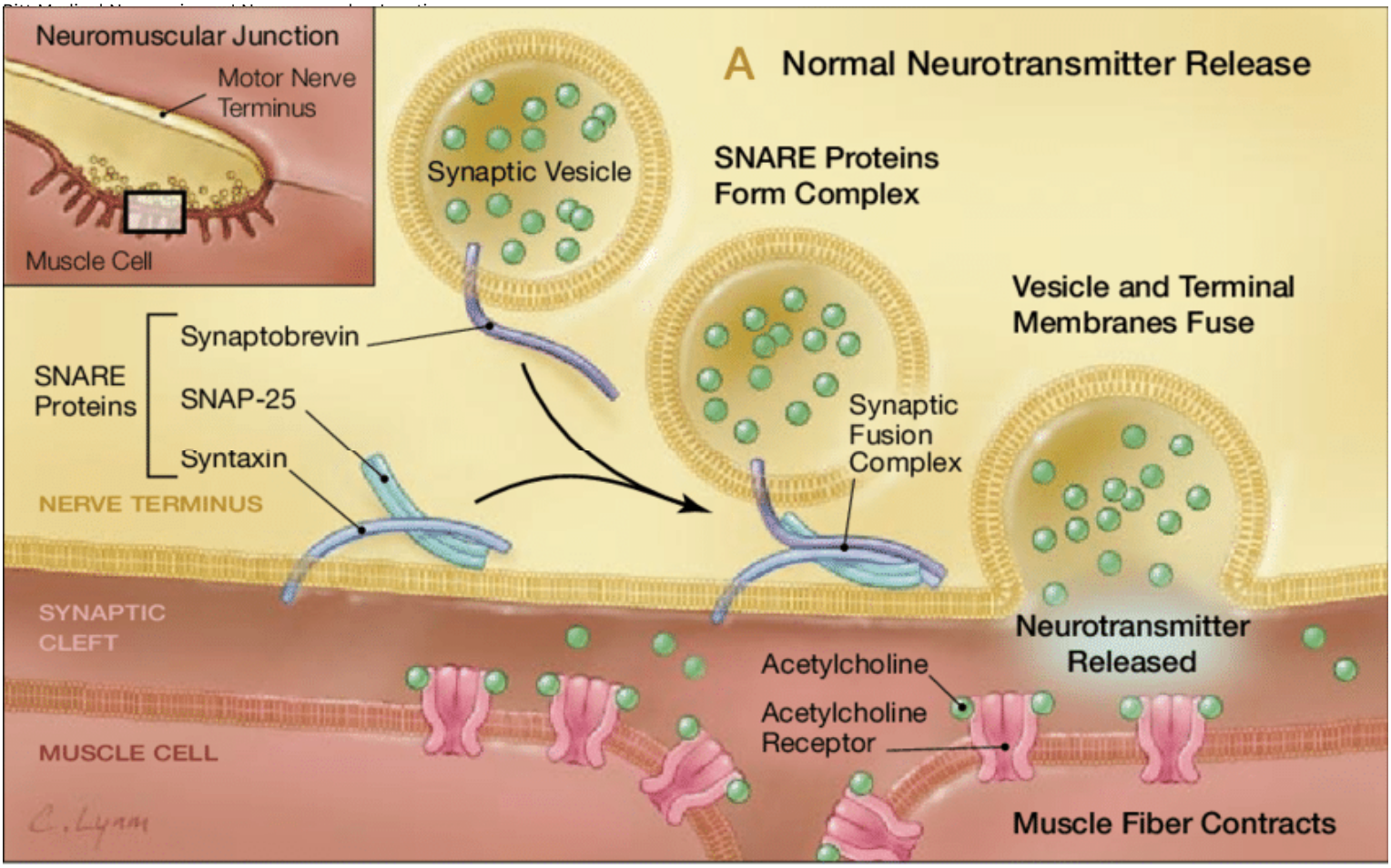
This outline provides a synopsis regarding neuromuscular junction disorders.

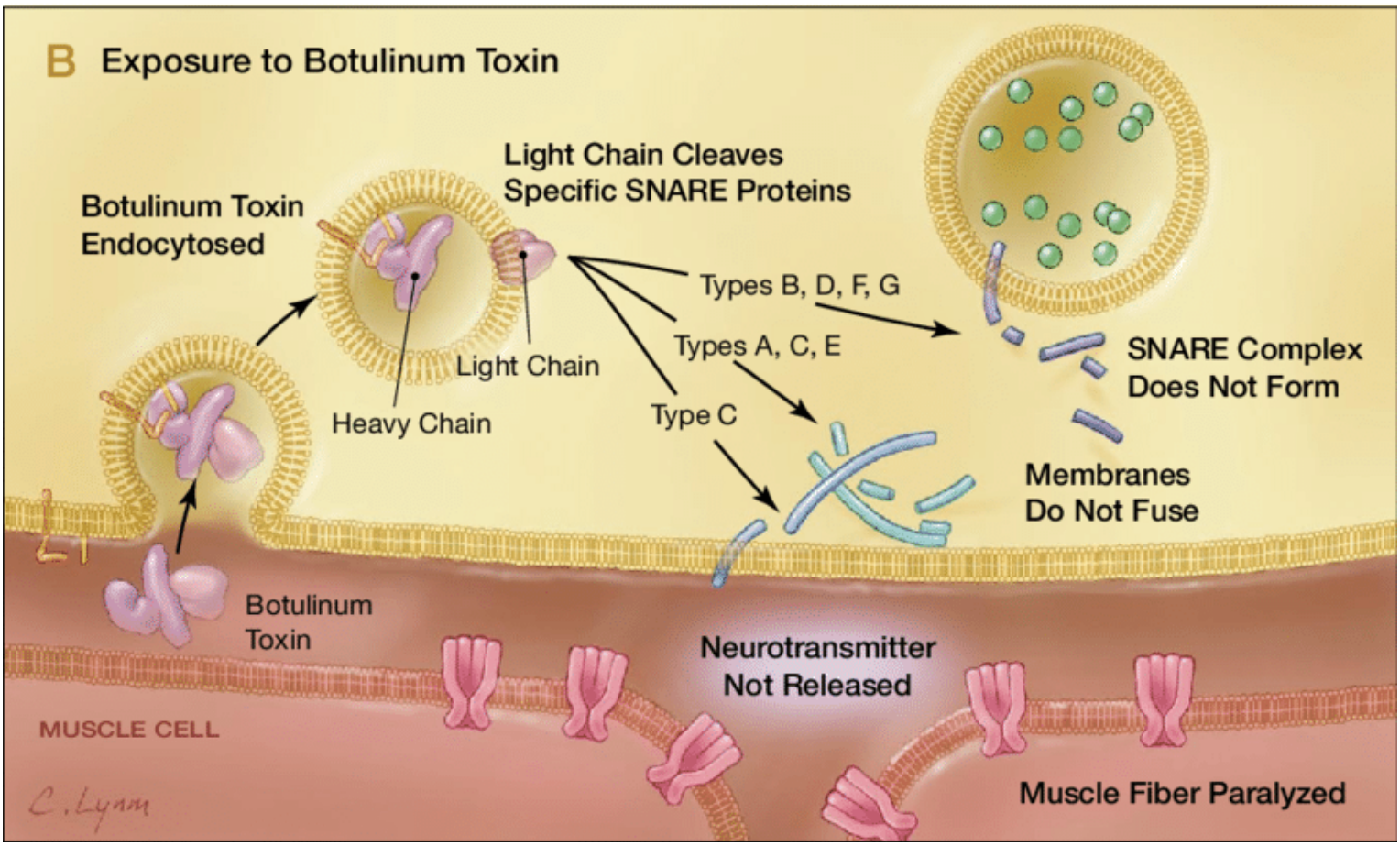
Neuromuscular Junction Toxins - Botulism

Organisms of the *Clostridium* genus, such as *C. botulinum*, *C. baratii*, and *C. butyricum*, are commonly found in soil. These organisms are gram-positive, anaerobic, spore-forming rods that evolved to produce potent neurotoxins. These neurotoxins are responsible for the clinical condition known as botulism, with approximately 200 cases reported annually in the United States.

In 2019, the distribution of botulism cases was as follows: approximately 70% were infant botulism (mainly from consuming contaminated food), 20% were wound botulism, 10% were food-borne botulism, and the remaining 1% were other types.

Botulinum toxin exerts its effects by targeting and cleaving key proteins required for neurotransmitter release at the neuromuscular junction, specifically the SNARE proteins. These proteins mediate vesicle fusion with their target membrane-bound compartments. When the botulinum toxin cleaves SNARE proteins, acetylcholine vesicles are unable to bind to the intracellular cell membrane. This prevents the release of neurotransmitter vesicles.


Neuromuscular Junction
Motor Nerve Terminus
Muscle Cell
A Normal Neurotransmitter Release
Synaptic Vesicle
SNARE Proteins Form Complex
Vesicle and Terminal Membranes Fuse
SNARE Proteins
Synaptobrevin
SNAP-25
Syntaxin
Synaptic Fusion Complex
NERVE TERMINUS
SYNAPTIC CLEFT
Neurotransmitter Released
Acetylcholine
Acetylcholine Receptor
MUSCLE CELL
Muscle Fiber Contracts


B Exposure to Botulinum Toxin
Light Chain Cleaves Specific SNARE Proteins
Botulinum Toxin Endocytosed
Types B, D, F, G
Types A, C, E
Type C
Light Chain
Heavy Chain
SNARE Complex Does Not Form
Membranes Do Not Fuse
Botulinum Toxin
Neurotransmitter Not Released
MUSCLE CELL
Muscle Fiber Paralyzed

Assessment: Neuromuscular Junction

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

Sarin gas (chemical formula: C4H10FO2P) is a highly toxic nerve agent that can have severe and potentially lethal effects on the human body when exposure occurs. Sarin inhibits the action of the enzyme acetylcholinesterase. In addition to effects on skeletal muscle, which of the following signs and symptoms might be expected in a patient with Sarin poisoning? *

- Pinpoint or constricted pupils (miosis)
- Dry mouth
- Dry skin and inability to sweat
- Contraction of sphincters

A 60-year old male with small cell lung carcinoma is evaluated with complaints about limb weakness. What is the likely cause of this limb weakness? *

- Autoantibodies against acetylcholine receptors at the neuromuscular junction
- Inhibition of acetylcholinesterase at the neuromuscular junction
- Antibodies directed against the presynaptic voltage-gated calcium channels at the neuromuscular junction
- Cleaving of SNARE proteins in motoneuron terminals

Which of the following drugs can e used to enhance seletal muscle contractions? *

- Botulinum Toxin
- Neostigmine
- Suxamethonium chloride
- Pancuronium Bromide

Pitt Medical Neuroscience

Fall 2025

Neuromuscular Junction: Self Assessment Questions

Sarin gas (chemical formula: C4H10FO2P) is a highly toxic nerve agent that can have severe and potentially lethal effects on the human body when exposure occurs. Sarin inhibits the action of the enzyme acetylcholinesterase. In addition to effects on skeletal muscle, which of the following signs and symptoms might be expected in a patient with Sarin poisoning?

- Dry skin and inability to sweat
- Dry mouth
- Pinpoint or constricted pupils (miosis)
- Contraction of sphincters

By inhibiting the breakdown of acetylcholine, the effects of acetylcholine are enhanced at parasympathetic postganglionic terminals, and sympathetic postganglionic terminals that release acetylcholine (such as at sweat glands). This results in pupillary constriction, which is why option C is correct. However, the individual would experience increased sweating (not decreased), increased salivation, and relaxation of sphincters.

A 60-year old male with small cell lung carcinoma is evaluated with complaints about limb weakness. What is the likely cause of this limb weakness?

- Antibodies directed against the presynaptic voltage-gated calcium channels at the neuromuscular junction
- Autoantibodies against acetylcholine receptors at the neuromuscular junction
- Cleaving of SNARE proteins in motoneuron terminals
- Inhibition of acetylcholnesterase at the neuromuscular junction

The patient likely has Lambert-Eaton Myasthenic Syndrome, which is often associated with small cell lung cancer. The expression of functional voltage-gated calcium channels on the surface of small cell lung cancer cells can trigger the formation of antibodies that target these channels on motoneuron terminals at the neuromuscular junction, resulting in decreased calcium influx and reduced acetylcholine release.

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

- Neostigmine
- Pancuronium Bromide
- Botulinum Toxin
- Suxamethonium Chloride

Neostigmine is a cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the effects of nondepolarizing muscle relaxants. The other drugs would weaken muscle contractions.

Return to Neuromuscular Junction Module

Next Module: Inhibitory Neurotransmitters

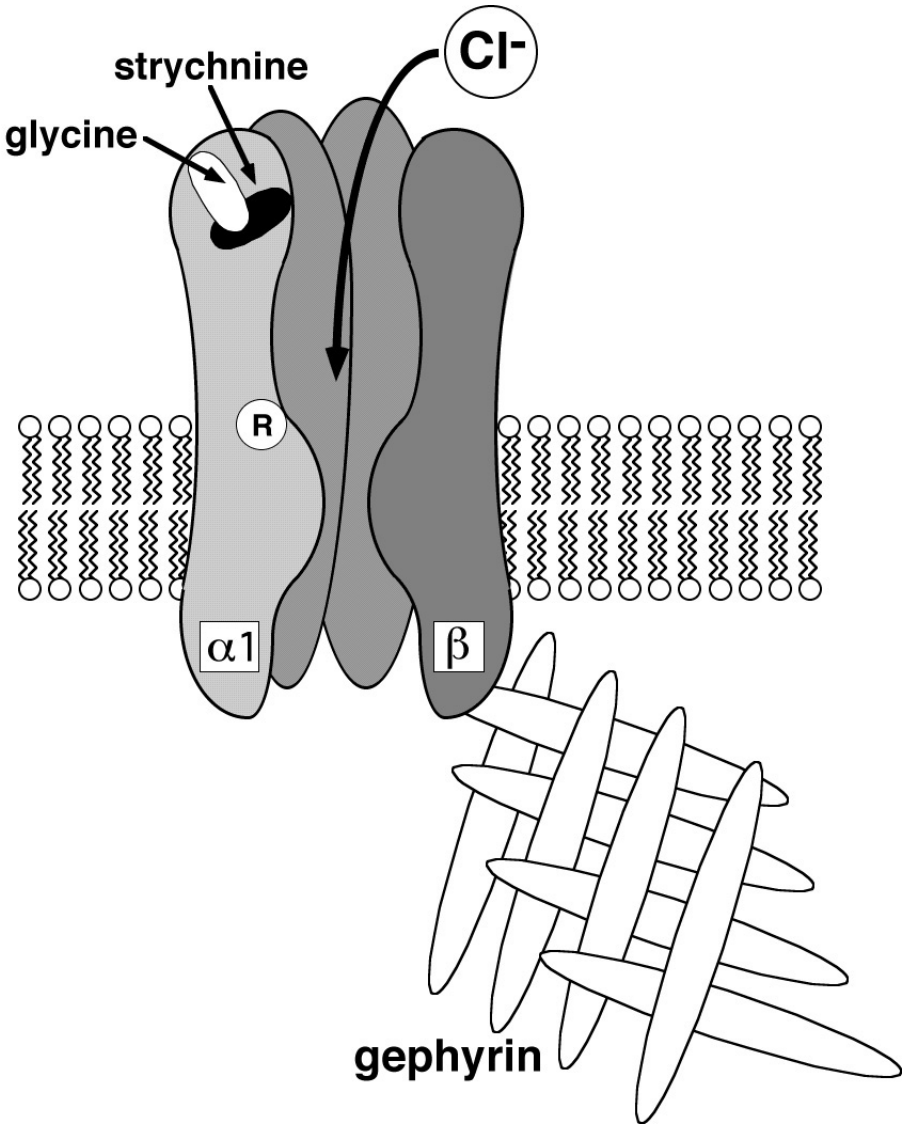
Neurophysiology Module 8

Inhibitory Neurotransmitters

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 ***GABAa receptor subtype***, are also ionotropic receptors. However, a minority of GABA receptors, which belong to the ***GABAb 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.



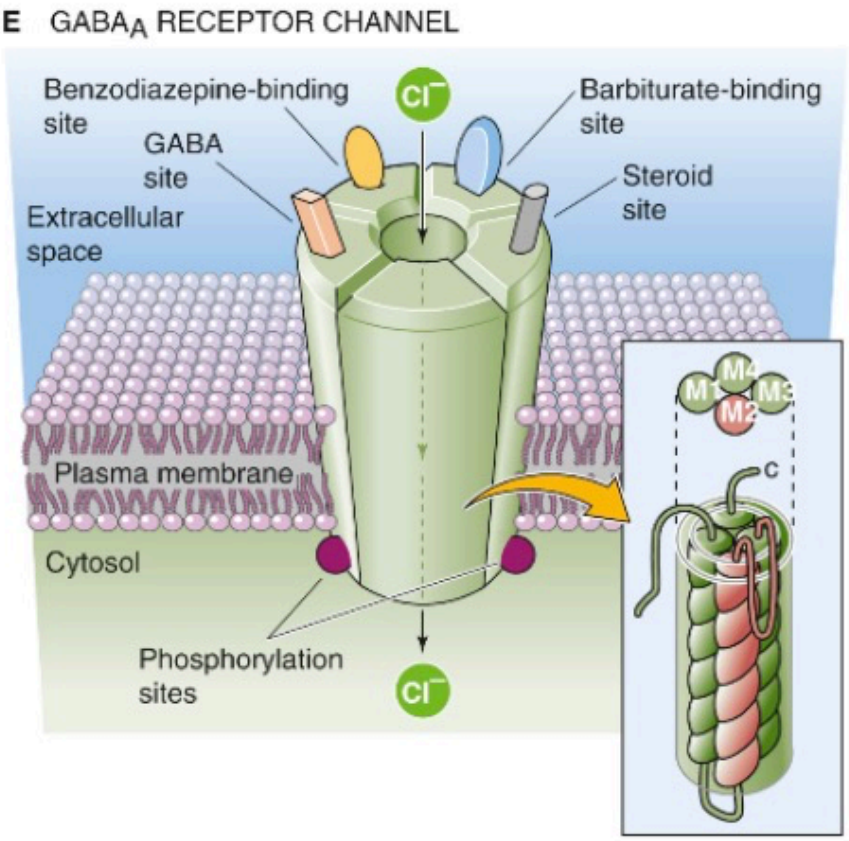
Glycine Receptors

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 GABAa 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.



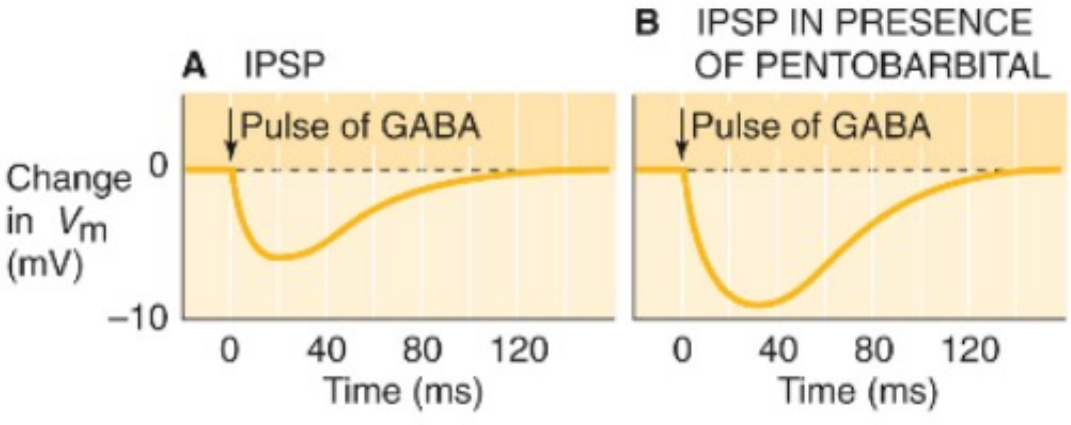
GABAa Receptors

GABAa 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.

GABAa 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 GABAa 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 GABAa 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 this example, the positive allosteric modulator pentobarbital (a barbiturate) results in a larger IPSP when GABA binds to the GABAa receptor.

Some examples of agonists and antagonists of GABAa 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 GABAa receptors)* is only used to reverse the effects of benzodiazepines. The GABAa receptor antagonist bicuculline causes hyperexcitability of neurons, and thus produces seizures. This drug is provided to laboratory animals to mimic epilepsy.

GABAb Receptors

GABA also acts on G protein-coupled ***GABAb receptors***. GABAb ***autoreceptors*** are located presynaptically at GABAergic synapses, and are also located on terminals that release glutamate. Binding of GABA to presynaptic GABAb 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 GABAb receptors are postsynaptic. Binding of GABA to the postsynaptic GABAb 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 GABAb 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 GABAa receptors
- Increase Cl- conductance through GABAa receptors when GABA binds to the receptor
- Bind to GABAb receptors
- Bind to the same site on GABAa receptors as GABA

Which of the following statements about GABAa antagonists is correct? *

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

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

- They can be present on the presynaptic or postsynaptic membrane of the synapse
- All are ionotropic receptors
- All are metabotropic receptors
- 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

Pitt Medical Neuroscience

Fall 2025

Inhibitory Neurotransmitters: Self Assessment Questions

Benzodiazepines:

- Decrease Cl- conductance through GABAa receptors
- Bind to the same site on GABAa receptors as GABA
- Bind to GABAb receptors
- Increase Cl- conductance through GABAa receptors when GABA binds to the receptor

Benzodiazepines are positive allosteric modulators; they bind to the GABAa receptor (at a site other than the GABA binding site) to increase Cl- conductance through the channel.

Which of the following statements about GABAa antagonists is correct?

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

GABAa antagonists inhibit the movement of Cl- into a postsynaptic neuron, making it hyperexcitable. Thus, the drugs induce seizures in animals (and humans when poisoned by the drug).

Which of the following statements about GABA receptors is correct?

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

GABAa receptors are postsynaptic, but GABAb receptors are both presynaptic and postsynaptic. GABAa receptors are ionotropic, but GABAb receptors are metabotropic. GABA receptors are located throughout the central nervous system.

Glycine receptors:

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

Glycine receptors are mainly confined to the brainstem and spinal cord, and are all postsynaptic. Strychnine is a glycine antagonist, and when it binds to the receptor Cl- conductance decreases.

Return to Inhibitory Neurotransmission Module

Next module: Monoamines

Neurophysiology Module 9

Monoamines

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 monamines are normally separated into three groups:

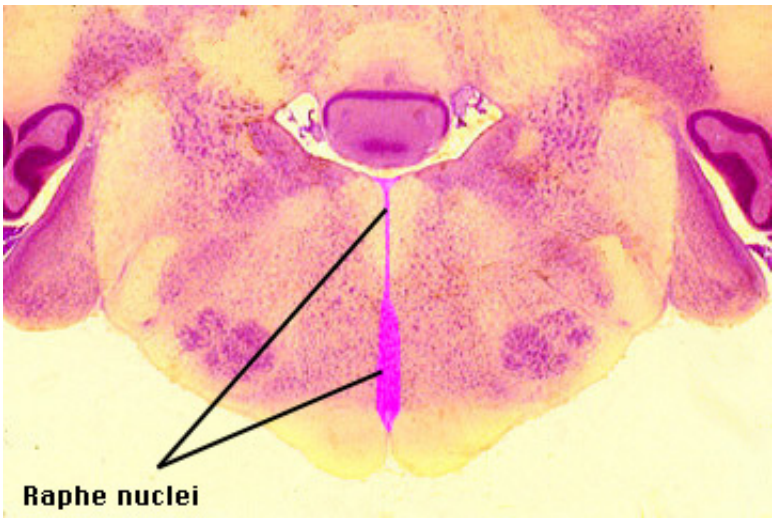
Group	Characteristics	Members
Histamine	Derived from decarboxylation of the amino acid histidine	Histamine
Catecholamines	Have a catechol *(benzene with two hydroxyl side groups at carbons 1 and 2)* and a side-chain amine	***Epinephrine***, ***Dopamine***, ***Norepinephrine***
Tryptamines	Contain an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

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 monamines 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 principal 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

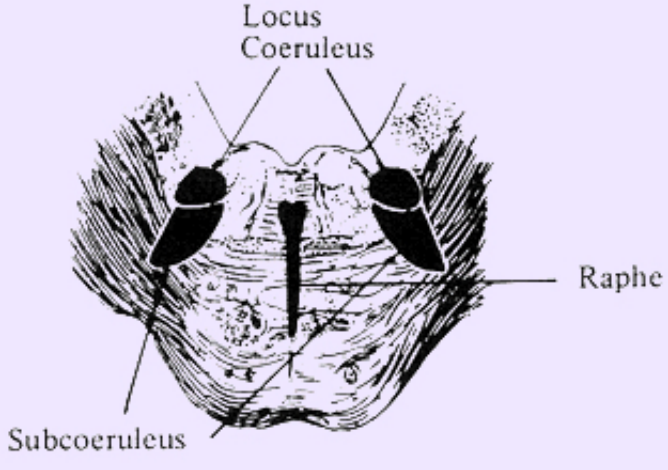


Neurons that synthesize serotonin (also called 5-hydroxytryptamine, or 5-HT) are mainly located in nuclei at the midline of the brainstem, called the ***raphe nuclei*** (raphe means "seam" in Greek). Generally, the raphe nuclei in the caudal brainstem (in the ***medulla***) project to the brainstem and 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 serotoninergic 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 ***α-1*** and ***α-2*** subtypes. The β subtype can be divided into ***β-1***, ***β-2*** and ***β-3*** receptors, although β-3 receptors are mainly in peripheral tissues (not the CNS) and are less important than the other subclasses.

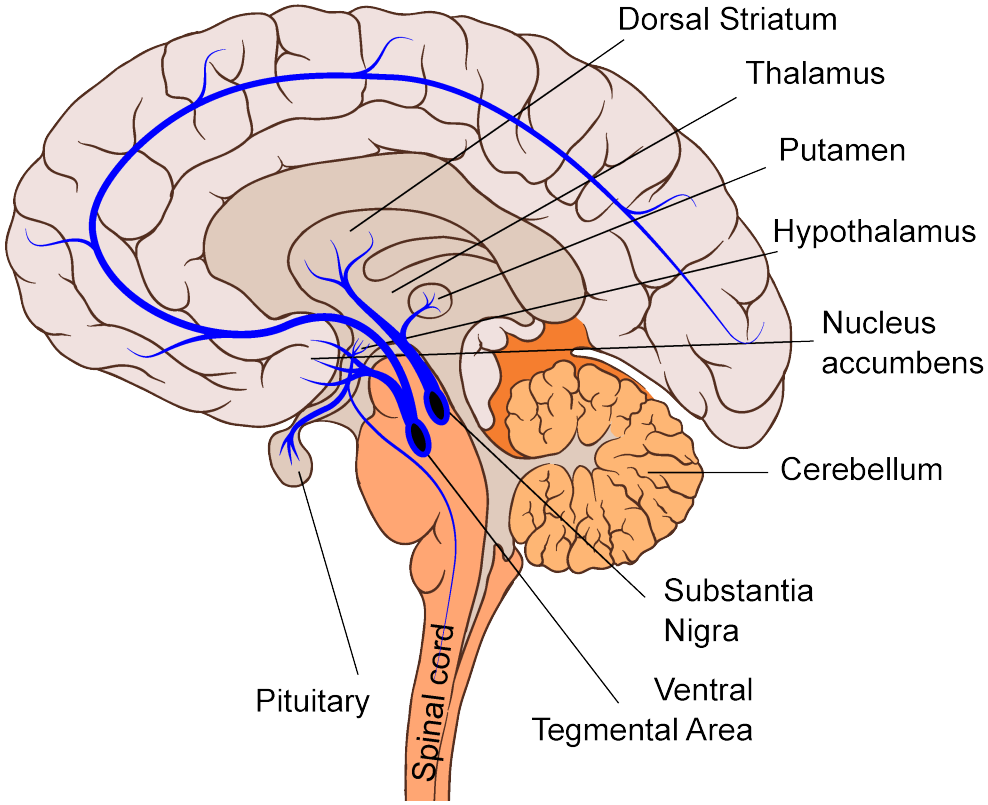
The actions of norepinephrine binding to these receptors is summarized in the table below:

Receptor	Effects of binding to the receptor
α1	Activates ***phospholipase C***, resulting in an increase in intracellular Ca2+
α2	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 α2 and β receptors would have opposite effects. While it is true that effects of transmitter binding to α1 and β receptors produces excitatory responses, whereas binding of norepinephrine to α2 causes inhibitory responses, there is a complication. In the central nervous system, α2 receptors are mostly presynaptic ***autoreceptors***, such that ligand binding to the receptor reduces norepinephrine release from the nerve terminal. In contrast, α1 and β receptors are usually postsynaptic.

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).



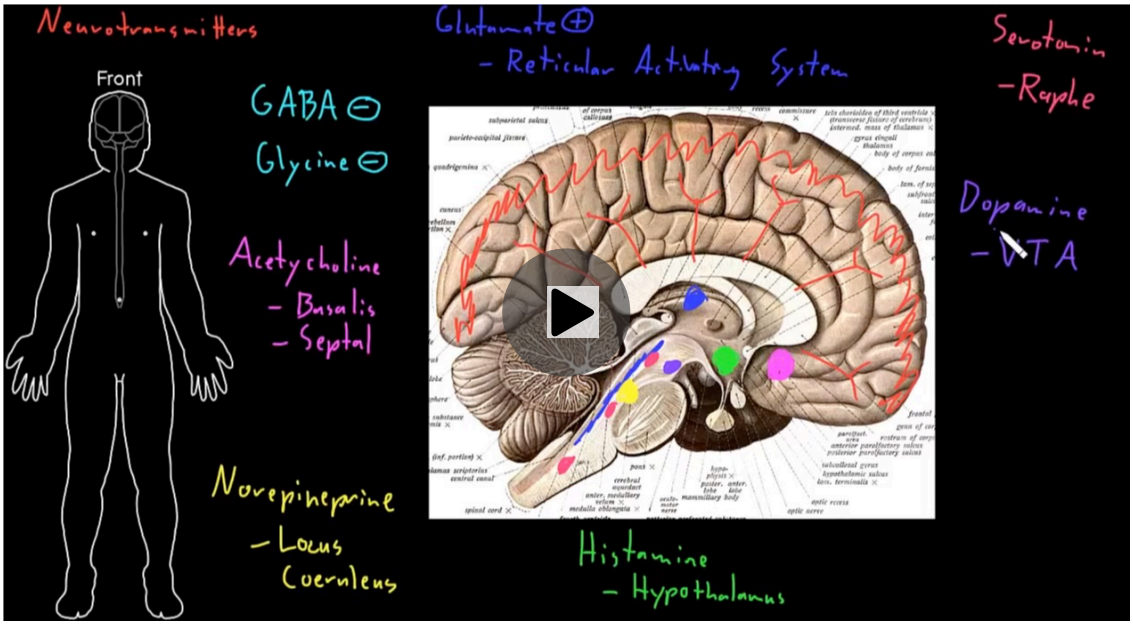
Most dopaminergic neurons are located in two midbrain areas, ***substantia nigra pars compacta*** and the ***ventral tegmental area***.

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 mainly synthesized by neurons located in the medulla
- Dopamine is inactivated by an enzyme in the synaptic cleft
- 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? *

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

Serotonin (5HT) receptors: *

- Can only be divided into only two subtypes
- Are present in cerebral cortex, but not the spinal cord
- Are entirely presynaptic
- 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

Pitt Medical Neuroscience

Fall 2025

Monoamines: Self Assessment Questions

Which of the following statements about dopamine is correct?

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

Dopamine is mainly synthesized by neurons in the midbrain, binds to metabotropic receptors, and is inactivated by reuptake into presynaptic nerve terminals. Changes in dopamine levels in the synaptic cleft have been linked to Parkinson's disease and schizophrenia, and thus drugs that alter dopaminergic neurotransmission are used to treat these conditions.

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

Monoaminergic neurons have axons that branch extensively to innervate many postsynaptic neurons. Although most monoaminergic neurons are in the CNS, they also include sympathetic postganglionic neurons. Receptors for monoamines can either be presynaptic or postsynaptic. The cell bodies of monoaminergic neurons are typically in the brainstem and midbrain (and autonomic ganglia of the sympathetic nervous system).

Serotonin (5HT) receptors:

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

Serotoninergic neurons project widely in the nervous system, including to the spinal cord. Thus, there are spinal 5HT receptors, which play a role in pain control. There are many subtypes of 5HT receptors, which are located on both the presynaptic and postsynaptic elements of the synapse.

Alpha-2 receptors:

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

Alpha-2 receptors in the CNS are usually autoreceptors, but they can be located on peripheral targets like smooth muscle in blood vessels. Alpha-2 receptors are broadly distributed in the CNS, and bind norepinephrine. Alpha-2 receptors are NOT located in autonomic ganglia, as neurotransmission in these ganglia is cholinergic.

Return to Monoamines Module

Final Module: Effects of Ca2+ and other ions

Neurophysiology Module 10

Effects of Ca^{2+} and Mg^{2+} on Neuronal Excitability

Calcium

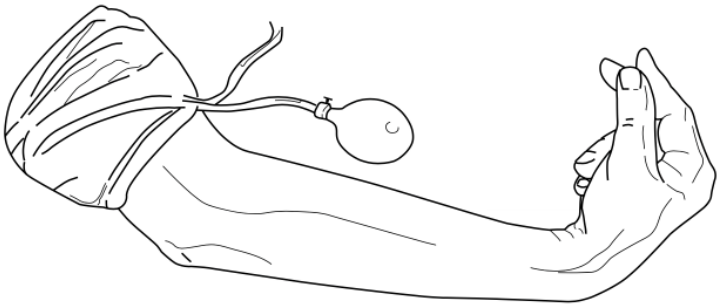
Calcium (Ca2+) is a prevalent element in the body, and comprises about 1.2 Kg of our weight. Although 99% of this Ca2+ is found in bones, the small amount of Ca2+ found in the extracellular fluid is critically important. Ca2+ is an important physiologic mediator, and participates in muscle contraction, 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 hyper-excitability 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.

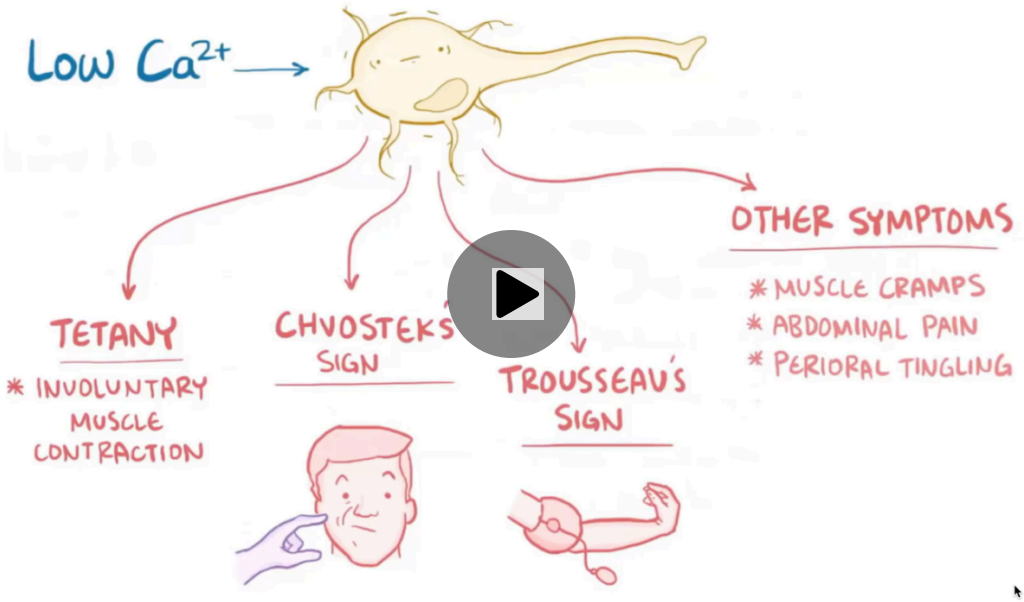
A rarer consequence of hypocalcemia is seizures.

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

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

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***.



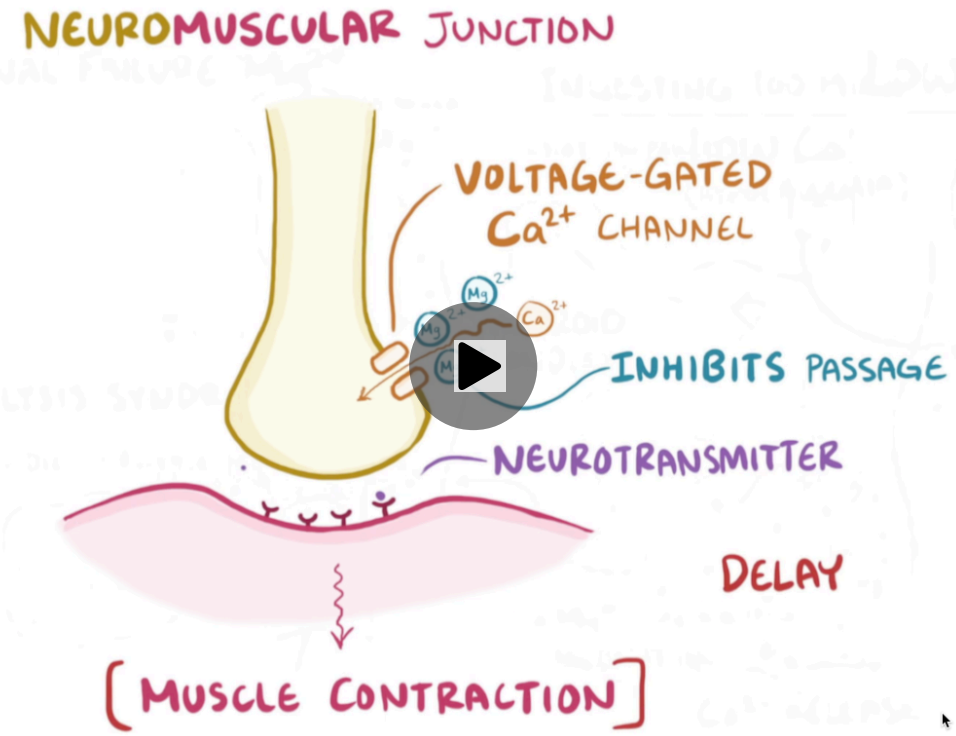
Magnesium

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.

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: 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+

- 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

Pitt Medical Neuroscience

Fall 2025

Ca2+ and Mg2+: Self Assessment Questions

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

Ca2+ inhibits the movement of sodium through voltage-gated sodium channels, whereas magnesium inhibits the movement of Ca2+ through voltage-gated Ca2+ channels. Thus, when Ca2+ levels are low, neurons become hyperexcitable. When Mg2+ levels are low, excess neurotransmitter is released when an action potential occurs in a motoneuron. Thus, both hypocalcemia and hypomagnesemia result in more activation of muscle fibers, resulting in Trousseau's sign.

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

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

Hypocalcemia results in more entry of sodium through voltage-gated sodium channels, such that motoneurons become hyperactive. This can result in spontaneously-occurring action potentials in motoneurons, producing tetany.

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

Mg2+ inhibits the movement of Ca2+ through voltage-gated Ca2+ channels, while Ca2+ inhibits the movement of sodium through voltage-gated sodium channels. Infusion of magnesium (hypermagnesemia) inhibits neurotransmitter release from sympathetic neurons, such that blood pressure drops.

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

Mg2+ inhibits the movement of Ca2+ through voltage-gated Ca2+ channels, such that hypomagnesemia results in more neurotransmitter release from motoneurons. This can produce positive Chvostek's and Trousseau's signs.

You have now completed the neurophysiology online modules.

Your feedback on these modules is helpful. Please complete this ***online form*** if you are inclined to give feedback.